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Finerenone in Patients With a Recent Worsening Heart Failure Event

The FINEARTS-HF Trial

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ABSTRACT

BACKGROUND Patients with heart failure (HF) and a recent worsening heart failure (WHF) event are known to be at high risk of recurrent hospitalization and death, regardless of ejection fraction.

OBJECTIVES This study examined the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone in relation to the recency of a WHF event.

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 $\geq 40\%$. In this prespecified analysis, we assessed the risk of cardiovascular (CV) events and response to finerenone vs placebo in relation to the time from WHF to randomization (during or within 7 days, 7 days to 3 months, >3 months, or no prior WHF). The primary outcome was a composite of total (first and recurrent) WHF events and CV death, analyzed using a proportional rates method.

RESULTS Of 6,001 patients validly randomized to finerenone or placebo, 1,219 (20.3%) were enrolled during (749 [12.5%]) or within 7 days (470 [7.8%]), 2,028 (33.8%) between 7 days and 3 months, and 937 (15.6%) >3 months from a WHF event; 1,817 (30.3%) had no prior history of WHF. Rates of the primary composite outcome varied inversely with time since WHF, with >2 -fold higher risk in those enrolled during or within 7 days of WHF compared with those enrolled >3 months from WHF or without prior WHF (risk ratio [RR]: 2.13; 95% CI: 1.82-2.55). Compared to placebo, finerenone appeared to lower the risk of the primary composite to a greater extent in those enrolled within 7 days of WHF (RR: 0.74; 95% CI: 0.57-0.95) or between 7 days and 3 months of WHF (RR: 0.79; 95% CI: 0.64-0.97) than in those >3 months from WHF or without prior WHF (RR: 0.99; 95% CI: 0.81-1.21); however, no definitive treatment-by-time interaction could be confirmed ($P = 0.07$). Greater absolute risk reductions with finerenone were accordingly seen in those with recent WHF ($P_{\text{trend}} = 0.011$). The risk of adverse events including hyperkalemia and worsening renal function among patients assigned to finerenone was not increased in those with recent WHF.

CONCLUSIONS Compared with those without recent WHF, patients with HF and mildly reduced or preserved ejection fraction who have experienced a recent WHF event are at higher risk for recurrent HF events and CV death; a possible signal of enhanced absolute treatment benefit with finerenone in this population requires further confirmation in future studies. (Study to Evaluate the Efficacy [Effect on Disease] and Safety of Finerenone on Morbidity [Events Indicating Disease Worsening] & Mortality [Death Rate] in Participants With Heart Failure and Left Ventricular Ejection Fraction [Proportion of Blood Expelled Per Heart Stroke] Greater or Equal to 40% [FINEARTS-HF], [NCT04435626](https://clinicaltrials.gov/ct2/show/study/NCT04435626); A study to gather information on the influence of study drug finerenone on the number of deaths and hospitalizations in participants with heart failure EudraCT 2020-000306-29) (JACC. 2024;■:■-■)

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**ABBREVIATIONS
AND ACRONYMS****CV** = cardiovascular**EF** = ejection fraction**HF** = Heart failure**HFmrEF** = heart failure with mildly reduced ejection fraction**HFpEF** = heart failure with preserved ejection fraction**MRA** = mineralocorticoid receptor antagonist**WHF** = worsening heart failure

Hospitalization for management of worsening HF symptoms has long been recognized as a sentinel event with important prognostic implications. Regardless of left ventricular ejection fraction (LVEF), patients hospitalized for HF have nearly 3-fold higher rates of mortality than those who are not hospitalized, with the highest rates of death observed during the vulnerable interval within the first month after discharge.¹ It is increasingly recognized, however, that many HF patients with worsening symptoms are managed outside the hospital in the emergency department or ambulatory setting, and these worsening ambulatory HF events are also prognostically important.²⁻⁴ Clinical trials enrolling patients with HF have accordingly begun to embrace a broader definition of worsening HF (WHF) incorporating both hospitalized and ambulatory events to more comprehensively capture clinically important disease progression.⁵⁻⁸

Due to their heightened risk of mortality and cardiovascular events, patients with WHF are attractive targets for intensification of disease-modifying therapies. Among hospitalized patients with HF enrolled in the STRONG-HF (Safety, Tolerability and Efficacy of Up-Titration of Guideline-Directed Medical Therapies for Acute Heart Failure) trial, a strategy of rapid intensification of HF therapies was associated with lower rates of HF readmission and death at 180 days compared with usual care.⁹ Guidelines for management of HF accordingly encourage in-hospital or early postdischarge optimization of medical therapies, particularly in patients with HF with reduced EF.^{10,11}

The value of intensive pharmacologic intervention in patients with heart failure and mildly reduced or preserved EF who have had a recent WHF event is less established, because most clinical trials have prioritized recruitment of stable ambulatory patients. Although trials of sodium-glucose cotransporter 2 inhibitors^{12,13} and angiotensin receptor-neprilysin

inhibitors¹⁴ in this population have suggested greater absolute benefits of treatment in recently hospitalized patients, a prior trial of steroidal mineralocorticoid receptor antagonists (MRAs) suggested lesser benefit in patients with prior HF hospitalization.^{15,16} Recently, among patients with heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) enrolled in the FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfeTy superioR to placebo in paTientS with Heart Failure; NCT04435626; EudraCT 2020-000306-29) trial, treatment with the nonsteroidal MRA finerenone was shown to reduce the risk of composite WHF events and cardiovascular (CV) death compared with placebo. In this prespecified secondary analysis, we sought to explore the efficacy of safety of finerenone in relation to the recency of a WHF event.

