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Finerenone and Kidney Outcomes in Patients With Heart Failure

The FINEARTS-HF Trial

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ABSTRACT

BACKGROUND Finerenone has kidney-protective effects in patients with chronic kidney disease with type 2 diabetes, but effects on kidney outcomes in patients with heart failure with and without diabetes and/or chronic kidney disease are not known.

OBJECTIVES The purpose of this study was to examine the effects of finerenone on kidney outcomes in FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure), a randomized trial of finerenone vs placebo among patients with heart failure with mildly reduced or preserved ejection fraction.

METHODS We explored the effects of finerenone on the secondary outcome of a sustained ≥50% estimated glomerular filtration rate (eGFR) decline or kidney failure (sustained eGFR decline <15 mL/min/1.73 m^2; initiation of maintenance dialysis; renal transplantation). In this prespecified analysis, we also report effects of finerenone on: 1) sustained ≥57% eGFR decline or kidney failure; 2) eGFR slope; and 3) changes in urine albumin/creatinine ratio (UACR).

RESULTS Among 6,001 participants, mean baseline eGFR was 62 ± 20 mL/min/1.73 m^2; 48% had eGFR <60 mL/min/1.73 m^2. Overall, 5,797 had baseline UACR data (median: 18 mg/g [Q1-Q3: 7-67 mg/g]). Over 2.6 years median follow-up, the incidence of the composite kidney outcome (≥50% eGFR decline or kidney failure) was numerically, but nonsignificantly, higher for finerenone vs placebo (75 vs 55 events; HR: 1.33; 95% CI: 0.94-1.89). Similar results were observed for the composite of ≥57% eGFR decline or kidney failure (41 vs 31 events; HR: 1.28; 95% CI: 0.80-2.05), although the overall event frequency was relatively low. During the first 3 months, finerenone led to an acute decline in eGFR of −2.9 mL/min/1.73 m^2 (95% CI: −3.4 to −2.4 mL/min/1.73 m^2) but did not alter chronic (from 3 months) eGFR slope (+0.2 mL/min/1.73 m^2 per year; 95% CI: −0.1 to 0.4 mL/min/1.73 m^2 per year), vs placebo. The difference in total slope was −0.7 mL/min/1.73 m^2 per year (95% CI: −0.9 to −0.4 mL/min/1.73 m^2 per year.). Finerenone reduced UACR by 30% (95% CI: 25%-34%) over 6 months vs placebo, an effect that persisted throughout follow-up. Finerenone reduced the risk of new-onset of microalbuminuria and macroalbuminuria by 24% (HR: 0.76; 95% CI: 0.68-0.83) and 38% (HR: 0.62; 95% CI: 0.53-0.73), respectively.

CONCLUSIONS In FINEARTS-HF, a population at low risk of adverse kidney outcomes, finerenone did not significantly modify the kidney composite outcomes. Finerenone led to a greater reduction in initial eGFR, but did not result in a significant difference in chronic eGFR slope vs placebo. Finerenone led to early and sustained reductions in albuminuria and reduced the risk of new-onset micro- and macroalbuminuria. (FINEARTS-HF [Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenon 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%]; NCT04435626) (JACC. 2025;85:159-168) © 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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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitors

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

SGLT2 = sodium-glucose cotransporter 2

T2DM = type 2 diabetes mellitus

UACR = urine albumin:creatinine ratio

Chronic kidney disease (CKD) affects around one-half of patients with heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF).[1] CKD and heart failure (HF) frequently coexist with other metabolic conditions, such as type 2 diabetes mellitus (T2DM), contributing to a cardio-kidney-metabolic overlap, with higher associated adverse outcomes compared with any individual condition alone.[2] Among patients with HFmrEF/HFpEF, the presence and magnitude of albuminuria is a potent predictor of both cardiovascular and kidney adverse outcomes.[3,4]

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Contemporary trials support the use of angiotensin receptor-neprilysin inhibitors (ARNI)[5] (in select individuals) and sodium-glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular outcomes among patients with HFmrEF/HFpEF.[6,7] In addition, both ARNI (sacubitril/valsartan) and SGLT2 inhibitors (dapagliflozin and empagliflozin) have beneficial effects on slowing the decline of estimated glomerular filtration rate (eGFR), compared with valsartan and placebo, respectively.[7-10] However, in trials with SGLT2 inhibitors, as well as among participants of TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial) (testing spironolactone, a steroidal mineralocorticoid receptor antagonist [MRA]), no treatment reductions in adverse kidney composite outcomes were observed, although effect estimates varied according to the definition of kidney disease progression.[10]

Finerenone, a nonsteroidal MRA, has proven efficacy in reducing kidney disease progression and albuminuria in patients with CKD and T2DM,[11,12] and was recently observed to lower the risk of the composite of HF events and cardiovascular death among patients with HFmrEF/HFpEF in the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial.[13] Here, in these prespecified analyses of FINEARTS-HF, we explore the effects of finerenone on kidney outcomes (kidney disease progression, eGFR slope, and albuminuria).

