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Initial Decline in Glomerular Filtration Rate With Finerenone in HFmrEF/HFpEF

A Prespecified Analysis of FINEARTS-HF

Shingo Matsumoto, MD, PhD,[a] Pardeep S. Jhund, MBChB, MSc, PhD,[a] Alasdair D. Henderson, PhD,[a] Johann Bauersachs, MD,[b] Brian L. Claggett, PhD,[c] Akshay S. Desai, MD, MPH,[c] Meike Brinker, MD,[d] Patrick Schloemer, PhD,[e] Prabhakar Viswanathan, MBBS, PhD,[f] Jon W. Mares, DO,[g] Andrea Scalise, MD,[h] Carolyn S.P. Lam, MBBS, PhD,[i] Gerard C.M. Linssen, MD, PhD,[j] Jose Francisco Kerr Saraiva, MD, PhD,[k] Michele Senni, MD,[l] Richard Troughton, MB, ChB, PhD,[m] Jacob A. Udell, MD, MPH,[n] Adriaan A. Voors, MD,[o] Faiez Zannad, MD,[p] Bertram Pitt, MD,[q] Muthiah Vaduganathan, MD, MPH,[c] Scott D. Solomon, MD,[c] John J.V. McMurray, MD[a]

ABSTRACT

BACKGROUND An initial decline in estimated glomerular filtration rate (eGFR) often leads to reluctance to continue life-saving therapies in patients with heart failure (HF).

OBJECTIVES The goal of this study was to describe the association between initial decline in eGFR and subsequent clinical outcomes in patients randomized to placebo or finerenone.

METHODS In this prespecified analysis of FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure), we examined the association between initial decline in eGFR (≥15%) from randomization to 1 month and subsequent outcomes in patients assigned to finerenone or placebo. The primary outcome was the composite of total HF events and cardiovascular death.

RESULTS Among 5,587 patients with an eGFR measurement at both baseline and 1 month, 1,018 (18.2%) experienced a ≥15% decline in eGFR. The proportion of patients experiencing a ≥15% decline in eGFR was 23.0% with finerenone and 13.4% with placebo (OR: 1.95; 95% CI: 1.69-2.24; $P < 0.001$). After adjustment, an eGFR decline was associated with a higher risk of the primary outcome in patients assigned to placebo (adjusted rate ratio: 1.50; 95% CI: 1.20-1.89) but not in those assigned to finerenone (adjusted rate ratio: 1.07; 95% CI: 0.84-1.35; $P_{interaction} = 0.04$). By contrast, the efficacy of finerenone was consistent across the range of change in eGFR from baseline to 1 month ($P_{interaction} = 0.50$ for percent change in eGFR), and safety, including hyperkalemia, was similar regardless of an early eGFR decline.

CONCLUSIONS Although an initial decline in eGFR was associated with worse outcomes in patients assigned to placebo, this relationship was not as strong in those treated with finerenone. An early decline in eGFR can be anticipated with finerenone and should not automatically lead to the discontinuation of this disease-modifying therapy (FINEARTS-HF Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure [NCT04435626]; A Multicenter, Randomized, Double-Bline, Parallel-Group, Placebo-Controlled Study to Evaluate the efficacy and safety of finerenone on morbidity and mortality in participants With Heart Failure [NYHA II-IV] and left ventricular ejection fraction ≥40% [EudraCT 2020-000306-29]). (JACC. 2025;85:173–185) © 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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From the [a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [b]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [c]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [d]Bayer AG, Research & Development, Pharmaceuticals, Wuppertal, Germany; [e]Bayer, Research & Development, Pharmaceuticals, Berlin, Germany; [f]Bayer, Research & Development, Pharmaceuticals, Whippany, New Jersey, USA; [g]Bayer US, US Medical Affairs, Whippany, New Jersey, USA; [h]Cardiology and Nephrology Clinical Development, Bayer Hispania S.L., Barcelona, Spain; [i]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [j]Department of Cardiology, Hospital Group Twente, Almelo, the Netherlands; [k]Cardiovascular Division, Instituto de Pesquisa Clínica de Campinas, Campinas, Brazil; [l]University of Milano-Bicocca, Papa Giovanni XXIII Hospital, Bergamo, Italy; [m]Christchurch Heart Institute, Department of Medicine, University of Otago, Christchurch, New Zealand; [n]Women's College Hospital and Peter Munk Cardiac Centre, Toronto General Hospital, University of Toronto, Toronto,

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure and mildly reduced ejection fraction

HFpEF = heart failure and preserved ejection fraction

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RR = rate ratio

Kidney dysfunction often leads to reluctance to continue disease-modifying therapies in patients with heart failure (HF). However, the initial decline in estimated glomerular filtration rate (eGFR) with renin-angiotensin-aldosterone system blockers and sodium-glucose cotransporter 2 inhibitors is not associated with worse outcomes or a diminished benefit of these treatments.[1-5] In contrast, physicians are often concerned by the reduction in eGFR with mineralocorticoid receptor antagonists (MRAs) because of its perceived association with hyperkalemia.[6-10] This is despite evidence that cardiovascular outcomes appear to be better in patients with HF and reduced ejection fraction experiencing an initial decline in eGFR with steroidal MRAs such as spironolactone and eplerenone.[11,12] Whether this is also the case in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) is less certain because there is 1 trial with spironolactone in this population, and there were problems with the conduct of that trial.[13,14]

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Therefore, we examined this question in FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure), which tested the novel nonsteroidal MRA finerenone. In FINEARTS-HF, finerenone, compared to placebo, reduced the primary outcome, a composite of total worsening HF events and cardiovascular death, in 6,001 patients with HFmrEF/HFpEF by 16% (rate ratio [RR]: 0.84; 95% CI: 0.74-0.95; $P = 0.007$) with an acceptable safety profile. In this prespecified analysis of FINEARTS-HF, we examined the occurrence of an initial decline in eGFR (defined as a ≥15% decrease) from randomization to 1 month. We analyzed its association with subsequent outcomes according to the treatment group and whether the efficacy and safety of finerenone, compared to placebo, were consistent in patients with and without an early eGFR decline.

METHODS

The FINEARTS-HF trial was a randomized, double-blind, placebo-controlled, event-driven trial in patients with HFmrEF/HFpEF. The design, baseline characteristics, and results of FINEARTS-HF are published.[15,16] Ethics committees for the 653 participating institutions in 37 countries approved the protocol and all patients gave written consent.