METHODS

FINEARTS-HF. The detailed design, baseline characteristics, and principal results of the FINEARTS-HF trial have been published previously.¹⁷⁻¹⁹ Briefly, FINEARTS-HF was a prospective, double-blind randomized comparison of finerenone (target dose 20 or 40 mg based on estimated glomerular filtration rate [eGFR] ≤ 60 or >60 mL/min/1.73 m²) vs placebo in addition to usual care in patients with chronic HF and mildly reduced or preserved EF. Eligible subjects included hospitalized or ambulatory patients aged ≥ 40 years with symptomatic (NYHA functional class II-IV) heart failure, LVEF $\geq 40\%$, elevated natriuretic peptides, and evidence of structural heart disease. The proportion of patients without a worsening ambulatory or hospitalized HF event within 3 months of randomization was prospectively capped at approximately 50% of total enrollment. Key exclusion criteria included serum potassium >5.0 mmol/L, eGFR <25 mL/min/1.73 m², any MRA use within 30 days, or uncontrolled systolic blood pressure. The study protocol was approved by ethics committees or

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

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Institutional Review Boards at each participating site, and all patients provided written informed consent for participation.

The primary study outcome was a composite of cardiovascular death and total worsening HF events (HF hospitalizations and urgent HF visits), with all primary events confirmed by a centralized adjudication committee blinded to study drug assignment. Key secondary endpoints included the individual components of the primary endpoint, composite renal events (defined as a sustained $\geq 50\%$ decline in eGFR, a sustained decline in eGFR to < 15 mL/min/1.73 m², or initiation of chronic dialysis or renal transplant), and all-cause mortality. The primary safety outcome for this analysis was the incidence of adverse events leading to study drug discontinuation.

STATISTICAL ANALYSES. The timing of the recent episode of hospitalized or ambulatory WHF relative to randomization was recorded by investigators at the time of randomization. As prespecified in the statistical analysis plan, time from WHF to randomization was analyzed as a 3-category variable, grouping those enrolled during or within 7 days of WHF, those enrolled between 7 days and 3 months of WHF, and those enrolled > 3 months from WHF or without prior WHF. Sensitivity analyses were performed using an alternate 5-category classification (during WHF, within 7 days, between 7 days and 3 months, > 3 months, no WHF).

All efficacy analyses were performed in the intention-to-treat population, and all safety analyses were performed in the population of patients receiving at least 1 dose of study drug. Baseline characteristics were compared across categories defined by time since WHF using standard parametric and nonparametric tests. The association between time since WHF and the primary composite outcome was analyzed in semiparametric proportional rates models according to the method of Lin et al.²⁰ Rate ratios were calculated based on total events over total exposure time, with CIs derived from Poisson regression models with robust variance estimators. Time to first endpoints were assessed using Cox proportional hazards models with effect sizes summarized with HR (95% CI). All models testing treatment effects of finerenone vs placebo on efficacy endpoints were stratified by the protocol-specified stratification factors (geographic region and baseline LVEF [$< 60\%$, $\geq 60\%$]). Interaction tests were used to assess for heterogeneity in the treatment effect of finerenone across ordered categories of time from WHF with a *P* value of 0.05 used to define statistical significance. Cumulative incidence of the primary

endpoint and time to first occurrence of the CV death or worsening HF event were additionally graphically displayed. All statistical analyses were conducted in STATA version 18 (StataCorp).

RESULTS

Of 6,001 patients validly randomized to finerenone or placebo between September 2020 and January 2023, 1,219 (20.3%) were enrolled either during (749 [12.5%]) or within 7 days (470 [7.8%]) of a WHF event; 2,028 (33.8%) were enrolled between 7 days and 3 months of a WHF event; and 2,754 (45.9%) were enrolled > 3 months from a WHF event (937 [15.6%]) or had no prior history of WHF (1,817 [30.3%]). No patients had missing data regarding the time from WHF to randomization. Of the 4,184 patients with an index WHF event, 3,619 (86.5%) had experienced prior HF hospitalization and 565 (13.5%) had a previous ambulatory WHF event. Complete follow-up for the primary endpoint was available for all but 13 patients who withdrew consent for participation and 6 patients who were lost to follow-up.

