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Effects of the Nonsteroidal MRA Finerenone With and Without Concomitant SGLT2 Inhibitor Use in Heart Failure

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BACKGROUND: Patients with heart failure (HF) with mildly reduced or preserved ejection fraction face heightened long-term risks of morbidity and mortality. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and the nonsteroidal mineralocorticoid receptor antagonist finerenone have both been shown to reduce the risk of cardiovascular events in this population, but the effects of their combined use are not known.

METHODS: FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) was a randomized, double-blind, placebo-controlled trial of finerenone in patients with HF and left ventricular ejection fraction ≥40%. Baseline SGLT2i use was a prespecified subgroup. The primary outcome was a composite of total (first and recurrent) worsening HF events and cardiovascular death. We first assessed for evidence of treatment heterogeneity on the basis of baseline SGLT2i use. We further examined SGLT2i uptake during the trial and evaluated the treatment effects of finerenone accounting for baseline and during-trial use of SGLT2i in time-varying analyses.

RESULTS: Among 6001 participants, 817 (13.6%) were treated with an SGLT2i at baseline. During 2.6 years median follow-up, treatment with finerenone similarly reduced the risk of the primary outcome in participants treated with an SGLT2i (rate ratio, 0.83 [95% CI, 0.60–1.16]) and without an SGLT2i at baseline (rate ratio, 0.85 [95% CI, 0.74–0.98]; $P_{interaction}$=0.76). In follow-up, 980 participants initiated SGLT2i, which was less frequent in the finerenone arm compared with placebo (17.7% versus 20.1%; hazard ratio, 0.86 [95% CI, 0.76–0.97]). Time-updated analyses accounting for baseline and subsequent use of SGLT2i did not meaningfully alter the treatment effects of finerenone on the primary end point.

CONCLUSIONS: The treatment benefits of the nonsteroidal mineralocorticoid receptor antagonist finerenone were observed irrespective of concomitant use of an SGLT2i. These data suggest that the combined use of SGLT2i and a nonsteroidal mineralocorticoid receptor antagonist may provide additive protection against cardiovascular events in patients with HF with mildly reduced or preserved ejection fraction.

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Key Words: aldosterone ■ heart failure ■ mineralocorticoid receptor antagonists ■ sodium-glucose transporter 2 inhibitors ■ therapeutics

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Clinical Perspective

What Is New?

- The efficacy of the nonsteroidal mineralocorticoid receptor antagonist finerenone in reducing cardiovascular death and worsening heart failure events and improving symptom burden was consistent irrespective of concomitant use of a sodium-glucose cotransporter-2 inhibitor in patients with heart failure with mildly reduced or preserved ejection fraction.
- There were no new untoward signals of safety when these therapies were used together.

What Are the Clinical Implications?

- These data suggest that the combined use of a sodium-glucose cotransporter-2 inhibitor and a nonsteroidal mineralocorticoid receptor antagonist may provide additional protection against cardiovascular events and have complementary roles in patients with heart failure with mildly reduced or preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

eGFR	estimated glomerular filtration rate
FINEARTS-HF	Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro–B-type natriuretic peptide
RR	rate ratio
SGLT2i	sodium-glucose cotransporter-2 inhibitor

Patients with heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF) experience high lifetime risks of premature death, excess hospitalizations, and adverse health status.[1] This population has historically had few evidence-based therapeutic options to modify their disease trajectory. The sodium-glucose cotransporter-2 inhibitors (SGLT2i) were shown recently to reduce cardiovascular death and HF-related hospitalizations in a broad range of patients with HFmrEF or HFpEF,[2] and are now strongly recommended for use in clinical practice guidelines.[3–5] More recently, FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) demonstrated that the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risks of cardiovascular death and total worsening HF events in this target population.[6]

SGLT2i and the nonsteroidal MRA might now be considered together as evidence-based therapies in patients with HFmrEF or HFpEF. Whereas evidence from trials in chronic kidney disease and type 2 diabetes showed that benefits of finerenone on cardiorenal outcomes were observed irrespective of SGLT2i use,[7,8] data examining the clinical effects of this combination in HF are lacking. FINEARTS-HF enrolled the most patients with concomitant SGLT2i of any previous trial of an MRA across disease states. Furthermore, treatment guidelines and regulatory indications in the management of this population evolved during the conduct of FINEARTS-HF, such that many patients were newly treated with SGLT2i during the trial.

In this prespecified analysis of FINEARTS-HF, we first examined the efficacy and safety of finerenone in those treated and not treated with an SGLT2i at baseline. We further examined SGLT2i uptake during the trial and evaluated the treatment effects of finerenone accounting for both baseline and during-trial use of SGLT2i.