TRIAL POPULATION. Briefly, the eligibility criteria were age ≥40 years, symptomatic heart failure in NYHA functional class II to IV, treatment with a diuretic for ≥30 days before randomization, and a left ventricular ejection fraction (LVEF) ≥40% with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) measured within 12 months of screening. Patients were also required to have elevated natriuretic peptide levels, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥300 pg/mL (or B-type natriuretic peptide ≥100 pg/mL) for patients in sinus rhythm, or NT-proBNP ≥900 pg/mL (or B-type natriuretic peptide ≥300 pg/mL) for patients in atrial fibrillation, measured within 90 days in those with a recent worsening HF event within 90 days of randomization, or measured 30 days before randomization in those without a recent worsening HF event. Both ambulatory and hospitalized patients were eligible for enrollment. Patients with prior LVEF <40% with subsequent improvement to ≥40% were also eligible for enrolment provided that ongoing HF symptoms were present and all other inclusion criteria were satisfied. Key exclusion criteria at randomization were any MRA use within 30 days, serum potassium >5.0 mmol/L or eGFR <25 mL/min/1.73 m^2, symptomatic hypotension with mean systolic blood pressure <90 mm Hg at screening or randomization, systolic blood pressure ≥160 mm Hg if not on treatment with ≥3 blood pressure-lowering medications, or systolic blood pressure ≥180 mm Hg irrespective of background antihypertensive therapy. A complete list of exclusion criteria is provided in the design paper.[15]

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo. The starting dose was 10 mg once daily in participants with an

Ontario, Canada; [O]University of Groningen, Groningen, the Netherlands; [P]Université de Lorraine, Inserm Clinical Investigation Center at Institut Lorrain du Coeur et des Vaisseaux, University Hospital of Nancy, Nancy, France; and the [Q]University of Michigan School of Medicine, Ann Arbor, Michigan, USA.

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eGFR ≤60 mL/min/1.73 m^2 with a maximum maintenance dose of 20 mg once daily, whereas the starting dose was 20 mg once daily if the eGFR was >60 mL/min/1.73 m^2 with a maximum maintenance dose of 40 mg once daily.

INITIAL DECLINE IN eGFR. In FINEARTS-HF, serial creatinine values were measured after randomization at each follow-up visit (at 1, 3, 6, 9, 12, 16, and every 4 months up to the end of the trial). Serum creatinine levels were measured using a certified assay in a core laboratory. eGFR levels at each visit were calculated by the CKD-EPI formula (for 286 Japanese participants recruited in Japan, the formula was adjusted).[17,18] In the current analysis, the initial eGFR decline was defined as a ≥15% decrease in eGFR between randomization and 1 month as well as a previous report.[10]

CLINICAL OUTCOMES. The primary trial outcome was the composite of cardiovascular death and total (first and recurrent) HF events (ie, HF hospitalization or urgent HF visit). In this prespecified analysis, we also examined the components of the primary outcome, the composite of a first HF event or cardiovascular death (and its components), and all-cause death. Safety outcomes including hyperkalemia were also examined.

STATISTICAL ANALYSIS. Patient characteristics and outcomes were compared according to the occurrence of initial decline in eGFR (≥15%) from randomization to 1 month. Baseline characteristics are summarized as frequencies with percentages for categorical variables and mean ± SD or median (Q1-Q3) for continuous variables. For continuous variables, Student's *t*-test or Mann-Whitney test was used for comparisons between 2 groups, and differences among ≥3 groups were assessed using a 1-way analysis of variance and the Kruskal-Wallis test. Differences in categorical variables were compared using the chi-square test.

Initial changes in eGFR and serum creatinine between randomization and 1 month were analyzed with linear regression and logistic regression, according to treatment assignment. These relationships were also analyzed in patients with an eGFR <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2, separately. The interaction between the effect of finerenone compared to placebo on the initial change in renal function and baseline eGFR category (<60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) was tested using the Wald test. In addition, absolute changes in eGFR according to baseline background therapies (angiotensin-converting enzyme, angiotensin receptor blocker, angiotensin receptor blocker and neprilysin inhibitor, and sodium-glucose cotransporter 2 inhibitors) were assessed as a sensitivity analysis. Also, the initial change in eGFR was analyzed according to the patient's location (ambulatory or hospitalized) at enrollment. Change in eGFR and NT-proBNP over time according to treatment assignment and initial decline in eGFR (≥15%) was analyzed using a linear mixed model for repeated measurements, adjusted for baseline levels and the interaction between treatment assignment, initial decline in eGFR, and study visit, with a random intercept and slope per patient.

All survival analyses were performed as a landmark analysis from 1 month after randomization. Incidence rates for the primary outcome were presented per 100 person-years of follow-up. 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, respectively, and presented graphically. The association between initial decreases in renal function, relative (≥15% and ≥30%) and absolute (≥5 and ≥10 mL/min/1.73 m^2) declines in eGFR and relative (≥15% and ≥30%) and absolute (≥0.3 and ≥0.5 mg/dL) increases in creatinine, and clinical outcomes was evaluated as a RR and 95% CI derived from semiparametric proportional-rates models for total (first and recurrent) events, stratified according to geographic region and baseline LVEF (<60%, ≥60%).[19] Further adjustment was performed for age, sex, body mass index, NYHA functional class III or IV, heart rate, systolic blood pressure, hypertension, diabetes mellitus, myocardial infarction, prior HF hospitalization, atrial fibrillation or flutter, baseline eGFR, and log-transformed NT-proBNP. The association between finerenone use and the adjusted risk of the primary outcome was also examined according to the initial declines in kidney function. The interaction between the effect of finerenone compared to placebo on subsequent outcomes and initial decline in renal function was examined using the Wald test. The effect of finerenone on the primary outcome across percent and absolute changes in eGFR from randomization to 1 month as a continuous variable was also examined using restricted cubic splines, based on semiparametric proportional-rates models (landmark analysis from 1 month after randomization). The incidence rate of the primary composite outcome (from 1 month) according to treatment assignment across the range of relative change in eGFR from baseline to 1 month was also estimated using a restricted cubic spline, based on a prediction from a Poisson model. The number of knots was set at 3, according to Akaike Information Criterion for the primary outcome.