METHODS

TRIAL DESIGN AND OVERSIGHT. The trial design, analysis plan, and primary results of the FINEARTS-HF trial have been published.[13,14] The trial protocol was approved by the ethics committees or Institutional Review Boards at all participating centers and all patients provided written informed consent. Trial oversight was provided by an independent data and safety monitoring committee.

STUDY PATIENTS. Briefly, FINEARTS-HF enrolled patients ≥40 years of age or older with symptomatic HF, left ventricular ejection fraction (LVEF) ≥40%, evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement within 12 months), and elevated serum concentration of natriuretic peptides. Notable exclusion criteria included: eGFR <25 mL/min/1.73 m^2; serum potassium >5 mmol/L; hemoglobin <10 g/dL; symptomatic hypotension (mean systolic blood pressure <90 mm Hg); treatment with >1 ACEI (angiotensin-converting enzyme inhibitor), ARB (angiotensin receptor blocker), or ARNI (or 2 simultaneously) at randomization. Patients were randomized in a 1:1 fashion to finerenone titrated to either 20 mg or 40 mg (depending on baseline eGFR) vs matching placebo.

KIDNEY OUTCOMES. A key prespecified secondary outcome was a kidney composite of either: a sustained ≥50% decline in eGFR from baseline, sustained decline in eGFR to <15 mL/min/1.73 m^2, or the initiation of long-term dialysis or kidney transplantation (the latter 2 adjudicated by a blinded clinical endpoints committee). In the present

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analyses, a prespecified kidney composite was also considered, consisting of either: a sustained ≥57% decline in eGFR from baseline, sustained decline in eGFR to <15 mL/min/1.73 m^2, or the initiation of long-term dialysis or kidney transplantation. To qualify as sustained, a repeat central laboratory confirmation was required at least 4 weeks after the initial measurement; if no confirmatory sample was available, events were only counted if the patient had subsequently died or kidney replacement therapy was initiated.

Other prespecified kidney outcomes in the present analyses include: the change in eGFR from baseline; the mean rate of change in eGFR (total slope and its subcomponents, acute [baseline to 3 months] and chronic [3 months to end of study] slope); and the change in urine albumin:creatinine ratio (UACR) from baseline. The development of new-onset microalbuminuria (UACR ≥30 mg/g) and macroalbuminuria (UACR ≥300 mg/g) were prespecified outcomes among those with baseline UACR <30 mg/g and <300 mg/g, respectively.

SAFETY OUTCOMES. Safety analyses were performed among those who took at least 1 dose of the study drug and considered events that occurred during treatment or up to 3 days after permanent drug discontinuation. Effects of finerenone vs placebo were examined on the incidence of at least 1 adverse event, at least 1 serious adverse event, hyperkalemia, elevations in serum creatinine, and systolic blood pressure <100 mm Hg, according to categories of the baseline eGFR ≥60, 45-<60, and <45 mL/min/1.73 m^2.

STATISTICAL ANALYSIS. Summary data were reported as mean ± SD when normally distributed, median (Q1-Q3) when non-normally distributed, and as frequencies and percentages for categorical data. The Student's *t*-test, Wilcoxon rank sum, or chi-square tests were used to assess for differences between baseline variables by eGFR category (≥60, 45 to <60, <45 mL/min/1.73 m^2), according to data distribution. Incidence rates and 95% CIs were calculated per 100 patient-years of follow-up.

Cox proportional hazards models, stratified by geographic region and LVEF (<60 or ≥60%), were fit to assess the effect of finerenone vs placebo on the kidney composite outcomes. Changes in eGFR (continuous) and UACR (using geometric means) over time were assessed with repeated measures mixed effect models, using available data from randomization, 1, 3, 6, 12, 16, 20, 24, 28, 32, and 36 months. Models were adjusted for treatment assignment, trial visit, geographic region, LVEF (<60 or ≥60%), interaction between treatment assignment, and visit. Intercepts and slopes over time were allowed to vary randomly between patients via the inclusion of patient and time as random effects. A single-slope model was used to estimate the overall slope from Month 0 to Month 36, whereas a 2-slope model with a specified change-point at Month 3 was used to estimate the acute slope (Month 0 to Month 3) and the chronic slope (Month 3 to Month 36). New-onset microalbuminuria and macroalbuminuria were assessed using Cox proportional hazards models stratified for the same factors as already listed and restricted to those with UACR <30 mg/g and <300 mg/g at baseline, respectively.

For the main kidney composite outcome, interaction terms were included in separate models to test if the treatment effect differed according to baseline CKD categories, history of diabetes, or category of baseline albuminuria (<300 mg/g vs ≥300 mg/g).