METHODS

Data Availability

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

FINEARTS-HF Study Design

The study design,[9] baseline characteristics,[10] and primary results[6] of FINEARTS-HF have been published previously. In brief, FINEARTS-HF was a randomized, double-blind, placebo-controlled trial of finerenone in adults ≥40 years of age with symptomatic HFmrEF or HFpEF conducted across 37 countries. Key inclusion criteria included left ventricular ejection fraction (LVEF) ≥40%, elevated natriuretic peptide levels (thresholds adjusted for atrial fibrillation status at screening and recency of worsening HF event), evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy), and recent diuretic use for at least the previous 30 days. Key exclusion criteria included estimated glomerular filtration rate (eGFR) <25 mL·min·1.73 m^2 or serum potassium >5.0 mmol/L. Patients were enrolled irrespective of clinical care setting (whether hospitalized, recently hospitalized, or

ambulatory). All participants provided explicit informed consent and the study protocol was approved at local institutional review boards or ethics committees at all participating sites.

Participants were randomized 1:1 to finerenone (versus matching placebo) with target dosing on the basis of baseline eGFR (20 mg if baseline eGFR was ≤60 mL·min·1.73 m² or 40 mg once daily if baseline eGFR was >60 mL·min·1.73 m²) in addition to usual therapy. Study investigators were encouraged to treat patients with other medications according to local recommendations, except for MRAs, which were prohibited during the trial.

Study End Points

The primary outcome was a composite of total (first and recurrent) worsening HF events and cardiovascular death. We also evaluated total worsening HF events, cardiovascular death, all-cause death, a renal composite end point (defined as sustained decrease in eGFR of ≥50% from baseline over at least 4 weeks, sustained eGFR decline <15 mL·min·1.73 m^2, or initiation of dialysis or renal transplantation), and change in symptom burden measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score, which were each secondary end points, and the occurrence of first worsening HF event or cardiovascular death and the conventional composite of first hospitalization for HF or cardiovascular death. All potential primary end points and deaths were specifically adjudicated by an independent clinical end points committee.

Concomitant SGLT2i Use

Any SGLT2i (regardless of type) at any dose taken at the time of randomization was considered to be "baseline" use. Combination therapies with other antihyperglycemic therapies inclusive of an SGLT2i were counted in this analysis. At each study visit, detailed case report forms captured all concomitant medications, including changes (initiations and discontinuations) from previous visits. In cases of missing specific date information, dates of initiation were imputed to the 14th of the month if month and year were recorded by the investigator. Only 17 patients had reported postbaseline SGLT2i use but had missing specific date information that could not be imputed. Among those who were not baseline SGLT2i users, first reported use after randomization was considered to be incident SGLT2i use during trial follow-up. Among those who were baseline SGLT2i users, SGLT2i discontinuation was additionally captured.

Statistical Analysis

First, we assessed primary and other key outcomes in those treated and those who were not treated with an SGLT2i at baseline. SGLT2i use was one of 17 prespecified subgroups. Recurrent events (primary end point and the secondary end point of total worsening HF events alone) were analyzed using the semiparametric proportional rates method of Lin et al,[11] as prespecified in the FINEARTS-HF statistical analysis plan. Time to first event (cardiovascular death, all-cause death, renal composite end point, composite cardiovascular death or worsening HF event, and composite cardiovascular death or HF hospitalization) was analyzed using Cox proportional hazards regression models. The proportional hazards assumption was verified for all time to first event models. All models for treatment effects on efficacy end points were stratified by geographic region and baseline LVEF (<60% and ≥60%). In each model, evidence of treatment effect heterogeneity was evaluated by including an interaction term by treatment randomization. The KCCQ total symptom score ranged from 0 (worst symptoms) to 100 (least symptoms). KCCQ was analyzed as a least square mean improvement from baseline to months 6, 9, and 12 using a generalized estimating equations model for repeated measurements with unstructured covariance matrix and adjusted for the aforementioned stratification factors as well as baseline KCCQ and interactions between study visit and baseline KCCQ. Early eGFR changes from baseline to 3 months with finerenone were assessed using a linear regression model including baseline eGFR, treatment arm, concomitant SGLT2i use, and the interaction between treatment randomization and SGLT2i use. All efficacy analyses were assessed using an intention-to-treat approach; all safety analyses were assessed in participants who received at least one dose of study drug.

Second, we assessed postbaseline changes in SGLT2i use, analyses that were prespecified in the FINEARTS-HF Academic Statistical Analysis Plan. New initiation (among baseline nonusers) and discontinuation (among baseline users) were assessed using Cox proportional hazards regression models. In time-updated analyses, we examined treatment effects of finerenone on subsequent risk of first primary efficacy outcomes accounting for baseline and during trial use of SGLT2i (treated as a time-varying covariate). All statistical analyses were performed using STATA version 18.

RESULTS

From September 2020 to January 2023, we screened 7463 participants and validly randomized 6001 participants to finerenone or placebo. The mean age was 72.0±9.6 years, 45.5% were women, and the majority were in New York Heart Association functional class II (69.1%). The mean LVEF was 52.6±7.8%, and the median NT-proBNP (N-terminal pro–B-type natriuretic peptide) level was 1041 pg/mL (25th–75th percentile, 448–1946).