TABLE 1 Baseline Characteristics According to Initial Decline in eGFR Between Baseline and 1 Month After Randomization (No Decline vs ≥15% Decline in eGFR)

	No Decline in eGFR (n = 4,569)	Initial Decline in eGFR ≥15% (n = 1,018)	*P* Value
Age, y	71.7 ± 9.7	72.9 ± 9.5	<0.001
Age >70 y	2,694 (59.0)	641 (63.0)	0.02
Male	2,542 (55.6)	535 (52.6)	0.07
Region			<0.001
Western Europe, Oceania, and Others	878 (19.2)	252 (24.8)	
Eastern Europe	2,077 (45.5)	424 (41.7)	
Asia	783 (17.1)	141 (13.9)	
North America	338 (7.4)	87 (8.5)	
Latin America	493 (10.8)	114 (11.2)	
Race			0.04
White	3,566 (78.0)	826 (81.1)	
Black	64 (1.4)	20 (2.0)	
Asian	792 (17.3)	144 (14.1)	
Others	147 (3.2)	28 (2.8)	
NYHA functional class III or IV	1,361 (29.8)	350 (34.4)	<0.01
KCCQ-OSS	63.6 ± 22.1	60.3 ± 22.7	<0.001
KCCQ-CSS	66.2 ± 22.3	62.6 ± 23.0	<0.001
BMI, kg/m^2	29.9 ± 6.1	29.9 ± 6.1	0.97
BMI category, kg/m^2			0.26
<18.5	50 (1.1)	10 (1.0)	
18.5-24.9	933 (20.5)	214 (21.1)	
25-29.9	1,502 (32.9)	351 (34.5)	
30-34.4	1,214 (26.6)	236 (23.2)	
≥35	860 (18.9)	205 (20.2)	
Heart rate, beats/min	71.4 ± 11.8	71.7 ± 11.8	0.45
Systolic blood pressure, mm Hg	129.0 ± 15.2	131.2 ± 15.4	<0.001
Systolic blood pressure >140 mm Hg	1,028 (22.5)	262 (25.8)	0.03
Diastolic blood pressure, mm Hg	75.5 ± 10.3	75.9 ± 10.5	0.18
LVEF, %	52.5 ± 7.8	52.9 ± 8.0	0.11
≥50	2,883 (63.2)	673 (66.1)	0.08
≥60	871 (19.1)	199 (19.5)	0.74
History of LVEF <40%	213 (4.7)	37 (3.6)	0.15
eGFR, mL/min/1.73 m^2	62.2 ± 20.0	62.6 ± 18.2	0.58
<60	2,214 (48.5)	459 (45.1)	0.05
<45	1,023 (22.4)	202 (19.8)	0.08
UACR, mg/g	17 (6-61)	23 (8-90)	<0.001
UACR category, mg/g			<0.001
<30	2,756 (62.3)	540 (54.7)	
30-299	1,251 (28.3)	333 (33.7)	
≥300	418 (9.4)	115 (11.6)	
Potassium, mmol/L	4.4 (4.1-4.7)	4.3 (4.0-4.7)	0.05
Hemoglobin, g/dL	13.5 (12.3-14.6)	13.1 (11.9-14.3)	<0.001
Anemia	1,128 (26.0)	323 (33.8)	<0.001
NT-proBNP, pg/mL	997 (425-1,865)	1,185 (560-2,318)	<0.001
With no atrial fibrillation, pg/mL	559 (299-1,223)	746 (385-1,560)	<0.001
With atrial fibrillation, pg/mL	1,694 (1,124-2,721)	1,833 (1,212-2,952)	0.02

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Safety outcomes are reported as counts and percentages according to randomized treatment and the treatment effect was analyzed with logistic regression, adjusted for geographic region and baseline LVEF (<60%, ≥60%). The interaction was also examined using the Wald test for safety outcomes. The safety analysis was restricted to the patients who received at least 1 dose of the study drug.

As a sensitivity analysis, a competing risk analysis of the composite of the first HF event or cardiovascular death (as a time-to-first event) was performed. In addition, the association between finerenone use and the primary outcome according to the initial decrease in renal function was examined in a per-protocol (on treatment) analysis.

The association between an initial decline in renal function and the subsequent primary outcome was also examined using imputed data, as a sensitivity analysis. In this analysis, missing values of eGFR and creatinine at 1 month were addressed by multiple imputations using the baseline variables listed in Table 1 and the components of the primary outcome. Logistic and multinominal logistic regressions and linear regression were used to impute missing values for categorical and continuous variables.

The association between study drug discontinuation at any time point and the subsequent risk of the primary outcome was also examined using study drug discontinuation as a time-updated covariate in patients who had received at least one dose of the study drug (as with safety analyses).

P values <0.05 were considered statistically significant. All analyses were performed using STATA version 18.0 (StataCorp).

RESULTS

Overall, 5,587 patients had an eGFR measurement both at baseline and 1 month and were included in this analysis. Of these, 1,018 (18.2%) experienced a ≥15% decline in eGFR, including 23.0% (n = 644 of 2,798) of the finerenone group and 13.4% (n = 374 of 2,789) of the placebo group. Among the 414 of 6,001 (6.9%) patients excluded from the current analysis, 23 (0.4%) were excluded due to death within 1 month after randomization, and 391 (6.5%) were excluded due to the missingness of eGFR measurement at 1 month. The median duration of follow-up was 32 months.

BASELINE CHARACTERISTICS ACCORDING TO DECLINE IN eGFR ≥15%. Baseline characteristics according to an eGFR decline ≥15% are shown in Table 1. Patients who experienced eGFR decline at 1 month were older and had worse HF status compared to those who did not. Baseline LVEF and eGFR were comparable regardless of the occurrence of a decrease in eGFR, but the urinary albumin-creatinine ratio was higher in patients experiencing an initial decline in eGFR. Patients in the initial

decline group more often had anemia and atrial fibrillation compared to those in the no-decline group. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers were more frequently used in patients experiencing eGFR decline.

Baseline characteristics according to initial decline in eGFR ≥15% and treatment assignment are summarized in Supplemental Table 1. Overall, characteristics according to study treatment were balanced between patients who experienced an eGFR decline and who did not.