Compared with those enrolled further from a WHF event, patients enrolled during or within 7 days of WHF tended to have lower systolic blood pressure, lower EF, higher N-terminal pro-B-type natriuretic peptide, and higher (worse) NYHA functional class (Table 1). Time from WHF to randomization was inversely related to the risk of the primary composite outcome with rates ranging from 24.4 per 100 patient-years (95% CI: 21.4-27.8 per 100 patient-years) in those enrolled during or within 7 days of WHF to 11.3 per 100 patient-years (95% CI: 10.2-12.4 per 100 patient-years) in those enrolled > 3 months from WHF or without WHF (risk ratio [RR]: 0.47; 95% CI: 0.40-0.55). Similar patterns were seen with regard to total HF hospitalizations, CV mortality, time to first occurrence of worsening HF or CV death, all-cause mortality, and the renal composite outcome (Table 2). Using the more granular 5-category classification revealed highest risk of the primary composite outcome in those enrolled during a WHF event (26.2 per 100 patient-years; 95% CI: 22.2-30.9 per 100 patient-years) and declining risk with increasing time from WHF and lowest risk in those without prior history of WHF (8.4 per 100 patient-years; 95% CI: 7.3-9.6 per 100 patient-years; RR: 0.32; 95% CI: 0.26-0.40). Aggregate incidences of adverse events leading to study drug discontinuation did not vary by time from WHF, with incidences of 2.9%, 2.6%, and 3.3% in those enrolled during or within 7 days, between 7 days and 3 months, and > 3 months or without WHF (*P* = 0.29).

TABLE 1 Baseline Characteristics by Time From WHF to Randomization in FINEARTS-HF

	Time From WHF to Randomization			P Value for Trend
	≤7 d (n = 1,219)	7 d to 3 mo (n = 2,028)	>3 mo or No Prior WHF (n = 2,754)	
Age, y	72.2 ± 9.7	71.3 ± 10.3	72.4 ± 9.1	0.11
Women	583 (47.8)	936 (46.2)	1,213 (44.0)	0.021
Race				<0.001
Asian	74 (6.1)	507 (25.0)	415 (15.1)	
Black	7 (0.6)	34 (1.7)	47 (1.7)	
Other	32 (2.6)	75 (3.7)	75 (2.7)	
White	1,106 (90.7)	1,412 (69.6)	2,217 (80.5)	
Region				0.06
Asia	74 (6.1)	505 (24.9)	404 (14.7)	
Eastern Europe	759 (62.3)	665 (32.8)	1,226 (44.5)	
Latin America	122 (10.0)	297 (14.6)	222 (8.1)	
North America	16 (1.3)	120 (5.9)	335 (12.2)	
Western Europe, Oceania, others	248 (20.3)	441 (21.7)	567 (20.6)	
Any prior HF hospitalization	106 (87.4)	1,685 (83.1)	869 (31.6)	<0.001
Systolic blood pressure, mm Hg	127.1 ± 13.9	128.6 ± 15.9	131.0 ± 15.3	<0.001
Body mass index, kg/m ²	30.5 ± 6.2	29.4 ± 6.3	30.1 ± 5.9	0.68
Creatinine, mg/dL	1.2 ± 0.5	1.1 ± 0.3	1.1 ± 0.3	0.003
eGFR, mL/min/1.73 m ²	60.2 ± 20.0	63.3 ± 20.2	62.1 ± 19.2	0.05
eGFR <60 mL/min/1.73 m ²	637 (52.3)	918 (45.3)	1,333 (48.4)	0.15
UACR, mg/g	19 (7-73)	19 (7-72)	18 (7-58)	0.11
Potassium, mmol/L	4.3 ± 0.5	4.4 ± 0.5	4.4 ± 0.4	<0.001
LVEF, %	51.7 ± 7.7	51.8 ± 7.3	53.5 ± 8.1	<0.001
NT-proBNP, pg/mL	1,168 (474-2,451)	1,119 (473-2,113)	952 (426-1,718)	<0.001
NYHA functional class				<0.001
II	618 (50.7)	1,456 (71.8)	2,072 (75.2)	
III	578 (47.4)	558 (27.5)	677 (24.6)	
IV	23 (1.9)	13 (0.6)	5 (0.2)	
Medical history				
Hypertension	1,117 (91.6)	1,762 (86.9)	2,446 (88.8)	0.08
Diabetes mellitus	510 (41.8)	829 (40.9)	1,100 (39.9)	0.25
Atrial fibrillation, baseline ECG	534 (43.8)	783 (38.6)	976 (35.4)	<0.001
Stroke	148 (12.1)	273 (13.5)	287 (10.4)	0.029
Myocardial Infarction	269 (22.1)	436 (21.5)	836 (30.4)	<0.001
Medications				
Beta-blocker	1,017 (83.4)	1,701 (83.9)	2,377 (86.3)	0.008
ACEI	474 (38.9)	639 (31.5)	1,042 (37.8)	0.56
ARB	411 (33.7)	696 (34.3)	995 (36.1)	0.10
ARNI	76 (6.2)	255 (12.6)	182 (6.6)	0.13
Calcium-channel blocker	427 (35.0)	615 (30.3)	926 (33.6)	0.88
SGLT2 inhibitor	188 (15.4)	371 (18.3)	258 (9.4)	<0.001
Loop diuretic	1,075 (88.2)	1,880 (92.7)	2,284 (82.9)	<0.001

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

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FINEARTS-HF = Finerenone trial to investigate Efficacy and sAfty superior to placebo in paTientS with Heart Failure; 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-to-creatinine ratio; WHF = worsening heart failure.