In the prespecified hierarchical testing plan, the kidney composite outcome was the fourth of the secondary outcomes to be tested (after total worsening HF events, change in KCCQ [Kansas City Cardiomyopathy Questionnaire] total symptom score, and improvement in NYHA functional class). Because the difference in NYHA functional class was nonsignificant, the subsequent testing of the main kidney composite was deemed exploratory.[13] All present analyses were performed at an alpha level of 0.05, without correction for multiple hypothesis testing, using Stata MP version 18.0 (Stata Corp).

RESULTS

PATIENTS. At baseline, among 6,001 participants the mean eGFR was 62 ± 20 mL/min/1.73 m^2, with 3,113 (52%) having an eGFR ≥60 mL/min/1.73 m^2; 1,556 (26%) having an eGFR 45-<60 mL/min/1.73 m^2, and 1,332 (22%) having an eGFR <45 mL/min/1.73 m^2. Baseline characteristics were well balanced according to randomized treatment assignments within these eGFR categories (Table 1).

KIDNEY COMPOSITE OUTCOME. The overall frequency of the kidney composite outcome (sustained ≥50% decline in eGFR, sustained eGFR decline <15 mL/min/1.73 m^2, or kidney failure) was low, occurring in 55 (1.8%) of 2,998 patients assigned to placebo and 75 (2.5%) of 3,003 patients assigned to finerenone (HR: 1.33; 95% CI: 0.94-1.89) (Table 2). Of the composite components, the majority of events were related to the ≥50% decline in eGFR from baseline (52 and 73 events in those randomized to

TABLE 1 Characteristics According to Category of CKD and Randomized Treatment Assignment

	eGFR ≥60 mL/min/1.73 m²		eGFR 45 to <60 mL/min/1.73 m²		eGFR <45 mL/min/1.73 m²	
	Placebo (n = 1,561)	Finerenone (n = 1,552)	Placebo (n = 754)	Finerenone (n = 802)	Placebo (n = 683)	Finerenone (n = 649)
Age, y	68 ± 10	69 ± 10	75 ± 8	74 ± 8	77 ± 8	77 ± 8
Female	643 (41.2)	637 (41.0)	375 (49.7)	400 (49.9)	359 (52.6)	318 (49.0)
Race						
Asian	255 (16.3)	252 (16.2)	118 (15.6)	122 (15.2)	126 (18.4)	123 (19.0)
Black	22 (1.4)	28 (1.8)	9 (1.2)	15 (1.9)	8 (1.2)	6 (0.9)
Other	39 (2.5)	47 (3.0)	27 (3.6)	22 (2.7)	25 (3.7)	22 (3.4)
White	1245 (79.8)	1225 (78.9)	600 (79.6)	643 (80.2)	524 (76.7)	498 (76.7)
Geographic region						
Asia	249 (16.0)	250 (16.1)	117 (15.5)	121 (15.1)	124 (18.2)	122 (18.8)
Eastern Europe	794 (50.9)	762 (49.1)	324 (43.0)	346 (43.1)	203 (29.7)	221 (34.1)
Latin America	175 (11.2)	179 (11.5)	67 (8.9)	77 (9.6)	77 (11.3)	66 (10.2)
North America	94 (6.0)	96 (6.2)	76 (10.1)	80 (10.0)	66 (9.7)	59 (9.1)
Western Europe, Oceania, and others	249 (16.0)	265 (17.1)	170 (22.5)	178 (22.2)	213 (31.2)	181 (27.9)
Any prior hospitalization for HF	913 (58.5)	905 (58.3)	453 (60.1)	474 (59.1)	456 (66.8)	418 (64.4)
Systolic blood pressure, mm Hg	130 ± 15	130 ± 15	130 ± 16	129 ± 15	128 ± 16	130 ± 16
BMI, kg/m²	30.2 ± 6.1	29.7 ± 6.0	30.2 ± 6.3	30.4 ± 6.3	29.4 ± 6.0	29.7 ± 6.1
Serum creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.6 ± 0.5	1.6 ± 0.3
eGFR, mL/min/1.73 m²	78 ± 12	77 ± 12	53 ± 4	53 ± 4	36 ± 6	36 ± 6
UACR, mg/g	14 (6-45)	14 (5-45)	20 (7-77)	19 (8-75)	31 (11-148)	36 (11-176)
Serum potassium, mmol/L	4.3 ± 0.5	4.4 ± 0.4	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5
LVEF	52 ± 8	52 ± 8	53 ± 8	53 ± 8	53 ± 8	54 ± 8
NT-proBNP, pg/mL	766 (338-1,486)	844 (372-1,529)	1,219 (535-2,339)	1,152 (536-2,030)	1,581 (790-3,025)	1,638 (784-2,946)
History of hypertension	1,370 (87.8)	1,319 (85.0)	687 (91.1)	731 (91.1)	628 (91.9)	590 (90.9)
History of diabetes	583 (37.3)	556 (35.8)	301 (39.9)	338 (42.1)	338 (49.5)	323 (49.8)
History of stroke	161 (10.3)	154 (9.9)	88 (11.7)	105 (13.1)	104 (15.2)	96 (14.8)
History of myocardial infarction	411 (26.3)	446 (28.7)	187 (24.8)	188 (23.4)	159 (23.3)	150 (23.1)
Beta-blocker	1,342 (86.0)	1,316 (84.8)	643 (85.3)	688 (85.8)	569 (83.3)	537 (82.7)
Angiotensin-converting enzyme inhibitor	616 (39.5)	613 (39.5)	257 (34.1)	275 (34.3)	199 (29.1)	195 (30.0)
Angiotensin-receptor blocker	521 (33.4)	503 (32.4)	287 (38.1)	316 (39.4)	247 (36.2)	228 (35.1)
ARNI	154 (9.9)	141 (9.1)	56 (7.4)	60 (7.5)	47 (6.9)	55 (8.5)
SGLT2 inhibitor	188 (12.0)	180 (11.6)	103 (13.7)	116 (14.5)	133 (19.5)	97 (14.9)
Loop diuretic	1,329 (85.1)	1,329 (85.6)	662 (87.8)	685 (85.4)	630 (92.2)	604 (93.1)
Thiazide diuretic	225 (14.4)	231 (14.9)	110 (14.6)	130 (16.2)	67 (9.8)	68 (10.5)

