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Effects of the Non-Steroidal MRA Finerenone With and Without Concomitant SGLT2 Inhibitor Use in Heart Failure

Running title: *Vaduganathan et al.; Combination SGLT2i and Non-Steroidal MRA in HFpEF*

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Abstract

Background: Patients with heart failure (HF) with mildly reduced or preserved ejection fraction face heightened long-term risks of morbidity and mortality. The sodium glucose-co-transporter-2 inhibitors (SGLT2i) and the non-steroidal mineralocorticoid receptor antagonist (MRA) 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 was a randomized, double-blind, placebo-controlled trial of finerenone in patients with HF and left ventricular ejection fraction (LVEF) $\geq 40\%$. 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 based on 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 6,001 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% confidence interval 0.60 to 1.16) and without an SGLT2i at baseline (rate ratio 0.85; 95% confidence interval 0.74 to 0.98); $P_{\text{interaction}}=0.76$. In follow-up, 980 participants initiated SGLT2i, which was less frequent in the finerenone arm compared with placebo (17.7% vs. 20.1%; hazard ratio 0.86; confidence interval 0.76 to 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 endpoint.

Conclusions: The treatment benefits of the non-steroidal MRA finerenone were observed irrespective of concomitant use of an SGLT2i. These data suggest that the combined use of SGLT2i and a non-steroidal MRA may provide additive protection against cardiovascular events in patients with HF with mildly reduced or preserved ejection fraction.

ClinicalTrials.gov Trial Registration: FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfeTy superior to placebo in paTientS with Heart Failure; NCT04435626)

Key Words: heart failure with preserved ejection fraction; mineralocorticoid receptor antagonist; SGLT2 inhibitor

Non-standard Abbreviations and Acronyms

CI = confidence interval

eGFR = estimated glomerular filtration rate

FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfeTy superior to placebo in paTientS with Heart Failure

HFmrEF/HFpEF = heart failure with mildly reduced or preserved ejection fraction

HR = hazard ratio

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

RR = rate ratio

SGLT2i = sodium glucose-co-transporter-2 inhibitors

Clinical Perspective

What is new?

- The efficacy of the non-steroidal MRA finerenone in reducing cardiovascular death and worsening HF events and improving symptom burden was consistent irrespective of concomitant use of a SGLT2i in patients with HF 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 SGLT2i and non-steroidal MRA may provide additive protection against cardiovascular events and have complementary roles in patients with HF with mildly reduced or preserved ejection fraction.



Circulation

Introduction

Patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF or HFpEF) experience high lifetime risks of premature mortality, excess hospitalizations, and adverse health status.¹ This population has historically had few evidence-based therapeutic options to modify their disease trajectory. Recently, the sodium glucose-co-transporter-2 inhibitors (SGLT2i) were shown to reduce cardiovascular death and heart failure-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, the FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superiorR to placebo in paTientS with Heart Failure) demonstrated that the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risks of cardiovascular death and total worsening HF events in this target population.⁶

SGLT2i and the non-steroidal MRA might now be considered together as evidence-based therapies in patients with HFmrEF or HFpEF. While 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 on <https://vivli.org/ourmember/bayer/>

FINEARTS-HF Study Design

The study design,⁹ baseline characteristics,¹⁰ and primary results⁶ 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 with symptomatic HFmrEF or HFpEF conducted across 37 countries. Key inclusion criteria included left ventricular ejection fraction (LVEF) $\geq 40\%$, elevated natriuretic peptide levels (thresholds adjusted for atrial fibrillation status at screening and recency of worsening HF event), evidence of structural heart disease (either 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 m² 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 (vs. matching placebo) with target dosing based on baseline estimated glomerular filtration rate: 20mg (if baseline eGFR ≤ 60 mL/min/1.73

m²) or 40mg once daily (if baseline eGFR>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 Endpoints

The primary outcome was a composite of total (first and recurrent) worsening HF events and cardiovascular death. We additionally evaluated total worsening HF events, cardiovascular death, all-cause death, a renal composite endpoint (defined as sustained decrease in eGFR of $\geq 50\%$ from baseline over at least 4 weeks, or sustained eGFR decline $< 15\text{ml}/\text{min}/1.73\text{m}^2$, 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 endpoints) 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 endpoints and deaths were specifically adjudicated by an independent clinical endpoints committee.

Concomitant SGLT2i Use

Any SGLT2i (regardless of type) and 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 prior 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 post-baseline 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 endpoint and the secondary endpoint 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 trial statistical analysis plan. Time-to-first events (cardiovascular death, all-cause death, renal composite endpoint, composite cardiovascular death or worsening HF event, and composite cardiovascular death or HF hospitalization) were 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 endpoints were stratified by geographic region and baseline LVEF (<60%, ≥60%). In each model, evidence of treatment effect heterogeneity was evaluated by including an interaction term by treatment randomization. The Kansas City Cardiomyopathy Questionnaire (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 above mentioned 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, while all safety analyses were assessed in participants who received at least one dose of study drug.