Clinical Profiles and Risk by Baseline SGLT2i Use

Overall, 817 participants (13.6%) were treated with an SGLT2i at baseline; 8 different SGLT2i were reported in use, with dapagliflozin (n=406 [48.7%]), empagliflozin (n=394 [47.2%]), and canagliflozin (n=25 [3.0%]) being most frequent. Participants who were treated with an SGLT2i at baseline were more likely to be men, experience a recent worsening HF event, and have higher levels of natriuretic peptides. Among SGLT2i users, 75.4% had a history of diabetes and 55.0% had an eGFR <60 mL·min·1.73 m^2 (Table 1). Baseline clinical profiles and concomitant medications were well balanced between treatment arms when examined separately in those taking or not taking an SGLT2i at baseline (Table S1).

During 2.6 years median follow-up, participants with baseline SGLT2i use were at higher risk of the primary

Table 1. Baseline Characteristics by Concomitant SGLT2i Use

Characteristics	No SGLT2i use (n=5184)	SGLT2i use (n=817)
Age, y	72.1±9.5	71.4±10.5
Women	2412 (46.5)	320 (39.2)
Race and ethnicity		
Asian	803 (15.5)	193 (23.6)
Black	77 (1.5)	11 (1.3)
Other	138 (2.7)	44 (5.4)
White	4166 (80.4)	569 (69.6)
Region		
Asia	793 (15.3)	190 (23.3)
Eastern Europe	2464 (47.5)	186 (22.8)
Latin America	530 (10.2)	111 (13.6)
North America	388 (7.5)	83 (10.2)
Western Europe, Oceania, and others	1009 (19.5)	247 (30.2)
Any previous HF hospitalization	3036 (58.6)	583 (71.4)
Recency of HF event		
≤7 d from randomization	1031 (19.9)	188 (23.0)
>7 d to ≤3 mo	1657 (32.0)	371 (45.4)
>3 mo or no index HF event	2496 (48.1)	258 (31.6)
Systolic blood pressure, mm Hg	129.9±15.1	126.4±16.5
Body mass index, kg/m2	29.9±6.1	30.0±6.3
Serum creatinine, mg/dL	1.1±0.4	1.2±0.4
eGFR, mL·min·1.73 m2	62.5±19.5	59.6±20.8
eGFR <60 mL·min·1.73 m2	2439 (47.0)	449 (55.0)
UACR, mg/g	17 (6–59)	32 (11–129)
Potassium, mmol/L	4.4±0.5	4.4±0.5
LVEF, %	52.7±7.8	51.5±7.8
40% to <50%	1836 (35.5)	336 (41.2)
50% to <60%	2308 (44.6)	366 (44.9)
≥60%	1034 (20.0)	113 (13.9)
NT-proBNP, pg/mL	1014 (438–1907)	1180 (527–2263)
NYHA class		
II	3577 (69.0)	569 (69.6)
III	1573 (30.3)	240 (29.4)
IV	33 (0.6)	8 (1.0)
Hypertension	4593 (88.6)	732 (89.6)
Diabetes	1823 (35.2)	616 (75.4)
Atrial fibrillation on ECG	1983 (38.3)	310 (37.9)
Previous stroke	605 (11.7)	103 (12.6)
Previous myocardial infarction	1314 (25.3)	227 (27.8)
Beta-blocker	4405 (85.0)	690 (84.5)
ACEI	1926 (37.2)	229 (28.0)
ARB	1819 (35.1)	283 (34.6)
ARNI	350 (6.8)	163 (20.0)
Calcium channel blockers	1710 (33.0)	258 (31.6)
Loop diuretic	4490 (86.6)	749 (91.7)

Values are mean±SD, n (%), or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and UACR, urine albumin creatinine ratio.

end point of cardiovascular death and total HF events (24.2 versus 15.2 per 100 patient-years; rate ratio [RR], 1.57 [95% CI, 1.30–1.88]; $P<0.001$). Risks of all other key end points were higher in participants with baseline SGLT2i use, including death (Table 2).

Treatment Effects of Finerenone by Baseline SGLT2i Use

Treatment with finerenone similarly reduced the risk of the primary outcome in participants treated with an SGLT2i (RR, 0.83 [95% CI, 0.60–1.16]) and without an SGLT2i at baseline (RR, 0.85 [95% CI, 0.74–0.98]; $P_{interaction}=0.76$). Because of higher baseline risk, absolute rate reduction was higher in participants with baseline SGLT2i use (4.7 versus 2.5 total events per 100 patient-years; Figure 1). Treatment effects of finerenone versus placebo were consistent by baseline SGLT2i use across all key efficacy end points (Table 3). Treatment effects on symptom burden as assessed by the KCCQ total symptom score improved similarly in those treated with an SGLT2i (finerenone arm +7.6 points; placebo arm +5.6 points; between-arm difference +2.0 [−0.2 to +4.3] points) and without an SGLT2i at baseline (finerenone arm +8.0 points; placebo arm +6.5 points; between-arm difference +1.5 [+0.7 to +2.3] points; $P_{interaction}=0.66$).