With regard to the primary outcome of total HF hospitalization and CV death, there appeared to be an inverse gradient of reduction in the relative risk of primary composite events with finerenone compared to placebo with increasing distance from WHF, with greater treatment effect in those with recent WHF (**Central Illustration A**). Risk reductions for the

primary composite were numerically largest in those randomized during or within 7 days of WHF (RR: 0.74; 95% CI: 0.57-0.95), slightly lower in those between 7 and 3 months of WHF (RR: 0.79; 95% CI: 0.64-0.97), and lowest in those >3 months or without prior WHF (RR: 0.99; 95% CI: 0.81-1.21). Absolute incidence rate reductions with finerenone were 7.8 per 100 patient-

TABLE 2 Clinical Event Rates and Treatment Effects According to Time From WHF to Randomization

	n	Total Events	Rate per 100 pt-y (95% CI)	RR/HR (95% CI)	Treatment Effect (Finerenone vs Placebo) (95% CI)	Interaction Trend P Value ^a
Total WHF events and death from CV causes						
≤7 d	1,219	642	24.4 (21.4-27.8)	Reference	0.74 (0.57-0.95)	0.07
7 d to 3 mo	2,028	896	19.8 (17.8-22.0)	0.81 (0.69-0.96)	0.79 (0.64-0.97)	
>3 mo or no WHF	2,754	828	11.3 (10.2-12.4)	0.47 (0.40-0.55)	0.99 (0.81-1.21)	
WHF or CV death (time-to-first)						
≤7 d	1,219	341	14.8 (13.3-16.4)	Reference	0.86 (0.69-1.06)	0.46
7 d to 3 mo	2,028	487	12.0 (11.0-13.1)	0.82 (0.71-0.94)	0.76 (0.63-0.91)	
>3 mo or no WHF	2,754	515	7.5 (6.9-8.2)	0.53 (0.46-0.61)	0.92 (0.78-1.10)	
Total WHF events						
≤7 d	1,219	517	19.6 (16.9-22.7)	Reference	0.72 (0.54-0.96)	0.11
7 d to 3 mo	2,028	732	16.2 (14.3-18.2)	0.83 (0.68-1.00)	0.78 (0.61-0.98)	
>3 mo or no WHF	2,754	613	8.4 (7.5-9.4)	0.44 (0.36-0.53)	0.96 (0.76-1.22)	
Death from CV causes						
≤7 d	1,219	127	4.8 (4.0-5.7)	Reference	0.83 (0.59-1.19)	0.26
7 d to 3 mo	2,028	164	3.6 (3.1-4.2)	0.75 (0.59-0.95)	0.83 (0.61-1.13)	
>3 mo or no WHF	2,754	211	2.9 (2.5-3.3)	0.58 (0.47-0.73)	1.06 (0.81-1.39)	
Renal composite						
≤7 d	1,219	35	1.5 (1.1-2.1)	Reference	0.99 (0.50-1.94)	0.06
7 d to 3 mo	2,028	46	1.2 (0.9-1.5)	0.74 (0.48-1.16)	1.10 (0.61-1.96)	
>3 mo or no WHF	2,754	49	0.7 (0.6-1.0)	0.44 (0.29-0.68)	2.13 (1.17-3.87)	
Death from any cause						
≤7 d	1,219	250	9.4 (8.4-10.7)	Reference	0.83 (0.54-1.07)	0.34
7 d to 3 mo	2,028	312	6.8 (6.1-7.6)	0.72 (0.61-0.85)	0.98 (0.78-1.22)	
>3 mo or no WHF	2,754	451	6.1 (5.6-6.7)	0.63 (0.54-0.74)	0.97 (0.81-1.17)	

^aP value represents trend for treatment-by-subgroup interaction.
CV = cardiovascular; pt-y = patient-years; RR = risk ratio; WHF = worsening heart failure.