EARLY CHANGES IN eGFR AT 1 MONTH AFTER RANDOMIZATION. Early changes in eGFR and serum creatinine between randomization and 1 month are shown in **Table 2**. The mean absolute change in eGFR was -2.72 mL/min/1.73 m^2 (95% CI: -3.11 to -2.32 mL/min/1.73 m^2) with finerenone and -0.28 mL/min/1.73 m^2 (95% CI: -0.63 to 0.07 mL/min/1.73 m^2) with placebo, giving a between-treatment difference of 2.49 mL/min/1.73 m^2 (95% CI: 1.98-3.00 mL/min/1.73 m^2) ($P < 0.001$). Similar trends were observed regardless of the presence of eGFR ≥60 mL/min/1.73 m^2 vs eGFR <60 mL/min/1.73 m^2 at baseline ($P_{interaction} = 0.17$). The effect of finerenone compared to placebo on the initial changes in renal function from baseline to 1 month was not modified by baseline background HF therapies and patient's location at enrollment (ambulatory or hospitalized) (Supplemental Tables 2 and 3). Supplemental Table 4 shows changes in urine albumin-creatinine ratio according to the early decline in eGFR (≥15%) and treatment assignment. The effect of finerenone compared to placebo on the early change in urine albumin-to-creatinine ratio was not modified by the occurrence of initial eGFR decline ($P_{interaction} = 0.67$).

Changes in eGFR over time after 1 month are shown in Supplemental Figure 1. Patients experiencing an initial decline in eGFR had lower eGFR levels until 32 months compared to those without initial eGFR decline.

Supplemental Figure 2 shows changes in NT-proBNP over time according to the initial eGFR decrease and treatment assignment. Finerenone reduced NT-proBNP levels compared to placebo, even in patients with an initial decrease in eGFR ≥15%.

PROPORTIONS OF PATIENTS WITH DIFFERENT THRESHOLD CHANGES IN eGFR AND SERUM CREATININE AT 1 MONTH. Percentage decline in eGFR of ≥15% and ≥30%. Overall, a ≥15% decline in eGFR at 1 month was observed more often in the finerenone group (23.0%) compared to the placebo group (13.4%) (OR: 1.95; 95% CI: 1.69-2.24; $P < 0.001$), and this was true for patients with baseline eGFR ≥60 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 ($P_{interaction} = 0.49$) (**Table 2**). The proportion of patients experiencing a ≥30% decline in eGFR at 1 month was also higher in those assigned to finerenone (4.9%) compared to placebo (2.0%) (OR: 2.51; 95% CI: 1.83-3.44; $P < 0.001$), irrespective of the baseline eGFR category (ie, eGFR ≥60 mL/min/1.73 m^2 vs eGFR <60 mL/min/1.73 m^2; $P_{interaction} = 0.87$).

Absolute decline in eGFR of ≥5 mL/min/1.73 m^2 and ≥10 mL/min/1.73 m^2. A similar trend was observed with analysis of absolute change in eGFR (**Table 2**). The proportion of patients experiencing an eGFR decrease ≥5 mL/min/1.73 m^2 at 1 month was larger with finerenone (38.3%) compared to placebo (27.1%) (OR: 1.71; 95% CI: 1.53-1.92; $P < 0.001$). An absolute decline in eGFR ≥10 mL/min/1.73 m^2 was also more frequent with finerenone (19.9%) compared to placebo (11.8%), (OR: 1.93; 95% CI: 1.66-2.24; $P < 0.001$). These associations were not modified by the baseline eGFR category ($P_{interaction} = 0.17$ for eGFR decrease ≥5 mL/min/1.73 m^2 and $P_{interaction} = 0.08$ for ≥10 mL/min/1.73 m^2, respectively).

TABLE 1 Continued

	No Decline in eGFR (n = 4,569)	Initial Decline in eGFR ≥15% (n = 1,018)	*P* Value
Medical history			
Prior hospitalization for HF	2,730 (59.8)	617 (60.6)	0.61
Type 2 diabetes mellitus[a]	1,873 (41.1)	410 (40.4)	0.71
Hypertension	4,055 (88.8)	910 (89.4)	0.56
Myocardial infarction	1,192 (26.1)	257 (25.2)	0.58
CABG	703 (15.4)	157 (15.4)	0.98
PCI	1,136 (24.9)	231 (22.7)	0.14
Peripheral arterial disease	391 (8.6)	112 (11.0)	0.01
Atrial fibrillation	2,442 (53.4)	587 (57.7)	0.02
COPD	582 (12.7)	128 (12.6)	0.89
Stroke	624 (13.7)	153 (15.0)	0.25
Treatment			
ACEI	1,655 (36.2)	364 (35.8)	0.78
ACEI or ARB[b]	3,233 (70.8)	753 (74.0)	0.04
ARNI	400 (8.8)	66 (6.5)	0.02
β-blocker	3,886 (85.1)	875 (86.0)	0.46
SGLT2i	627 (13.7)	140 (13.8)	0.98
Loop diuretics	3,980 (87.1)	893 (87.7)	0.60
Thiazide	619 (13.5)	153 (15.0)	0.22
Digoxin	348 (7.6)	86 (8.4)	0.37
Pacemaker	255 (5.6)	56 (5.5)	0.92

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Type 1 diabetes was excluded in this analysis. [b]Without ARNI.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker and neprilysin inhibitor; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CSS = clinical summary score; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OSS = overall summary score; PCI = percutaneous coronary intervention; SGLT2i = sodium-glucose cotransporter 2 inhibitor; UACR = urine albumin-creatinine ratio.

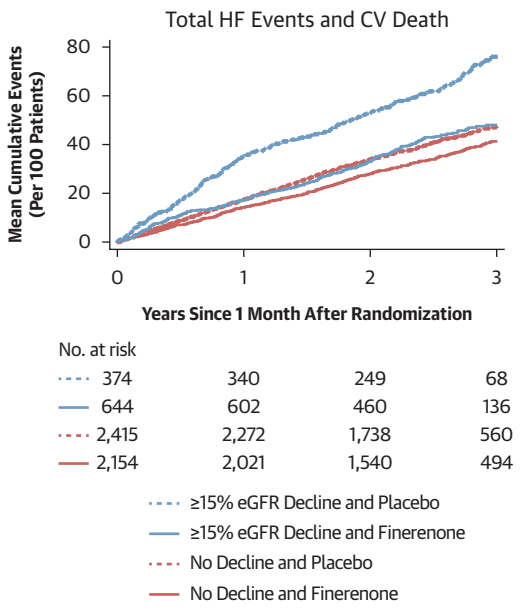
TABLE 2 Changes in eGFR and Serum Creatinine From Baseline to 1 Month in Each Treatment Group