Safety Outcomes of Finerenone by Baseline SGLT2i Use

In terms of safety, participants in both treatment arms experienced similar incidences of serious adverse events, irrespective of concomitant SGLT2i use. Incidences of any laboratory-based hyperkalemia were higher and laboratory-based hypokalemia were lower with finerenone compared with placebo, regardless of concomitant SGLT2i use. Incidences of hyperkalemia leading to hospitalization were relatively infrequent and there were no cases of hyperkalemia leading to death in either group (Table 4). At 1 month, finerenone increased potassium levels by +0.19 mmol/L (0.17–0.21) in those not treated with SGLT2i and +0.19 mmol/L (0.13–0.25) in those treated with an SGLT2i at baseline ($P_{interaction}=1.00$; Figure S1). The decline in eGFR from baseline to 3 months was greater with finerenone than placebo, irrespective of concomitant SGLT2i use ($P_{interaction}=0.21$).

SGLT2i Initiation and Discontinuation During the Trial

In follow-up, 980 participants (18.9%) initiated SGLT2i. In time-updated analyses, similar to the baseline analysis, SGLT2i use at any time was associated with higher risk of a subsequent first primary end point (hazard ratio [HR], 1.60 [95% CI, 1.42–1.81]; $P<0.001$). Among 5184 participants without baseline use, SGLT2i initiation during

Table 2. Key Outcomes by Concomitant SGLT2i Use

Outcomes	No SGLT2i use (reference; n=5184)	SGLT2i use (n=817)	RR or HR (95% CI) relative to no SGLT2i use	*P* value
Cardiovascular death and total worsening HF events	1956 (15.2/100 person-years)	410 (24.2/100 person-years)	RR 1.57 (1.30–1.88)	<0.001
Total worsening HF events	1533 (11.9/100 person-years)	333 (19.7/100 person-years)	RR 1.61 (1.31–1.97)	<0.001
Cardiovascular death	425 (8.2%; 3.3/100 person-years)	77 (9.4%; 4.6/100 person-years)	HR 1.40 (1.10–1.79)	0.007
All-cause death	876 (16.9%; 6.8/100 person-years)	137 (16.8%; 8.0/100 person-years)	HR 1.20 (1.00–1.43)	0.050
Renal composite outcome	112 (2.2%; 1.0/100 person-years)	18 (2.2%; 1.2/100 person-years)	HR 1.31 (0.80–2.17)	0.284
Cardiovascular death or first worsening HF event	1126 (21.7%; 9.6/100 person-years)	217 (26.6%; 14.5/100 person-years)	HR 1.45 (1.25–1.68)	<0.001
Cardiovascular death or first HF hospitalization	1054 (20.3%; 8.9/100 person-years)	209 (25.6%; 13.8/100 person-years)	HR 1.50 (1.29–1.74)	<0.001

HF indicates heart failure; HR, hazard ratio; RR, rate ratio; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

the trial was less common among those randomized to finerenone compared with placebo (17.7% versus 20.1%; HR, 0.86 [95% CI, 0.76–0.97]; *P*=0.02; Figure 2). Analyses treating SGLT2i as a time-varying covariate did not meaningfully alter the treatment effects of finerenone on a first primary end point (HR, 0.85 [95% CI, 0.76–0.95]; *P*=0.003). Among 817 participants reporting baseline use, SGLT2i discontinuation during the trial occurred in 198 individuals and was similar between finerenone and placebo arms (24.7% versus 23.8%; HR, 1.02 [95% CI, 0.77–1.35]; *P*=0.89; Figure 2).

DISCUSSION

This prespecified analysis of FINEARTS-HF demonstrates that the nonsteroidal MRA finerenone similarly benefits patients with HFmrEF or HFpEF, irrespective of background use of SGLT2i. The relative effects of finerenone in reducing the risk of cardiovascular death and total worsening HF events and improving symptom burden were similar regardless of baseline treatment with an SGLT2i. Because those treated with an SGLT2i faced higher risks of clinical outcomes, the absolute rate reductions observed with finerenone were nearly double in the SGLT2i-treated subgroup. During the course of FINEARTS-HF, almost 1000 participants were newly initiated on an SGLT2i, more frequently in the placebo arm. Accounting for baseline or during-trial use of an SGLT2i did not meaningfully alter estimates of treatment effects of finerenone. Taken together, these data suggest that the combined use of SGLT2i and nonsteroidal MRA may provide additive protection against cardiovascular events in patients with HF with mildly reduced or preserved ejection fraction.