Values are mean ± SD, n (%), or median (Q1-Q3). Percentages may not total 100 because of rounding. BMI is the weight in kilograms divided by the square of the height in meters. Significant differences were noted for BMI and baseline eGFR in eGFR category >60 mL/min/1.73 m²; systolic BP and baseline SGLT2 inhibitor use in eGFR category <45 mL/min/1.73 m². Race was determined by the patient.

ARNI = angiotensin receptor-neprilysin inhibitors; BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter 2; UACR = urine albumin:creatinine ratio.

placebo and finerenone, respectively). Only 6 patients in the placebo group and 7 patients in the finerenone group developed kidney failure requiring dialysis.

Treatment effects on the kidney composite outcome did not significantly differ according to categories of baseline eGFR ($P = 0.18$) (Supplemental Table 1), or by categories of baseline UACR (<300 mg/g vs ≥300 mg/g) or history of diabetes (0.58 and 0.31, respectively) (Supplemental Table 2).

The overall frequency of the kidney composite outcome (sustained ≥57% decline in eGFR, sustained eGFR decline <15 mL/min/1.73 m², or kidney failure) was low, occurring in 31 (1.0%) of 2,998 patients assigned to placebo and 41 (1.4%) of 3,003 patients assigned to finerenone (HR: 1.28; 95% CI: 0.80-2.05) (Table 2).

eGFR CHANGES OVER TIME. An initial acute decline in eGFR was observed in those assigned to finerenone between baseline and Month 3 (−3.0 mL/min/1.73 m²; 95% CI: −3.4 to −2.7 mL/min/1.73 m²), compared with those assigned to placebo (−0.1 mL/min/1.73 m²; 95% CI: −0.5 to 0.2 mL/min/1.73 m²), with a mean difference of −2.9 mL/min/1.73 m² (95% CI: −3.4 to −2.4 mL/min/1.73 m²). Between Month 3 through

the end of the trial, the mean change in eGFR was −0.9 mL/min/1.73 m^2 per year (95% CI: −1.1 to −0.7 mL/min/1.73 m^2 per year) for those assigned to finerenone, compared with −1.1 mL/min/1.73 m^2 per year (95% CI: −1.3 to −0.9 mL/min/1.73 m^2 per year) for those assigned to placebo, with a mean difference of 0.2 mL/min/1.73 m^2 per year (95% CI: −0.1 to 0.4 mL/min/1.73 m^2 per year). The mean difference for total slope was −0.7 mL/min/1.73 m^2 (95% CI: −0.9 to −0.4 mL/min/1.73 m^2). Changes in mean eGFR over time are displayed graphically in Figure 1.

UACR CHANGES OVER TIME AND THE DEVELOPMENT OF MICROALBUMINURIA AND MACROALBUMINURIA. Overall, 5,797 participants had baseline UACR data, of which 3,511 (61%) had UACR <30 mg/g; 1,712 (30%) had UACR 30-<300 mg/g; and 574 (10%) had UACR ≥300 mg/g. The median baseline UACR was 18 mg/g (7-67 mg/g). Finerenone led to an early reduction in UACR, which was 30% (95% CI: 25%-34%) lower at 6 months compared with placebo, and remained reduced throughout the remainder of the follow-up period (Figure 2).

Among those with baseline UACR <300 mg/g, macroalbuminuria (UACR ≥300 mg/g) developed in 386 (15%) of 2,614 patients assigned to placebo and 250 (10%) of 2,609 assigned to finerenone (HR: 0.62; 95% CI: 0.53-0.73) (Figure 3). This treatment effect was consistent according to baseline eGFR (*P* interaction = 0.51 and 0.28 for continuous [linear] eGFR and categories of eGFR, respectively) (Supplemental Table 1).