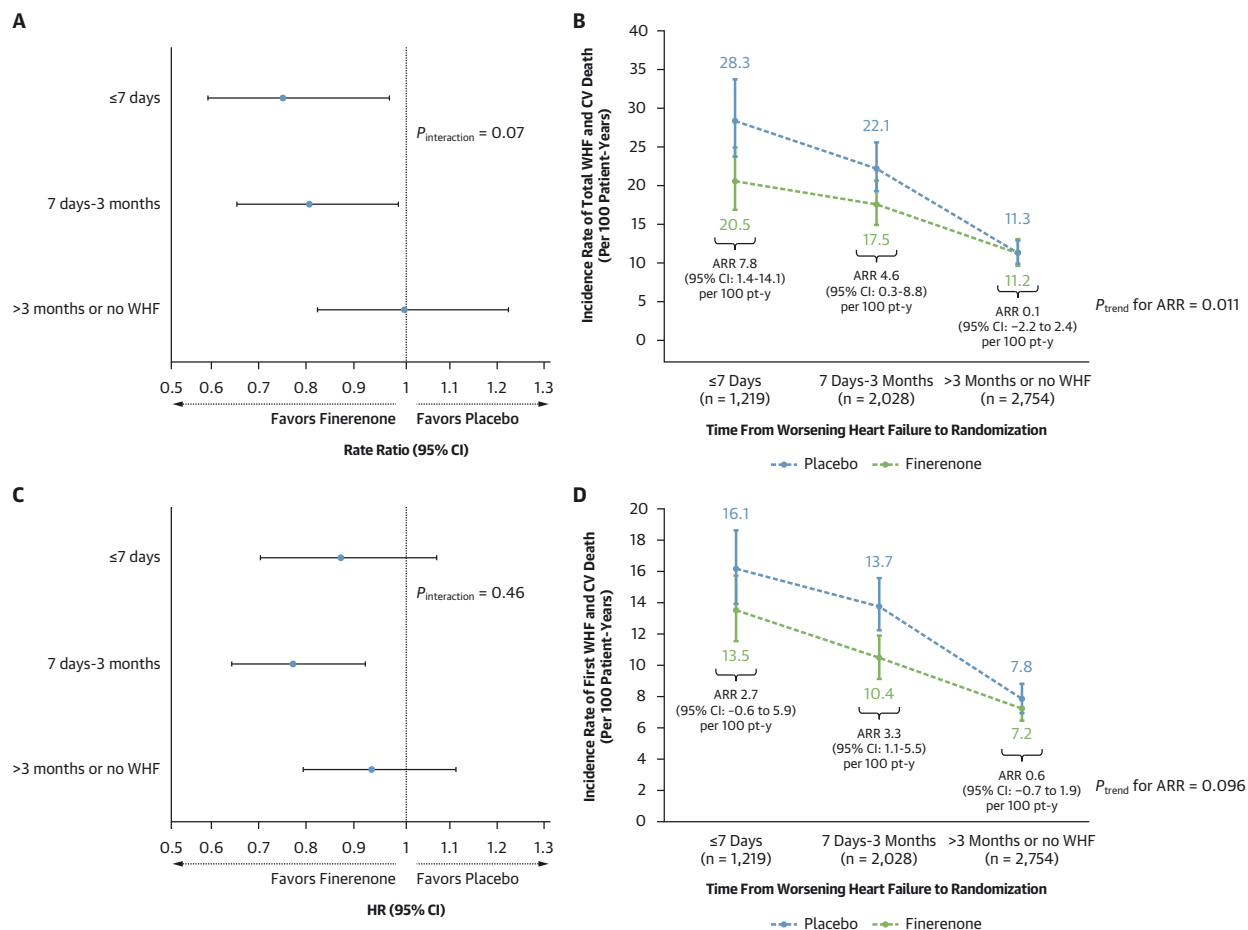
years (95% CI: 1.4-14.1 per 100 patient-years), 4.6 per 100 patient-years (95% CI: 0.3-8.8 per 100 patient-years), and 0.1 per 100 patient-years (95% CI: -2.2 to 2.4 per 100 patient-years) across the respective categories ($P = 0.011$ for trend across ordinal categories) (Central Illustration B, Figure 1A). A similar gradient of absolute risk reduction was observed for time to first occurrence of WHF or CV death (Central Illustration D) and using the 5-category classification of time from WHF (Supplemental Figures 1A and 1B). Despite this trend, there was no formal statistical interaction between time from worsening HF and treatment assignment with regard to the relative risk of the primary composite outcome ($P = 0.07$); moreover, this trend was less pronounced when looking at time to first occurrence of WHF or CV death, where relative risk reductions with finerenone were more consistent across categories of time from WHF to randomization (interaction $P = 0.46$) (Central Illustration B and C, Figure 1B, Supplemental Figure 1).

With regard to safety, there was no formal interaction between treatment and time from WHF for any

of the outcomes examined; however, the incidence study drug discontinuation for adverse events appeared to be higher for finerenone than placebo in those >3 months from or without WHF ($P_{\text{interaction}} = 0.07$) (Table 3). Increased odds of developing hyperkalemia, elevated serum creatinine, and SBP <100 mm Hg with finerenone compared with placebo were consistent among those with very recent WHF and those with more remote or no history of WHF, while lower odds of potassium <3.5 mmol/L were seen regardless of the timing of prior WHF.