SGLT2i and MRAs target nonoverlapping pharmacologic targets and theoretically influence distinct pathways

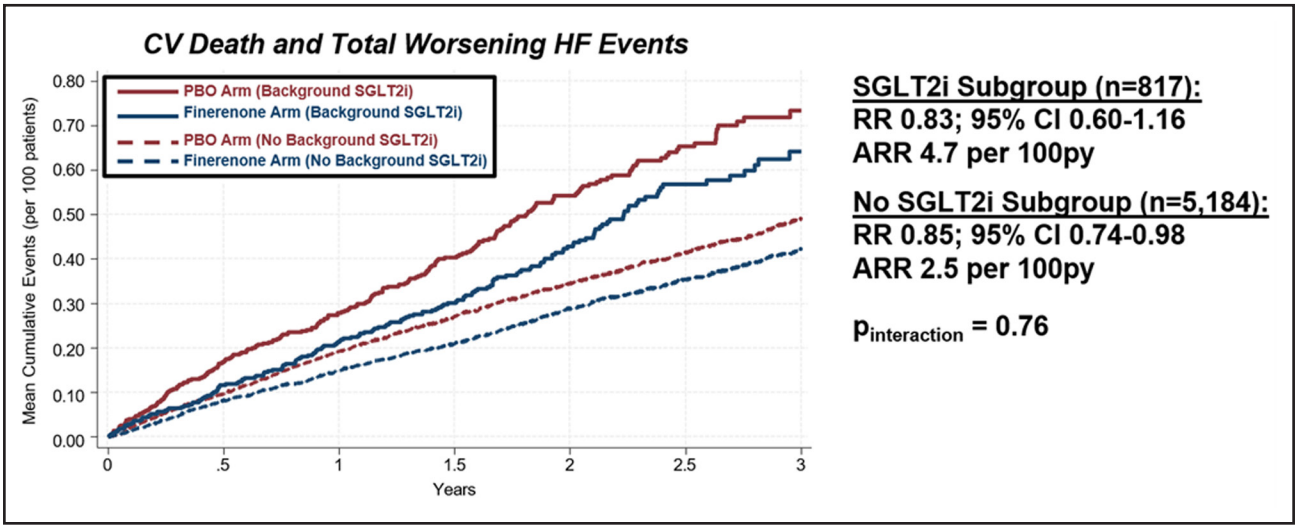

Figure 1. Treatment effects of finerenone on primary end point by concomitant sodium-glucose cotransporter-2 inhibitor use. Absolute rate reductions (ARRs) were calculated as the between-arm difference in event rates incorporating all events throughout the duration of the trial. CV indicates cardiovascular; HF, heart failure; RR, rate ratio; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Table 3. Treatment Effects of Finerenone by Concomitant SGLT2i Use

Events	No SGLT2i use		SGLT2i use		$P_{interaction}$
	Finerenone (n=2610)	Placebo (n=2574)	Finerenone (n=393)	Placebo (n=424)	
Cardiovascular death and total worsening HF events					
Events	907	1049	176	234	
Rate (per 100 patient-years)	14.0	16.5	21.8	26.5	
RR (95% CI)	0.85 (0.74–0.98)		0.83 (0.60–1.16)		0.76
Total worsening HF events					
Events	703	830	139	194	
Rate (per 100 patient-years)	10.9	13.0	17.2	22.0	
RR (95% CI)	0.83 (0.71–0.97)		0.80 (0.55–1.15)		0.68
Cardiovascular death					
Events (%)	205 (7.9)	220 (8.5)	37 (9.4)	40 (9.4)	
Rate (per 100 patient-years)	3.2	3.5	4.6	4.5	
HR (95% CI)	0.92 (0.76–1.11)		1.03 (0.65–1.62)		0.73
All-cause death					
Events (%)	428 (16.4)	448 (17.4)	63 (16.0)	74 (17.5)	
Rate (per 100 patient-years)	6.6	7.0	7.7	8.4	
HR (95% CI)	0.94 (0.82–1.07)		0.90 (0.64–1.27)		0.78
Renal composite end point					
Events (%)	67 (2.6)	45 (1.7)	8 (2.0)	10 (2.4)	
Rate (per 100 patient-years)	1.2	0.8	1.1	1.3	
HR (95% CI)	1.43 (0.98–2.08)		0.95 (0.37–2.45)		0.37
Cardiovascular death or first worsening HF event					
Events (%)	529 (20.3)	597 (23.2)	95 (24.2)	122 (28.8)	
Rate (per 100 patient-years)	8.9	10.4	13.1	15.7	
HR (95% CI)	0.85 (0.76–0.96)		0.85 (0.65–1.12)		0.76
Cardiovascular death or first HF hospitalization					
Events (%)	505 (19.3)	549 (21.3)	94 (23.9)	115 (27.1)	
Rate (per 100 patient-years)	8.4	9.4	12.9	14.6	
HR (95% CI)	0.89 (0.79–1.01)		0.90 (0.68–1.19)		0.86

HF indicates heart failure; HR, hazard ratio; RR, rate ratio; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

(metabolic, hemodynamic, and inflammatory) of disease progression. Small mechanistic studies have suggested their combined use result in favorable additive improvements in surrogate cardio-kidney markers of disease status.[12] Furthermore, clinical trials of finerenone in chronic kidney disease with type 2 diabetes did not identify heterogeneity in treatment response by background SGLT2i therapy, but few patients in these trials had comorbid HF.[7,8] Conversely, trials of SGLT2i in patients with HF with mildly reduced or preserved ejection fraction have not shown heterogeneity based on background use of an MRA.[13–16] This analysis from FINEARTS-HF provides further support that the clinical benefits of finerenone are not modified by background use of an SGLT2i. Whereas FINEARTS-HF enrolled patients with the highest background use of SGLT2i of any contemporary trial of this population, SGLT2i use at baseline was modest; these therapies were not part of global standard of care in this population at the start of trial. To improve the precision of our study, we carried out a separate supportive analysis accounting for SGLT2i use during the course of the trial. These analyses did not meaningfully change our primary findings supporting consistency in treatment effects of finerenone irrespective of concomitant use of an SGLT2i.