Among those with baseline UACR <30 mg/g, microalbuminuria or macroalbuminuria (UACR ≥30 mg/g or UACR ≥300 mg/g) developed in 884 (51%) of 1,746 patients assigned to placebo and 742 (42%) of 1,765 assigned to finerenone (HR: 0.76; 95% CI: 0.68-0.83) (Figure 3). The treatment effect appeared to be consistent according to baseline eGFR (*P* = 0.09 and 0.08 for continuous [linear] eGFR and categories of eGFR, respectively) (Supplemental Table 1).

SAFETY OUTCOMES. Serious adverse events, elevations in serum creatinine ≥3.0 mg/dL, and adverse events related to hyperkalemia were more frequent among patients in lower (vs eGFR ≥60 mL/min/1.73 m^2) categories of baseline eGFR (Table 3).

Among all categories of baseline eGFR, the frequency of serious adverse events was broadly similar between randomized treatment groups. Among all categories of baseline eGFR, the frequency of hyperkalemia was higher in those assigned to finerenone than those assigned to placebo, but few events led to hospitalization: 5 (0.3%) vs 1 (0.1%) among those with eGFR ≥60 mL/min/1.73 m^2; 3 (0.4%) vs 2 (0.3%) among those with eGFR 45-<60 mL/min/1.73 m^2; and 8 (1.2%) vs 3 (0.4%) among those with eGFR <45 mL/min/1.73 m^2 (Table 3). There were no deaths related to hyperkalemia in either arm. Any systolic blood pressure <100 mm Hg was more common in finerenone compared with placebo across all categories of baseline eGFR (Table 3).

TABLE 2 Treatment Effect on Kidney Outcomes

Outcome	Placebo	Finerenone
Composite kidney outcome (including ≥50% eGFR decline)		
No. of events/no. of patients (%)	55/2,998 (1.8)	75/3,003 (2.5)
Rate/100 PY (95% CI)	0.9 (0.7-1.1)	1.2 (0.9-1.5)
HR (95% CI)	1.33 (0.94-1.89)	
≥50% eGFR decline		
No. of events/no. of patients (%)	52/2,998 (1.7)	73/3,003 (2.4)
eGFR decline <15 mL/min/1.73 m^2		
No. of events/no. of patients (%)	12/2,998 (0.4)	25/3,003 (0.8)
Dialysis initiation		
No. of events/no. of patients (%)	6/2,998 (0.2)	7/3,003 (0.2)
Composite kidney outcome (including ≥57% eGFR decline)		
No. of events/no. of patients (%)	31/2,998 (1.0)	41/3,003 (1.4)
Rate/100 PY (95% CI)	0.5 (0.3-0.7)	0.6 (0.5-0.9)
HR (95% CI)	1.28 (0.80-2.05)	

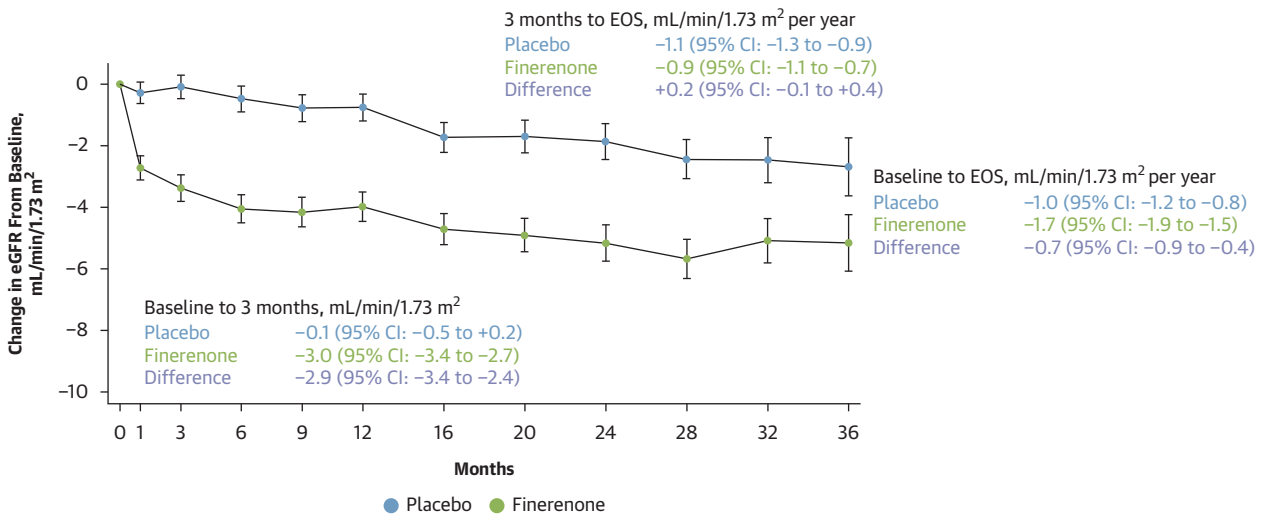
Composite kidney outcome includes: sustained ≥50% or ≥57% eGFR decline from baseline, sustained eGFR decline <15 mL/min/1.73 m^2; kidney failure.
PY = patient years; other abbreviations as in Table 1.