	Overall		Baseline eGFR ≥60 mL/min/1.73 m²		Baseline eGFR <60 mL/min/1.73 m²		
	Placebo (n = 2,789)	Finerenone (n = 2,798)	Placebo (n = 1,463)	Finerenone (n = 1,451)	Placebo (n = 1,326)	Finerenone (n = 1,347)	*P* for Interaction
Changes in eGFR, mL/min/1.73 m²							
Absolute change							
Mean change from baseline to 1 month (95% CI)	-0.28 (-0.63 to 0.07)	-2.72 (-3.11 to -2.32)	-2.13 (-2.63 to -1.63)	-4.87 (-5.42 to -4.32)	1.76 (1.28 to 2.23)	-0.39 (-0.93 to 0.14)	
Mean difference[a] (95% CI)	-2.49 (-3.00 to -1.98)		-2.83 (-3.56 to -2.09)		-2.13 (-2.83 to -1.43)		0.17
≥15% decline							
n (%)	374 (13.4)	644 (23.0)	211 (14.4)	348 (24.0)	163 (12.3)	296 (22.0)	
OR for decline with finerenone over placebo[a] (95% CI)	1.95 (1.69-2.24)		1.85 (1.53-2.24)		2.05 (1.66-2.53)		0.49
≥30% decline							
n (%)	56 (2.0)	136 (4.9)	26 (1.8)	65 (4.5)	30 (2.3)	71 (5.3)	
OR for decline with finerenone over placebo[a] (95% CI)	2.51 (1.83-3.44)		2.59 (1.64-4.12)		2.46 (1.59-3.80)		0.87
≥5 mL/min/1.73 m² decline							
n (%)	757 (27.1)	1071 (38.3)	512 (35.0)	668 (46.0)	245 (18.5)	403 (29.9)	
OR for decline with finerenone over placebo[a] (95% CI)	1.71 (1.53-1.92)		1.58 (1.36-1.84)		1.89 (1.57-2.27)		0.17
≥10 mL/min/1.73 m² decline							
n (%)	329 (11.8)	556 (19.9)	258 (17.6)	395 (27.2)	71 (5.4)	161 (12.0)	
OR for decline with finerenone over placebo[a] (95% CI)	1.93 (1.66-2.24)		1.75 (1.46-2.09)		2.41 (1.80-3.24)		0.08
Changes in creatinine							
15% increase							
n (%)	391 (14.0)	673 (24.1)	242 (16.5)	392 (27.0)	149 (11.2)	281 (20.9)	
OR for increase with finerenone over placebo[a] (95% CI)	1.98 (1.72-2.27)		1.91 (1.59-2.29)		2.13 (1.72-2.64)		0.41
30% increase							
n (%)	83 (3.0)	188 (6.7)	42 (2.9)	100 (6.9)	41 (3.1)	88 (6.5)	
OR for increase with finerenone over placebo[a] (95% CI)	2.37 (1.82-3.08)		2.55 (1.76-3.69)		2.23 (1.53-3.27)		0.65
≥0.3 mg/dL increase							
n (%)	111 (4.0)	225 (8.0)	33 (2.3)	71 (4.9)	78 (5.9)	154 (11.4)	
OR for decline with finerenone over placebo[b] (95% CI)	2.17 (1.72-2.76)		2.20 (1.45-3.36)		2.17 (1.63-2.89)		0.94
≥0.5 mg/dL increase							
n (%)	40 (1.4)	77 (2.8)	13 (0.9)	21 (1.5)	27 (2.0)	56 (4.2)	
OR for decline with finerenone over placebo[b] (95% CI)	2.02 (1.37-2.99)		1.63 (0.81-3.28)		2.23 (1.39-3.57)		0.47

[a]Adjusted for baseline eGFR, region, and left ventricular ejection fraction. [b]Adjusted for baseline creatinine, region, and left ventricular ejection fraction.
Abbreviation as in Table 1.

Absolute increase in serum creatinine of ≥0.3 mg/dL and ≥0.5 mg/dL. Consistent with absolute changes in eGFR, increases in creatinine were more often observed in patients randomized to finerenone compared to placebo, regardless of whether a threshold of ≥0.3 mg/dL and ≥0.5 mg/dL was examined, and across baseline eGFR categories (Table 2).

FIGURE 1 The Primary Outcome According to Initial Decline in eGFR (≥15%) and Study Treatment (Landmark Analysis)



A landmark analysis from 1 month after randomization was performed. CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure.

ASSOCIATION BETWEEN EACH THRESHOLD OF INITIAL CHANGES IN RENAL FUNCTION AND THE SUBSEQUENT PRIMARY OUTCOME. Initial decline in eGFR ≥15% and subsequent outcome. Table 3 and Figure 1 show the association between the initial decline in eGFR (≥15%) in a landmark analysis starting at 1 month after randomization. Overall, an early decline in eGFR was associated with a higher unadjusted risk of total HF events and cardiovascular death (RR: 1.26; 95% CI: 1.07-1.49; $P < 0.01$). This was notably the case in patients assigned to placebo (RR: 1.56; 95% CI: 1.22-1.99; $P < 0.01$); however, in the finerenone group, an initial decline in eGFR ≥15% was somewhat less likely to be associated with worse outcomes (RR: 1.14; 95% CI: 0.90-1.43; $P = 0.27$; $P_{interaction} = 0.06$) (Table 3, Figure 1). These trends were consistent after adjustment for baseline prognostic variables, including baseline eGFR levels, and in the adjusted analysis the interaction was significant ($P_{interaction} = 0.04$) (Table 3).

Other threshold changes in renal function and subsequent outcome. The associations between other thresholds for the initial decline in kidney function and subsequent outcomes (beyond 1 month) are summarized in Table 3. After adjustment, the initial decline in kidney function was not associated with worse outcomes in patients treated with finerenone, whereas some definitions of initial decrease in renal function were associated with poorer outcomes in those assigned to placebo.

Similar associations (ie, a weaker association between the initial decline in renal function and subsequent outcomes in patients treated with finerenone, compared to placebo) were observed for the other outcomes examined (total HF events, cardiovascular death, and the first HF event or cardiovascular death) (Supplemental Tables 5 to 7).

Additionally, the association between initial decline in renal function and time-to-first HF event or cardiovascular death was similar, including in an analysis taking account of the competing risk of death (Supplemental Tables 7 and 8). A sensitivity analysis using imputed data also showed similar associations (Supplemental Table 9).

ASSOCIATION BETWEEN FINERENONE USE AND THE RISK OF THE PRIMARY OUTCOME, ACCORDING TO CHANGES IN KIDNEY FUNCTION FROM BASELINE TO 1 MONTH. The associations between finerenone use and the risk of the primary outcome according to each definition of change in renal function examined are shown in Figure 2. Regardless of the definition of early decrease in kidney function, finerenone use was associated with a lower risk of the primary outcome, compared to placebo, in patients experiencing an early decline in kidney function, even after adjustment for key prognostic variables.