Patients treated with an SGLT2i were at higher risk for a broad range of clinical outcomes. This heightened risk profile might reflect underlying comorbid disease burden and indications for SGLT2i use (ie, type 2 diabetes and chronic kidney disease). However, these data underscore the high residual risks in this population that persist despite use of guideline-recommended SGLT2i therapy and the unmet need for additional risk-lowering therapeutic options. Indeed, in light of higher baseline risks, the absolute benefits of the addition of finerenone in the SGLT2i-treated subgroup were magnified.

Table 4. Adverse Events and Other Safety Markers of Interest by Concomitant SGLT2i Use

Adverse Events	No SGLT2i use, n (%)		SGLT2i use, n (%)	
	Finerenone (n=2601)	Placebo (n=2570)	Finerenone (n=392)	Placebo (n=423)
Any serious adverse event	995 (38.3)	1042 (40.5)	162 (41.3)	171 (40.4)
Elevated serum creatinine ≥2.5 mg/dL	120 (4.8)	78 (3.1)	21 (5.5)	11 (2.7)
Elevated serum creatinine ≥3.0 mg/dL	50 (2.0)	29 (1.2)	7 (1.8)	5 (1.2)
Elevated serum potassium >5.5 mmol/L	358 (14.2)	176 (7.1)	55 (14.5)	23 (5.6)
Elevated serum potassium >6.0 mmol/L	76 (3.0)	39 (1.6)	10 (2.6)	2 (0.5)
Reduced serum potassium <3.5 mmol/L	118 (4.7)	246 (9.9)	9 (2.4)	35 (8.5)
Investigator-reported hyperkalemia	246 (9.5)	102 (4.0)	43 (11.0)	23 (5.4)
Investigator-reported hyperkalemia leading to hospitalization	14 (0.5)	3 (0.1)	2 (0.5)	3 (0.7)
Systolic blood pressure <100 mm Hg	435 (17.2)	291 (11.7)	103 (27.0)	70 (16.8)
Investigator-reported hypotension	190 (7.3)	116 (4.5)	36 (9.2)	24 (5.7)
Investigator-reported hypotension leading to hospitalization	11 (0.4)	7 (0.3)	1 (0.3)	1 (0.2)

Treatment-emergent adverse events are defined as any adverse event occurring in any patient who has received at least one dose of study drug and within 3 days of permanent discontinuation. The data reported on creatinine, potassium, and systolic blood pressure levels were further restricted to patients with at least one assessment. SGLT2i indicates sodium-glucose cotransporter-2 inhibitor.

We did not identify an effect of finerenone on the kidney composite end point among patients with HFmrEF or HFpEF, irrespective of background SGLT2i use. This appears to be in contrast with the strong kidney protection afforded by finerenone in populations with chronic kidney disease with type 2 diabetes.[7,8] The underlying reasons in FINEARTS-HF may be low event rates (yielding unstable estimates), relatively shorter follow-up duration, and possibly that the operative mechanisms of kidney disease progression might differ by underlying disease state. Renin-angiotensin system inhibitors, which are strongly recommended for kidney protection in diabetic kidney disease, do not afford similar degrees of kidney benefits in HF.[17–19]

We did not identify any new safety signals among patients cotreated with an SGLT2i and the nonsteroidal MRA finerenone. The known safety events (hyperkalemia and blood pressure lowering) with finerenone were similar in patients on and off SGLT2i treatment at baseline. Previous carefully done crossover experiments have suggested that treatment with an SGLT2i may mitigate the risks of hyperkalemia with an MRA.[10] Meta-analyses of large-scale trials have demonstrated that SGLT2i meaningfully reduce risks of hyperkalemia, including among those treated with an MRA.[16,20] In FINEARTS-HF, we observed similar trajectories of potassium levels and similar risks of hyperkalemia and lower risks of hypokalemia with finerenone, even in patients concomitantly treated with an SGLT2i. Serious hyperkalemia leading to hospitalization was not common, and there were no deaths attributable to hyperkalemia. These data should be interpreted with caution because of indication bias underlying