DISCUSSION

Among patients with HFmrEF/HFpEF in the FINEARTS-HF trial, who were at relatively low risk of adverse clinical kidney outcomes, the frequency of kidney composite events was numerically higher, but not statistically significantly different, for finerenone vs placebo. Finerenone caused an initial decline in eGFR (and total slope), but did not alter the longer-term "chronic" eGFR slope, compared with placebo. The frequency of hyperkalemia and elevation in serum creatinine was higher for patients treated with finerenone, but rarely led to discontinuation of treatment. Finerenone reduced albuminuria and the development of new-onset microalbuminuria and macroalbuminuria.

Albuminuria is a potent predictor of adverse outcomes across a broad spectrum of patients, including those with HFmrEF/HFpEF,[3,4] although in post hoc analyses of trials with patients with CKD and T2DM (which included patients with UACR >30 mg/g), reductions in UACR were estimated to mediate 84% and 37% of the treatment effect of finerenone vs placebo

FIGURE 1 Change in eGFR During 36 Months

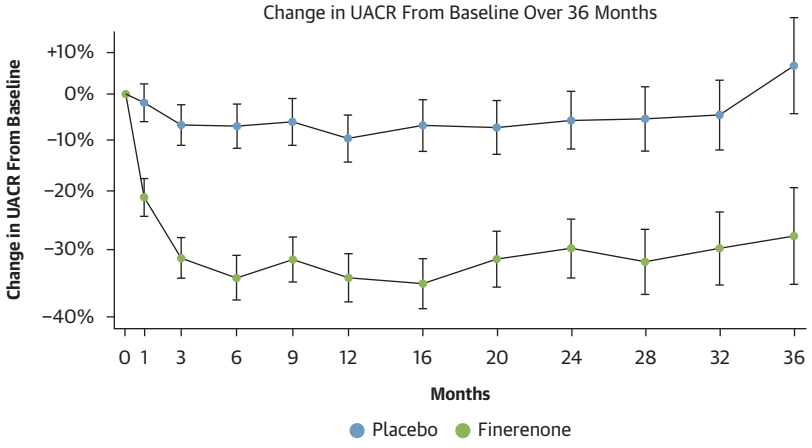


Means for the eGFR during a period of 36 months. The I bars indicate 95% CIs. eGFR = estimated glomerular filtration rate; EOS = end of study.

on the kidney and cardiovascular outcomes, respectively.[15] In the present analyses, finerenone caused an early reduction in albuminuria that persisted throughout the duration of follow-up. The proportional magnitude of UACR lowering was similar to that observed in the trials of patients with CKD and T2DM, and is thought to be related to lowering of intraglomerular pressure.[12,16]

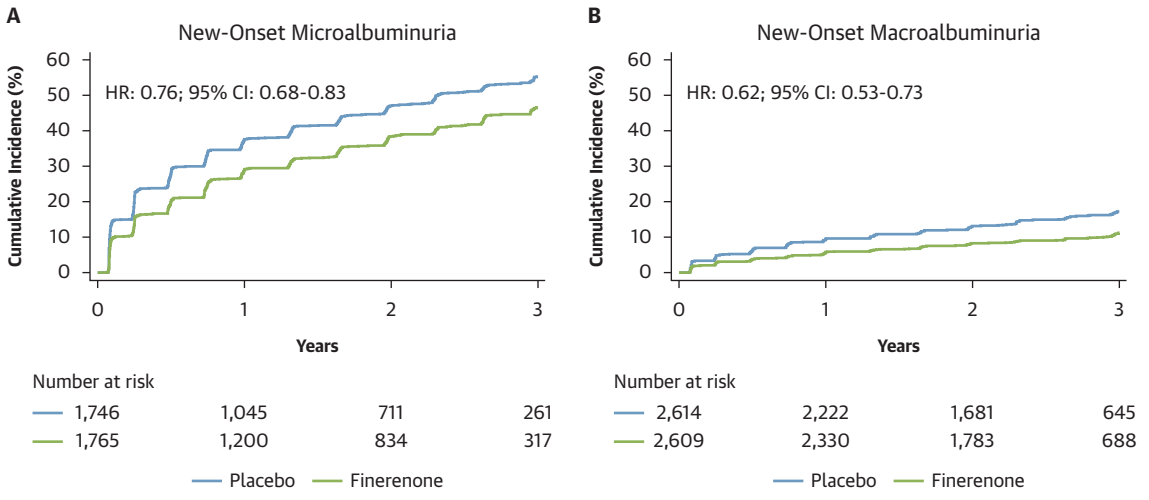
In 2 large placebo-controlled trials (FIGARO-DKD [Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease] or FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease]), finerenone lowered the risk of adverse kidney composite outcomes (sustained ≥40% or ≥57% eGFR decline, kidney failure, or death from kidney causes)

FIGURE 2 Change in UACR During 36 Months



Means for the percentage decline in the UACR during a period of 36 months. The I bars indicate 95% CIs. UACR = urine albumin:creatinine ratio; other abbreviations as in Figure 1.