A per-protocol (on treatment) analysis showed similar findings to the main analysis, and the association between finerenone use and the adjusted risk of the primary outcome was maintained in patients with an initial decline in renal function (Supplemental Table 10).

The **Central Illustration** shows the effects of finerenone compared to placebo on the incidence of the primary outcome after 1 month according to the percentage change in eGFR from baseline to 1 month (with percent change in eGFR analyzed as a continuous variable). In this landmark analysis, the benefits of finerenone appeared to be consistent regardless of the percentage change in eGFR between baseline and 1 month ($P_{interaction} = 0.50$). Similarly, the benefit of finerenone vs placebo was consistent according to the absolute change in eGFR from baseline to 1 month (Supplemental Figure 3). The subsequent incidence rate of the primary outcome appeared to be lower in patients assigned to finerenone compared to placebo across the range of relative change in eGFR from baseline to 1 month (Supplemental Figure 4).

TABLE 3 Early Decline in Kidney Function at 1 Month and the Subsequent Occurrence of the Primary Outcome in Each Treatment Group (Landmark Analysis)

	Placebo		Finerenone		
	No Decline	Decline in Kidney Function	No Decline	Decline in Kidney Function	*P* for Interaction
Changes in eGFR					
≥15% decline					
Event rate[a]	15.7 (14.2-17.4)	24.9 (19.8-31.4)	13.3 (11.9-15.0)	16.2 (13.2-19.8)	
RR	Reference	1.56 (1.22-1.99)	Reference	1.14 (0.90-1.43)	0.06
Adjusted RR[b]	Reference	1.50 (1.20-1.89)	Reference	1.07 (0.84-1.35)	0.04
≥30% decline					
Event rate[a]	16.7 (15.2-18.3)	28.9 (18.4-45.3)	13.7 (12.3-15.1)	21.0 (13.4-32.9)	
RR	Reference	1.76 (1.13-2.75)	Reference	1.42 (0.90-2.23)	0.43
Adjusted RR[b]	Reference	1.48 (0.91-2.41)	Reference	0.97 (0.58-1.63)	0.18
≥5 mL/min/1.73 m^2 decline					
Event rate[a]	16.7 (15.0-18.6)	17.6 (14.8-20.8)	13.2 (11.7-14.9)	15.3 (12.8-18.2)	
RR	Reference	1.06 (0.87-1.29)	Reference	1.11 (0.90-1.36)	0.70
Adjusted RR[b]	Reference	1.25 (1.02-1.53)	Reference	1.17 (0.94-1.45)	0.46
≥10 mL/min/1.73 m^2 decline					
Event rate[a]	16.6 (15.0-18.3)	19.6 (15.5-24.9)	14.3 (12.8-16.0)	12.9 (10.1-16.3)	
RR	Reference	1.25 (0.97-1.61)	Reference	0.88 (0.68-1.15)	0.05
Adjusted RR[b]	Reference	1.47 (1.13-1.91)	Reference	0.97 (0.73-1.28)	0.01
Changes in creatinine					
15% increase					
Event rate[a]	15.9 (14.4-17.5)	23.4 (18.7-29.2)	13.6 (12.1-15.3)	15.2 (12.4-18.6)	
RR	Reference	1.45 (1.15-1.85)	Reference	1.03 (0.82-1.29)	0.04
Adjusted RR[b]	Reference	1.50 (1.20-1.88)	Reference	1.00 (0.79-1.27)	0.01
30% increase					
Event rate[a]	16.5 (15.0-18.1)	32.7 (22.0-48.5)	13.8 (12.4-15.3)	17.3 (11.6-26.0)	
RR	Reference	1.98 (1.34-2.94)	Reference	1.18 (0.78-1.79)	0.06
Adjusted RR[b]	Reference	1.78 (1.20-2.62)	Reference	0.89 (0.56-1.41)	0.01
≥0.3 mg/dL increase					
Event rate[a]	16.0 (14.6-17.6)	40.4 (28.8-56.7)	13.0 (11.7-14.5)	25.7 (18.9-35.0)	
RR	Reference	2.39 (1.69-3.37)	Reference	1.72 (1.24-2.37)	0.18
Adjusted RR[b]	Reference	1.73 (1.25-2.40)	Reference	1.17 (0.83-1.65)	0.15
≥0.5 mg/dL increase					
Event rate[a]	16.6 (15.1-18.2)	40.9 (24.5-68.5)	13.7 (12.4-15.2)	24.8 (14.4-42.6)	
RR	Reference	2.49 (1.53-4.06)	Reference	1.66 (0.95-2.90)	0.20
Adjusted RR[b]	Reference	1.93 (1.11-3.36)	Reference	0.83 (0.45-1.52)	0.03

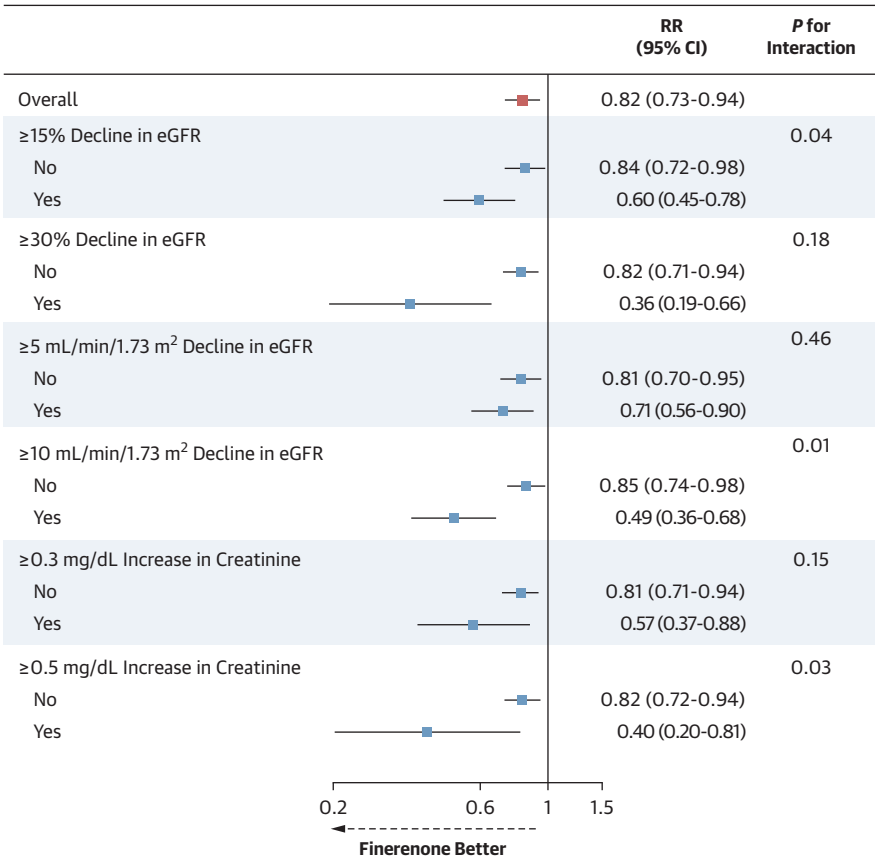
Values in parentheses are 95% CIs. Landmark analyses from 1 month after randomization were performed. [a]Per 100 person-years. [b]Adjusted for age, sex, body mass index, NYHA III or IV, heart rate, systolic blood pressure, hypertension, diabetes mellitus, myocardial infarction, prior HF hospitalization, atrial fibrillation or flutter, baseline eGFR, and log-transformed NT-proBNP.