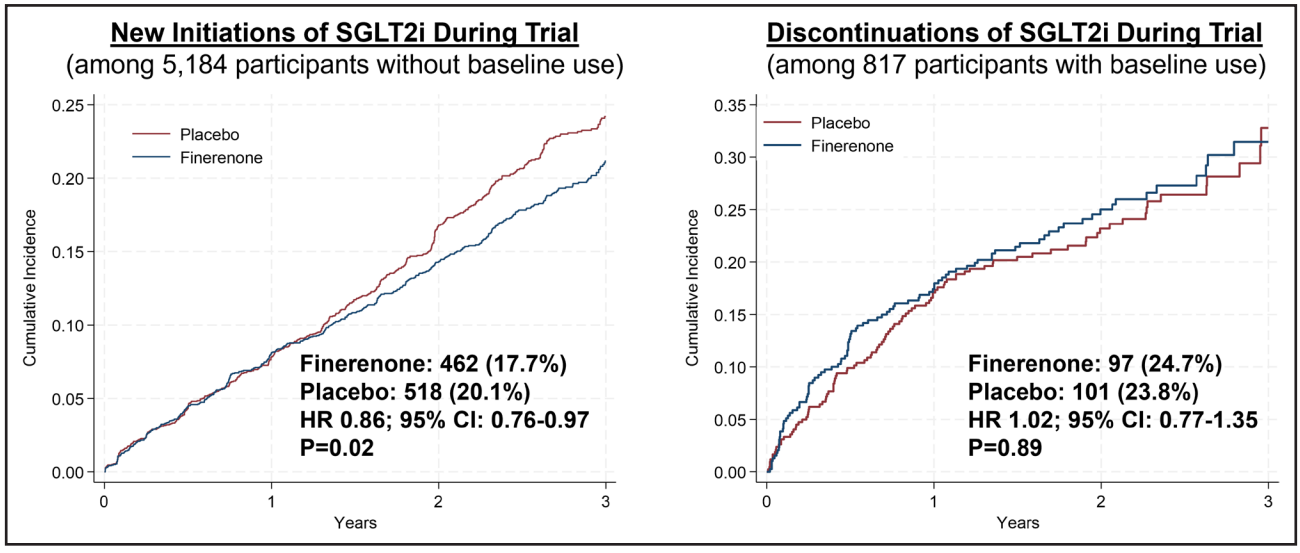

Figure 2. New initiations and discontinuations of sodium-glucose cotransporter-2 inhibitor during trial follow-up.
HR indicates hazard ratio; and SGLT2i, sodium-glucose-co-transporter-2 inhibitor.

the high risk profile of SGLT2i users with higher rates of diabetes, worse kidney function, and higher levels of albuminuria, all of which represent hyperkalemia risk factors.[21] The consistent safety profile of finerenone with and without an SGLT2i was also seen in trials of chronic kidney disease.[7] Dedicated trials (CONFIDENCE [Combination Effect of Finerenone and Empagliflozin in Participants With Chronic Kidney Disease and Type 2 Diabetes Using a UACR Endpoint Study; URL: https://www.clinicaltrials.gov; Unique identifier: NCT05254002] and CONFIRMATION-HF [A Study to Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients With Heart Failure; URL: https://www.clinicaltrials.gov; Unique identifier: NCT06024746]) examining the initial combination of finerenone and an SGLT2i in heart and kidney diseases are underway to confirm additive efficacy signals and potential protection against treatment-related hyperkalemia.

We observed unbalanced SGLT2i drop-in during trial follow-up that preferentially occurred in the placebo arm. Postbaseline SGLT2i use likely often occurred in the context of worsening HF status, which was more common in the placebo arm. Clinically stable and less symptomatic patients in ambulatory care in the finerenone arm may be less likely to be optimized with a new therapy. Unequal drop-in of background therapies in the placebo arm has also been seen in previous trials of effective HF therapies.[13] The effect size of treatment effects of finerenone on new initiation of an SGLT2i was comparable to the effects of the therapy on the primary efficacy end point. Time-updated analysis also confirmed that those newly initiated on an SGLT2i were at high subsequent risks of clinical outcomes, which might reflect initiation in the context of disease state worsening. We did not observe any excess SGLT2i discontinuation in patients randomized to finerenone, suggesting that the combined use of these therapies can be feasibly continued in well-monitored settings.

Study Strengths and Limitations

These analyses were strengthened by evaluation of randomized treatment in the context of a large, global clinical trial. Medications at baseline and during the trial were carefully captured, and all major SGLT2i in contemporary use were well represented. Clinical outcomes were independently and blindly adjudicated. Despite these strengths, the findings from this selected trial population may not be generalizable to the broader cohort of patients with HF treated in clinical practice. Although this was a prespecified subgroup analysis, FINEARTS-HF was not specifically powered to evaluate treatment effects based on background SGLT2i use, and thus within-group subgroup findings should be interpreted with caution. We did not specifically collect the primary reasons for SGLT2i use (eg, glycemic control, risk reduction in kidney disease) or reasons for SGLT2i discontinuation during the trial. Because we did not have access to historical medication records, it is possible that some participants were previously treated with an SGLT2i but had stopped therapy before randomization and thus classified as a nonuser. We counted the first instance of reporting of drug discontinuation, which might not represent permanent drug discontinuation of an SGLT2i.

Conclusions

This prespecified analysis of FINEARTS-HF found that the nonsteroidal MRA finerenone reduced cardiovascular death and total HF events irrespective of baseline or subsequent SGLT2i use and supports the complementary roles of the nonsteroidal MRA finerenone and SGLT2i in the management of patients with HFmrEF or HFpEF.