FIGURE 3 Effect of Finerenone vs Placebo on New-Onset Microalbuminuria and Macroalbuminuria



Effect of finerenone vs placebo on new-onset microalbuminuria (A) and macroalbuminuria (B). Kaplan-Meier estimates for the development of new-onset microalbuminuria (UACR ≥30 mg/g) among those with baseline UACR <30 mg/g macroalbuminuria (UACR ≥300 mg/g) among those with baseline UACR <300 mg/g. Abbreviations as in Figure 2.

among patients with CKD, T2DM, and albuminuria.[11,12] Based on these results, finerenone has received indications to reduce the risk of sustained decline in eGFR and end-stage kidney disease in adult patients with CKD associated with T2DM. However, similar to post hoc analyses of steroidal MRAs among patients with HFrEF or HFpEF,[10,17,18] in the present analyses, finerenone did not alter the occurrence of the kidney composite outcomes, nor the longer-term "chronic" (from 3 months) slope in eGFR.

There are several potential reasons for the lack of observed benefits on eGFR-based outcomes.[19] First, patients enrolled in FINEARTS-HF were at lower overall risk of adverse kidney outcomes, compared with those enrolled in FIGARO-DKD or FIDELIO-DKD. For example, higher degrees of albuminuria and the presence of T2DM are known risk factors for CKD progression.[20] Patients in FINEARTS-HF had a median baseline UACR concentration of 18 mg/g, compared with 852 mg/g in FIDELIO-DKD and

TABLE 3 Safety Outcomes According to Category of CKD and Randomized Treatment Assignment

	eGFR ≥60 mL/min/1.73 m²		eGFR 45 to <60 mL/min/1.73 m²		eGFR <45 mL/min/1.73 m²		All Patients	
	Placebo (n = 1,557)	Finerenone (n = 1,547)	Placebo (n = 754)	Finerenone (n = 800)	Placebo (n = 682)	Finerenone (n = 646)	Placebo (n = 2,993)	Finerenone (n = 2,993)
Any serious adverse event	552 (35.5)	498 (32.2)	344 (45.6)	341 (42.6)	317 (46.5)	318 (49.2)	1213 (40.5)	1157 (38.7)
Serum creatinine ≥3.0 mg/dL	2 (0.1)	11 (0.7)	5 (0.7)	5 (0.6)	27 (4.2)	41 (6.7)	34 (1.2)	57 (2.0)
Acute kidney injury	18 (1.2)	31 (2.0)	21 (2.8)	26 (3.2)	25 (3.7)	54 (8.4)	64 (2.1)	111 (3.7)
Acute kidney injury that led to hospitalization	7 (0.4)	8 (0.5)	7 (0.9)	9 (1.1)	11 (1.6)	31 (4.8)	25 (0.8)	48 (1.6)
Investigator-reported hyperkalemia	29 (1.9)	97 (6.3)	45 (6.0)	79 (9.9)	51 (7.5)	113 (17.5)	125 (4.2)	289 (9.7)
Serum potassium >5.5 mmol/L	86 (5.7)	175 (11.6)	55 (7.6)	118 (15.1)	58 (8.9)	120 (19.7)	199 (6.9)	413 (14.3)
Serum potassium >6.0 mmol/L	16 (1.1)	36 (2.4)	12 (1.7)	27 (3.5)	13 (2.0)	23 (3.8)	41 (1.4)	86 (3.0)
Serum potassium >7.0 mmol/L	5 (0.3)	8 (0.5)	1 (0.1)	6 (0.8)	0 (0.0)	2 (0.3)	6 (0.2)	16 (0.6)
Hyperkalemia that led to hospitalization	1 (0.1)	5 (0.3)	2 (0.3)	3 (0.4)	3 (0.4)	8 (1.2)	6 (0.2)	16 (0.5)
Systolic blood pressure <100 mm Hg	164 (10.8)	270 (17.9)	94 (12.9)	150 (19.2)	103 (15.7)	118 (19.1)	361 (12.4)	538 (18.5)

Values are n (%). Reported events are those that occurred in patients who had received at least 1 dose of finerenone or placebo and occurred during treatment or up to 3 days after permanent discontinuation of finerenone or placebo (n = 5,986). Data reported on creatinine, potassium, and systolic blood pressure were further restricted to patients with at least 1 assessment (5,785, 5,787, and 5,815 patients, respectively).