DISCUSSION

In this prespecified analysis of the FINEARTS-HF trial, in which more than one-half (54%) of the study population was deliberately enrolled during or within 3 months of a worsening HF event, rates of the primary outcome were nearly 2-fold higher in patients randomized during or within 7 days of an episode of WHF compared with those randomized >3 months from WHF or without prior WHF, and similar patterns were

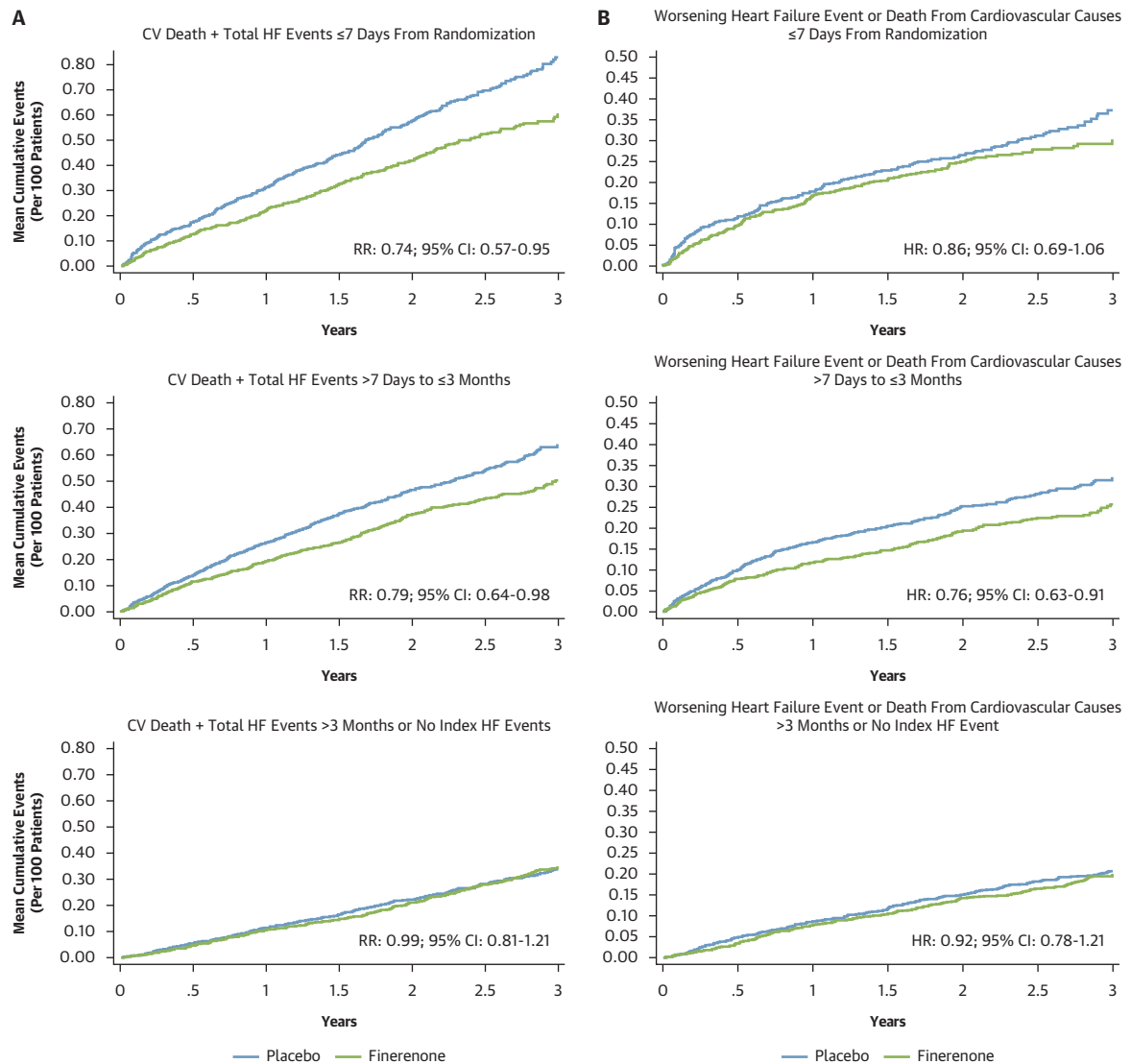
CENTRAL ILLUSTRATION Incidence Rates of Cardiovascular Outcomes by Treatment Assignment and Treatment Effect According to Time From Worsening Heart Failure to Randomization: The FINEARTS-HF Trial

Desai AS, et al. JACC. 2024; ■(■):■-■.