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Supplemental Material

Table S1

Figure S1

REFERENCES

1. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70:2476–2486. doi: 10.1016/j.jacc.2017.08.074
2. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400:757–767. doi: 10.1016/S0140-6736(22)01429-5
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al; ESC Scientific Document Group. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44:3627–3639. doi: 10.1093/eurheartj/ehad195
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421. doi: 10.1016/j.jacc.2021.12.012
5. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, Januzzi JL Jr, Yancy CW. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81:1835–1878. doi: 10.1016/j.jacc.2023.03.393
6. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, et al; FINEARTS-HF Committees and Investigators. Finerenone in heart failure with mildly reduced or preserved ejection fraction [posted online September 1, 2024]. *N Engl J Med*. doi: 10.1056/NEJMoa2407107. https://www.nejm.org/doi/10.1056/NEJMoa2407107
7. Rossing P, Anker SD, Filippatos G, Pitt B, Ruilope LM, Birkenfeld AL, McGill JB, Rosas SE, Joseph A, Gebel M, et al; FIDELIO-DKD and FIGARO-DKD Investigators. Finerenone in patients with chronic kidney disease and type 2 diabetes by sodium-glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care*. 2022;45:2991–2998. doi: 10.2337/dc22-0294
8. Eissing T, Goulooze SC, van den Berg P, van Noort M, Ruppert M, Snelder N, Garmann D, Lippert J, Heinig R, Brinker M, et al. Pharmacokinetics and pharmacodynamics of finerenone in patients with chronic kidney disease and type 2 diabetes: insights based on FIGARO-DKD and FIDELIO-DKD. *Diabetes Obes Metab*. 2024;26:924–936. doi: 10.1111/dom.15387
9. Vaduganathan M, Claggett BL, Lam CSP, Pitt B, Senni M, Shah SJ, Voors AA, Zannad F, Desai AS, Jhund PS, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1324–1333. doi: 10.1002/ejhf.3253
10. Solomon SD, Ostrominski JW, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Lam CSP, Pitt B, Senni M, Shah SJ, et al. Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1334–1346. doi: 10.1002/ejhf.3266
11. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J Royal Stat Soc Ser B Stat Methodol*. 2000;62:711–730. doi: 10.1111/1467-9868.00259
12. Provenzano M, Puchades MJ, Garofalo C, Jongs N, D'Marco L, Andreucci M, De Nicola L, Gorriz JL, Heerspink HJL; ROTATE-3 study group. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized crossover clinical trial. *J Am Soc Nephrol*. 2022;33:1569–1580. doi: 10.1681/ASN.2022020207
13. Yang M, Butt JH, Kondo T, Jering KS, Docherty KF, Jhund PS, de Boer RA, Claggett BL, Desai AS, Hernandez AF, et al. Dapagliflozin in patients with heart failure with mildly reduced and preserved ejection fraction treated with a mineralocorticoid receptor antagonist or sacubitril/valsartan. *Eur J Heart Fail*. 2022;24:2307–2319. doi: 10.1002/ejhf.2722
14. Ferreira JP, Butler J, Zannad F, Filippatos G, Schueler E, Steubl D, Zeller C, Januzzi JL, Pocock S, Packer M, et al. Mineralocorticoid receptor antagonists and empagliflozin in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2022;79:1129–1137. doi: 10.1016/j.jacc.2022.01.029
15. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400:757–767. doi: 10.1016/S0140-6736(22)01429-5
16. Banerjee M, Maisnam I, Pal R, Mukhopadhyay S. Mineralocorticoid receptor antagonists with sodium-glucose co-transporter-2 inhibitors in heart failure: a meta-analysis. *Eur Heart J*. 2023;44:3686–3696. doi: 10.1093/eurheartj/ehad522
17. Damman K, Solomon SD, Pfeffer MA, Swedberg K, Yusuf S, Young JB, Rouleau JL, Granger CB, McMurray JJ. Worsening renal function and outcome in heart failure patients with reduced and preserved ejection fraction and the impact of angiotensin receptor blocker treatment: data from the CHARM-study programme. *Eur J Heart Fail*. 2016;18:1508–1517. doi: 10.1002/ejhf.609
18. Damman K, Perez AC, Anand IS, Komajda M, McKelvie RS, Zile MR, Massie B, Carson PE, McMurray JJ. Worsening renal function and

outcome in heart failure patients with preserved ejection fraction and the impact of angiotensin receptor blocker treatment. *J Am Coll Cardiol*. 2014;64:1106–1113. doi: 10.1016/j.jacc.2014.01.087

19. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011;4:685–691. doi: 10.1161/CIRCHEARTFAILURE.111.963256
20. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, Langkilde AM, Mahaffey KW, McGuire DK, Neal B, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145:1460–1470. doi: 10.1161/CIRCULATIONAHA.121.057736
21. Agarwal R, Joseph A, Anker SD, Filippatos G, Rossing P, Ruilope LM, Pitt B, Kolkhof P, Scott C, Lawatscheck R, et al; FIDELIO-DKD Investigators. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol*. 2022;33:225–237. doi: 10.1681/ASN.2021070942