308 mg/g in FIGARO-DKD.[11,12] Further, T2DM was not an inclusion criterion in FINEARTS-HF and was present in only 41% of patients at baseline. For further context, the differences in risk profiles are evident from the differences in the overall frequency of a harmonized kidney composite outcome (133 in FINEARTS-HF, 380 in FIGARO-DKD, and 729 in FIDELIO-DKD).[21]

Second, the initiation of finerenone is known to cause an initial decline in eGFR that is sustained throughout the duration of treatment.[11,12] In the absence of an off-drug measurement of eGFR, an excessive initial eGFR decline in select patients could contribute to a higher likelihood of meeting the threshold of a sustained decline in eGFR of ≥50% from baseline. In an attempt to mitigate the influence of excessive initial eGFR declines, higher thresholds have been incorporated in prior trials (eg, sustained ≥57% eGFR decline), meaning that greater decrements in kidney function are needed to reach the outcome definition. Interestingly, more potent risk reductions in the kidney outcomes for finerenone vs placebo were noted in the aforementioned trials (FIDELIO-DKD and FIGARO-DKD) with this more restrictive definition.[11,12,21]

Third, the duration of follow-up in HF trials may be shorter than that of CKD progression trials, where kidney outcomes tend to accumulate much later.[22] Combined with a lower overall rate of CKD progression (the observed eGFR decline in the placebo arm of FINEARTS-HF was only 1.1 mL/min/1.73 m^2 per year, similar to that expected with aging alone), a shorter duration of follow-up provides less opportunity to "overcome" the initial decline in eGFR observed with finerenone. For context, the rate of decline in the placebo arm in FINEARTS-HF was even lower than that of other contemporary trials among patients with HFmrEF/HFpEF (1.5 mL/min/1.73 m^2 per year in DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) and 2.6 mL/min/1.73 m^2 per year in EMPEROR [Empagliflozin Outcome Trial in Patients With Chronic Heart Failure]-Preserved),[9,23] perhaps reflecting greater use of background nephroprotective therapy in more contemporary populations. The tendency for kidney outcomes to occur later in the disease course, particularly in this HFmrEF/HFpEF cohort, also predisposes to the issue of competing risks, where fatal events that occur earlier in the disease course preclude the future development of adverse kidney outcomes.

Finerenone resulted in a higher frequency of hyperkalemia than placebo, although the overall number of severe events (eg, leading to hospitalization) was low and there were no deaths related to hyperkalemia observed in follow-up. Not surprisingly, the frequency of hyperkalemic events was higher among those with lower baseline eGFR (among both treatment arms). Although a prior phase 2 trial suggested a potentially lower risk of hyperkalemia and worsening renal function for finerenone vs spironolactone, FINEARTS-HF was a placebo-controlled trial, precluding a direct comparison of finerenone with other MRAs.[24] Overall, the present results highlight the need for regular monitoring of such patients on initiation of therapies that can increase serum potassium concentration.

STUDY STRENGTHS AND LIMITATIONS. The strengths of our analyses include the examination of prespecified kidney outcomes that required confirmatory measurements of eGFR, all collected in the setting of a large, robust, placebo-controlled randomized trial. The main limitations of our analyses include the low/modest number of kidney composite outcomes, the relatively short follow-up, the inability to assess off-drug eGFR measurements, and the fact that the included patients were at relatively low risk of developing longer-term adverse kidney outcomes. Certain subgroup analyses of interest, eg, baseline use of SGLT2 inhibitors, were precluded due to small numbers of patients.

CONCLUSIONS

In this prespecified analysis to examine kidney outcomes among patients with HFmrEF/HFpEF, finerenone did not alter eGFR-based kidney outcomes compared with placebo, but did lower albuminuria and reduce the risk of new-onset microalbuminuria and macroalbuminuria. Given the benefits of finerenone to lower the risk of the primary outcome of cardiovascular death and total HF events,[13] these data provide ancillary information for patients and clinicians on the expected kidney-specific effects of finerenone among patients with HFmrEF/HFpEF.

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FINEARTS-HF was sponsored by Bayer. FINEARTS-HF was designed by the academic members of the executive committee in

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Dr Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Bristol Myers Squibb, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Claggett has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket; and has served on a data safety monitoring board for Novo Nordisk. 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Dr Pitt has served as a consultant for Bayer, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lexicon, Anacardia, and G3 Pharmaceuticals; has served as a consultant and received stock options or stocks from Sea Star Medical, Vifor, scPharmaceuticals, SQinnovations, KBP Biosciences, Sarfez, Cereno Scientific, Prointel, and Brainstorm Medical; holds a U.S. Patent (9931412-site specific delivery of Eplerenone to the myocardium); and has a U.S. Patent pending (63/045,783 HistoneModulating agents for the prevention and treatment of organ damage). 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Chemicals & Pharmaceuticals Ltd, Lupin Pharmaceuticals, Medscape/Heart.Org., ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, Translational Medicine Academy; has served on the Data Safety Monitoring Board fromWIRB-Copernicus Group Clinical Inc; and is a director of Global Clinical Trial Partners Ltd. 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APPENDIX For supplemental tables, please see the online version of this paper.