(A and B) Data for the primary composite outcome of total WHF events and death from CV causes. (C and D) Data for the key secondary outcome of time to first occurrence of WHF or death from CV causes. ARR = absolute risk reduction; CV = cardiovascular; FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfeTy superior to placebo in paTients with Heart Failure; WHF = worsening heart failure.

seen in the risk of all secondary outcomes examined including total HF hospitalizations, CV death, all-cause death, and the composite renal outcome. Compared to treatment with placebo, treatment with finerenone appeared to lower the risk of the primary composite outcome to a larger extent among those enrolled during or in close proximity to a worsening HF event compared with those enrolled remote from WHF or those without prior WHF; however, no definitive interaction between treatment efficacy and time from WHF to randomization could be confirmed, and this trend was not seen in analysis of the

additional outcome of time to first occurrence of WHF or CV death. Absolute risk reductions with finerenone were accordingly greatest in patients with recent WHF. There was no apparent variation in the safety of finerenone in patients enrolled in close proximity to WHF vs those enrolled remote from WHF, with similar incidence of hyperkalemia, renal dysfunction, and hypotension among those with and without recent WHF. These data underscore the potential value of finerenone as a treatment for patients with HF and mildly reduced or preserved ejection fraction who have recently experienced worsening HF.

FIGURE 1 Cumulative Incidence of Cardiovascular Outcomes by Treatment Assignment According to Time From Worsening Heart Failure to Randomization, FINEARTS-HF Trial

(A) Data for the primary composite outcome of total worsening heart failure (HF) events and death from cardiovascular (CV) causes. (B) Data for the key secondary outcome of time to first occurrence of a worsening HF event or death from CV causes. FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfeTy superior to placebo in paTientS with Heart Failure; pt-y = patients-years.

Our data extend and amplify the growing literature highlighting the prognostic importance of worsening HF episodes in the trajectory of patients with HF across the spectrum of ejection fraction.^{2,3} Although much attention has been paid to the importance of HF hospitalization as a sentinel event, our data emphasize the additional clinical importance of worsening HF episodes outside the hospital, which similarly portend higher risk of subsequent HF

hospitalization, cardiovascular death, and all-cause death. Notably, these data also highlight the importance of worsening HF, regardless of treatment setting, as a risk factor for adverse renal outcomes, which although infrequent during follow-up of FINEARTS-HF, were more than twice as likely in those enrolled during or within 7 days of a WHF event compared with those enrolled remote from or without WHF. Together these data underscore that

TABLE 3 Adverse Events and Safety Markers of Interest and Treatment Effects According to Time From WHF to Randomization

	n	Total Events	Placebo	Finerenone	OR (Finerenone vs Placebo) (95% CI)	Interaction Trend P Value ^a
Drug discontinuation for adverse event						
≤7 d	1,219	35 (2.9)	18 (3.0)	17 (2.8)	0.94 (0.48-1.84)	0.07
7 d to 3 mo	2,028	52 (2.6)	29 (2.9)	23 (2.2)	0.76 (0.44-1.33)	
>3 mo or no WHF	2,754	92 (3.3)	36 (2.6)	56 (4.1)	1.62 (1.06-2.47)	
Any serum creatinine ≥2.5 mg/dL						
≤7 d	1,219	49 (4.3)	22 (3.9)	27 (4.7)	1.22 (0.69-2.17)	0.69
7 d to 3 mo	2,028	84 (4.3)	28 (2.9)	56 (5.6)	1.99 (1.26-3.17)	
>3 mo or no WHF	2,754	97 (3.6)	39 (2.9)	58 (4.4)	1.54 (1.02-2.33)	
Any serum creatinine ≥3.0 mg/dL						
≤7 d	1,219	20 (1.7)	10 (1.8)	10 (1.7)	0.99 (0.41-2.39)	0.09
7 d to 3 mo	2,028	25 (1.3)	10 (1.0)	15 (1.5)	1.46 (0.65-3.27)	
>3 mo or no WHF	2,754	46 (1.7)	14 (1.0)	32 (2.4)	2.37 (1.26-4.46)	
Any serum potassium >5.5 mmol/L						
≤7 d	1,219	138 (12)	55 (9.6)	83 (14.3)	1.56 (1.09-2.25)	0.07
7 d to 3 mo	2,028	186 (9.5)	54 (5.6)	132 (13.3)	2.58 (1.85-3.59)	
>3 mo or no WHF	2,754	288 (10.7)	90 (6.6)	198 (14.9)	2.47 (1.90-3.21)	
Any serum potassium >6.0 mmol/L						
≤7 d	1,219	25 (2.2)	10 (1.8)	15 (2.6)	1.49 (0.66-3.34)	0.27
7 d to 3 mo	2,028	40 (2.0)	13 (1.4)	27 (2.7)	2.04 (1.05-3.98)	
>3 mo or no WHF	2,754	62 (2.3)	18 (1.3)	44 (3.3)	2.56 (1.47-4.45)	
Any serum potassium <3.5 mmol/L						
≤7 d	1,219	80 (6.9)	55 (9.6)	25 (4.3)	0.42 (0.26-0.69)	0.36
7 d to 3 mo	2,028	155 (7.9)	99 (10.3)	56 (5.6)	0.52 (0.37-0.73)	
>3 mo or no WHF	2,754	173 (6.5)	127 (9.4)	46 (3.5)	0.35 (0.25-0.49)	
Any systolic blood pressure <100 mm Hg						
≤7 d	1,219	125 (10.8)	56 (9.7)	69 (11.8)	1.24 (0.86-1.80)	0.56
7 d to 3 mo	2,028	343 (17.5)	128 (13.2)	215 (21.6)	1.81 (1.43-2.30)	
>3 mo or no WHF	2,754	431 (16.0)	177 (13.0)	254 (19.1)	1.57 (1.28-1.94)	

Values are n (%) unless otherwise indicated. ^aP value represents trend for treatment-by-subgroup interaction. All adverse events and safety markers of interest displayed in this table are treatment-emergent observations, defined as any observation occurring after first dose of study drug and up to 3 d after permanent discontinuation.