RR = rate ratio; other abbreviations as in Table 1.

TOLERABILITY OF FINERENONE COMPARED TO PLACEBO ACCORDING TO THE INITIAL DECLINE IN eGFR. Among the patients who received at least 1 dose of randomized treatment, those experiencing a ≥15% decline in eGFR had a higher risk of hyperkalemia defined as a potassium >5.5 mmol/L (17.3% in the eGFR decline group vs 9.4% in the no eGFR decline group; OR: 2.07; 95% CI: 1.71-2.51; $P < 0.001$) or >6.0 mmol/L (4.0% in the eGFR decline group vs 1.8% in the no eGFR decline group (OR 2.32; 95% CI: 1.58-3.43; $P < 0.001$). However, the excess risk of hyperkalemia with finerenone vs placebo was similar in patients experiencing an eGFR decline at 1 month vs those not having an early decline in eGFR (Table 4). The risk of hypokalemia and hypotension did not differ between patients with and without an early eGFR decline and the differential effects of finerenone vs placebo on these 2 outcomes were consistent in patients with and without an eGFR decline.

STUDY DRUG DISCONTINUATION AND SUBSEQUENT OUTCOMES IN PATIENTS WITH AND WITHOUT THE INITIAL DECLINE IN eGFR. Overall, the rate of study drug discontinuation during follow-up was similar in patients assigned to finerenone and placebo (31.5% with finerenone vs 32.5% with placebo, $P = 0.45$), and

FIGURE 2 **Association Between Finerenone Use and Adjusted Risk for the Primary Outcome According to Initial Changes in Renal Function (Landmark Analysis)**



A landmark analysis from 1 month after randomization was performed. Rate ratios (RRs) were adjusted for age, sex, body mass index, NYHA functional class III or IV, heart rate, systolic blood pressure, hypertension, diabetes mellitus, myocardial infarction, prior HF hospitalization, atrial fibrillation or flutter, baseline eGFR, and log-transformed N-terminal pro-B-type natriuretic peptide. Abbreviations as in Figure 1.

this association was not modified by the initial decline in eGFR ≥15% ($P_{interaction} = 0.19$) (Table 4).

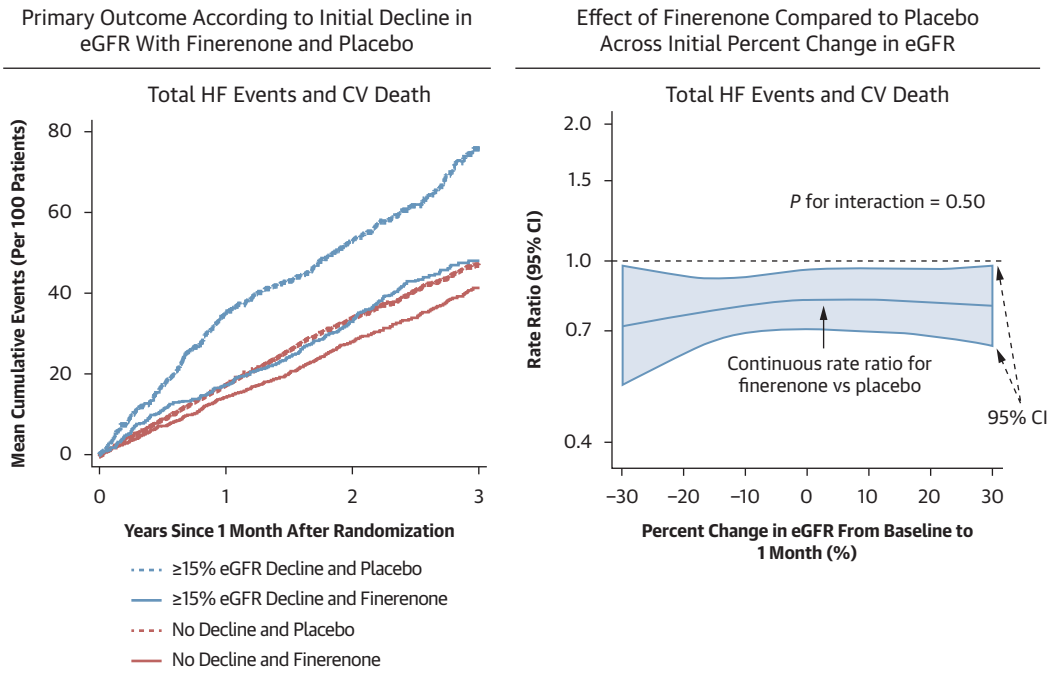
By contrast, patients experiencing study drug discontinuation had a substantially higher subsequent risk of the primary outcome compared to those who did not (RR: 3.33; 95% CI: 2.94-3.78; $P < 0.001$). Additionally, this association was enhanced in patients with finerenone compared to placebo even after adjustment for key prognostic variables (RR: 4.05; 95% CI: 3.37-4.86 in patients with finerenone and RR: 1.93; 95% CI: 1.60-2.32 in those with placebo; $P_{interaction} < 0.001$) (Supplemental Table 11).