WHF = worsening heart failure.

the occurrence of worsening HF in any context heralds an inflection point in risk for patients with HFmrEF and HFpEF, and should prompt consideration of treatment intensification.

In this context, these data highlighting the efficacy and safety of finerenone among patients with HFmrEF and HFpEF with recent worsening HF are particularly notable. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial of the steroidal mineralocorticoid receptor antagonist spironolactone in patients with HF and LVEF ≥45%, patients with an HF hospitalization within the 12 months before randomization appeared to experience lesser treatment benefit than those enrolled based on elevated natriuretic peptides alone, even after accounting for

possible confounding by notable regional differences in the enrolled population.^{15,16} By contrast, in FINEARTS-HF, finerenone treatment appeared to be at least as effective in patients with recent WHF as in those enrolled remote from WHF or without a prior WHF event. Because these patients are at higher overall risk, greater relative risk reductions with finerenone translate into large absolute risk reductions of approaching 8% in this group. As well, there were no concerning signals of heightened risk for key adverse events with finerenone treatment among those with recent WHF, with similar rates of hyperkalemia, renal dysfunction, and hypotension regardless of time from WHF to randomization. Whether these data reflect peculiar efficacy of nonsteroidal vs steroidal MRAs in patients with

HFmrEF and HFpEF with recent WHF or a broader class effect requires further clarification in future studies.

In the interim, however, these data support a favorable balance of efficacy and safety with use of finerenone in patients with HF, EF $\geq 40\%$, and recent WHF and particular urgency to consider finerenone treatment in this population either at the time of or shortly after a WHF event. HF treatment guidelines already emphasize the importance of therapeutic intensification for patients with HF with reduced EF during hospitalization or in the early postdischarge period to reduce rates of hospital readmissions and overall mortality; with increasing evidence suggesting a treatment benefit of SGLT2 inhibitors, angiotensin-receptor neprilysin inhibitors, and now MRAs in patients with higher EF, our data emphasize that a similar approach to optimization of pharmacologic therapy may be appropriate in HFmrEF and HFpEF.

STUDY LIMITATIONS. Although FINEARTS-HF embraced a broad definition of WHF events, the proportion of patients enrolled after an ambulatory WHF episode was relatively small compared with the proportion enrolled after an HF hospitalization. Accordingly, statistical power is limited to explore the temporal variation in treatment effects by treatment setting in this subpopulation. Moreover, because the date of the index WHF event was not recorded by investigators, we are unable to perform an analysis of time from WHF to randomization as a continuous measure to confirm the associations noted in the categorical time measures utilized in this analysis. As well, although treatment effects appeared to be greater among those enrolled proximate to a WHF in the primary analysis of total WHF events and CV death, there was no definitive treatment-by-time interaction and secondary analysis of time-to-first occurrence of CV death or WHF event analysis did not suggest the same pattern of diminishing treatment efficacy over time from WHF. Because interaction testing may lack power to detect true differences in treatment effects across subgroups, the absence of a clear statistical interaction does not exclude the possibility of a meaningful difference in the efficacy of finerenone according to the proximity to a worsening HF event; however, it also remains unclear if higher rates of treatment discontinuations among finerenone patients enrolled >3 months from WHF or without WHF may have confounded treatment effects on recurrent events in this population. As such, these observations should be considered hypothesis-generating and may require further confirmation in future trials. In

particular, the ongoing REDEFINE-HF (A Study to Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Hospitalized Heart Failure Patients; [NCT06008197](#)) trial is specifically designed to investigate the efficacy of safety of finerenone compared with placebo in reducing total HF events and CV death among patients with HF and LVEF $\geq 40\%$ who are currently hospitalized or recently discharged from hospitalization for worsening HF and CONFIRMATION-HF (A Study to Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients With Heart Failure; [NCT06024746](#)) will explore the effect of combination treatment with SGLT2 inhibitors and finerenone in this population.

CONCLUSIONS

Patients with HFmrEF/HFpEF who experience a WHF event, regardless of treatment setting, are at higher risk for subsequent hospital admission and mortality than those without recent WHF, but appear to derive greater absolute treatment benefit from finerenone. Because the risk of adverse events with finerenone does not appear to be enhanced in those with recent WHF and absolute risk reductions are amplified, this population may be a particularly attractive target for use of finerenone in clinical practice.

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APPENDIX For a supplemental figure, please see the online version of this paper.