DISCUSSION

In this prespecified analysis of FINEARTS-HF, there were several key findings. First, an early decline in kidney function was more often observed with finerenone compared to placebo. Second, although there was a much higher subsequent event rate for cardiovascular death and total HF events in placebo-treated patients experiencing an early decline in kidney function, this association was not seen or was not as strong in those assigned to finerenone. Third, the efficacy of finerenone was consistent across the range of per cent or absolute change in eGFR between baseline and 1 month. Finally, the relative excess of hyperkalemia with finerenone vs placebo was not different between patients with and without an initial decline in eGFR.

Using the primary definition of a decrease in kidney function, we observed that 13% of patients assigned to placebo experienced a ≥15% decline in eGFR over the first month after randomization with

CENTRAL ILLUSTRATION **Effect of Finerenone According to Initial Change in Estimated Glomerular Filtration Rate**



An early decline in eGFR should not automatically lead to the discontinuation of the MRA finerenone.

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A landmark analysis from 1 month after randomization was performed. CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; MRA = mineralocorticoid receptor antagonist.

the proportion increasing to 27% using the alternative threshold of an absolute 5-mL/min/1.73 m^2 decrease. Both these figures serve to show how labile kidney function is in patients with HFmrEF/HFpEF and how easy it is for physicians to mistakenly attribute decreases in kidney function to newly commenced treatments. The obvious concern is that such decreases in kidney function might lead to discontinuation of effective treatments. This could be highly disadvantageous for patients because an incidental

TABLE 4 **The Safety of Finerenone Compared to Placebo According to the Initial Decline in eGFR (≥15%) and Treatment Assignment**

	No Decline in eGFR		≥15% Decline in eGFR		
	Placebo (n = 2,415)	Finerenone (n = 2,152)	Placebo (n = 374)	Finerenone (n = 644)	*P* for Interaction
Hyperkalemia, mmol/L					
K >5.5	157 (6.5)	269 (12.5)	38 (10.2)	137 (21.4)	0.40
K >6.0	30 (1.3)	52 (2.4)	8 (2.2)	32 (5.0)	0.62
Hypokalemia, mmol/L					
K <3.5	236 (9.8)	90 (4.2)	34 (9.1)	33 (5.2)	0.34
K <3.0	32 (1.3)	6 (0.3)	5 (1.3)	2 (0.3)	0.92
Systolic blood pressure <100 mm Hg	298 (12.4)	386 (18.0)	51 (13.7)	134 (20.9)	0.84

Values are n (%). All analyses were restricted to the patients who received at least 1 dose of the study drug.
eGFR = estimated glomerular filtration rate; K = potassium.

decline in eGFR (ie, as seen with placebo) has very different implications than one induced by a drug such as finerenone (or other treatments like a sodium-glucose cotransporter 2 inhibitor or sacubitril/valsartan). This is because even modest incidental decreases in kidney function (ie, in the placebo group) are associated with worse subsequent outcomes (eg, adjusted RR: 1.50; 95% CI: 1.20-1.89 for ≥15% decline in eGFR). Conversely, a similar decline in eGFR with finerenone was not associated with a higher risk (adjusted RR: 1.07; 95% CI: 0.84-1.35) and the reduction in the risk of the primary endpoint was not diminished in patients with an eGFR decline (RR: 0.60; 95% CI: 0.44-0.81) and those without (RR: 0.86; 95% CI: 0.74-1.00).

The association between initial decline in eGFR with certain HF therapies without a subsequent elevation in poor outcomes (or attenuated increase in these outcomes compared to placebo) has been reported in previous trials, especially in patients with HF and reduced ejection fraction. Importantly, as with the current analysis, early decline in renal function after the initiation of an angiotensin receptor neprilysin inhibitor or sodium-glucose cotransporter 2 was not associated with adverse outcomes in these trials.[3,10,20-22] Also, in TOPCAT-Americas (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist-Americas), early worsening of kidney function after initiation of spironolactone was not associated with worse outcomes compared to patients experiencing worsening renal function on placebo.[23]

Although an initial decline in eGFR was common in patients started on finerenone, the mean decrease between baseline to 1 month was small (2.72 mL/min/1.73 m^2 vs 0.28 mL/min/1.73 m^2 on placebo) and similar to the early decline reported with renin-angiotensin-aldosterone system inhibitors (approximately 2.0- to 3.0-mL/min/1.73 m^2 decline with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers),[22,24] supporting the suggestion of a similar underlying mechanism reflecting changes in glomerular hemodynamics.[25] Whatever the mechanism, the important finding is that the decrease in eGFR with all 3 of these drug classes is not associated with worse outcomes (assuming eGFR does not reach a dangerously low level), as is also the case with sodium-glucose cotransporter 2 inhibitors which have a different effect on tubular and glomerular function.[3,21,26]

As discussed above, a decrease in eGFR with an MRA may raise a particular concern about hyperkalemia.[6-10] An initial decline in eGFR was associated with a higher incidence of hyperkalemia (in patients assigned to placebo, 10.2% incidence of hyperkalemia in the decline group vs 6.5% in the no-decline group for >5.5 mmol/L; 2.2% vs 1.3%, respectively, for >6 mmol/L). Finerenone approximately doubled the risk of hyperkalemia and the relative excess in risk was similar in patients with and without an initial decrease in eGFR. Importantly, even in patients with an early decline in eGFR, the absolute risk of serious hyperkalemia (>6.0 mmol/L) was not high (5.0% on finerenone vs 2.2% on placebo), which must be considered in the context of the risk of the primary endpoint in these individuals (approximately 25% per year in patients assigned to placebo with a ≥15% decline in eGFR over the first month after randomization).

STUDY LIMITATIONS. Because we studied patients enrolled in a randomized clinical trial with specific inclusion and exclusion criteria, our results may not be generalizable to all patients with HFmrEF/HFpEF in the general population. The initial decline in eGFR was a nonrandomized exposure; therefore, the association between the incidence of eGFR decline and subsequent outcomes may be confounded by variables beyond those we adjusted for in our models. This conditional nature of our analysis may also constrain the generalizability of our results.

CONCLUSIONS

Patients assigned to finerenone compared to placebo were more likely to experience an initial decline in eGFR between randomization and 1 month. Although an initial decline in eGFR was associated with worse subsequent outcomes in patients assigned to placebo, this association was not as strong in those assigned to finerenone. An early decline in eGFR can be anticipated with finerenone and should not automatically lead to the discontinuation of finerenone, as with other effective treatments in patients with HF.

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All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr 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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APPENDIX For supplemental figures and tables, please see the online version of this paper.