Second, we assessed post-baseline changes in SGLT2i use, analyses that were prespecified in the FINEARTS-HF Academic Statistical Analysis Plan. New initiation (among baseline non-users) 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 7,463 participants and validly randomized 6,001 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 $52.6 \pm 7.8\%$ and the median N-terminal pro-B-type natriuretic peptide was 1,041 (25th to 75th percentiles 448 – 1,946) pg/mL.

Clinical Profiles and Risk by Baseline SGLT2i Use

Overall, 817 (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 m² (**Table 1**). Baseline clinical profiles and concomitant medications

were well-balanced between treatment arms when separately examined in those on and off an SGLT2i at baseline (**Table S1**).

During 2.6 years median follow-up, participants with baseline SGLT2i use were at higher risks of the primary endpoint of cardiovascular death and total HF events (24.2 per 100py vs. 15.2 per 100py; rate ratio [RR] 1.57; 95% confidence interval [CI] 1.30 to 1.88; $P < 0.001$). Risks of all other key endpoints 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 (rate ratio [RR] 0.83; 95% confidence interval [CI] 0.60 to 1.16) and without an SGLT2i at baseline (RR 0.85; 95% CI 0.74 to 0.98); $P_{\text{interaction}} = 0.76$. Owing to higher baseline risk, absolute rate reduction was higher in participants with baseline SGLT2i use (4.7 vs. 2.5 total events per 100py; **Figure 1**). Treatment effects of finerenone vs. placebo were consistent by baseline SGLT2i use across all key efficacy endpoints (**Table 3**). Treatment effects on symptom burden as assessed 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); $P_{\text{interaction}} = 0.66$.

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 hyperkalemia leading to death in either group (**Table 4**). At 1 month, finerenone increased potassium levels by +0.19 (0.17 to 0.21) mmol/L in those not treated with SGLT2i and +0.19 (0.13 to 0.25) mmol/L in those treated with an SGLT2i at baseline ($P_{\text{interaction}}=1.00$; **Figure S1**). The decline in eGFR from baseline to 3 months was greater with finerenone than placebo (finerenone -3.4 ± 11.5 mL/min/1.73m² and placebo -0.1 ± 10.0 mL/min/1.73m²); this was observed irrespective of concomitant SGLT2i use ($P_{\text{interaction}}=0.21$).

SGLT2i Initiation and Discontinuation During the Trial

In follow-up, 980 (18.9%) participants 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 endpoint (hazard ratio [HR] 1.60; 95% CI 1.42 to 1.81; $P < 0.001$). Among 5,184 participants without baseline use, SGLT2i initiation during the trial was less common among those randomized to finerenone compared with placebo (17.7% vs. 20.1%; HR 0.86; 95% CI 0.76 to 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 endpoint (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% vs. 23.8%; HR 1.02; 95% CI 0.77 to 1.35; $P=0.89$); **Figure 2**.

Discussion

This prespecified analysis of the FINEARTS-HF trial demonstrates that the non-steroidal 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. As 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 the FINEARTS-HF trial, almost 1,000 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 non-steroidal MRA may provide additive protection against cardiovascular events in patients with HF with mildly reduced or preserved ejection fraction.

SGLT2i and MRAs target non-overlapping pharmacological targets and theoretically influence distinct pathways (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 now provides further support that the clinical benefits of finerenone are not modified by background use of an SGLT2i. While FINEARTS-HF enrolled patients with the highest background use of SGLT2i of any contemporary trial of this population, we recognize that SGLT2i use at baseline was still modest as 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 (namely, type 2 diabetes and chronic kidney disease). However, these data do 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.

We did not identify an effect of finerenone on the kidney composite endpoint 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 of 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. Interestingly, 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 co-treated with an SGLT2i and the non-steroidal 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 cross-over experiments have suggested that treatment with an SGLT2i may potentially 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 due to hyperkalemia. These data should be interpreted cautiously due to indication bias underlying 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 similarly seen in trials of chronic kidney disease.⁷ Dedicated trials (CONFIDENCE [NCT05254002] and CONFIRMATION-HF [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. Post-baseline 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 previously seen in prior trials of effective HF therapies.¹³ In fact, the effect size of treatment effects of finerenone on new initiation of an SGLT2i was very comparable to the effects of the therapy on the primary efficacy endpoint. 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. Reassuringly, 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 are 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 are 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 cautiously interpreted. We did not specifically collect the primary reasons for SGLT2i use (e.g. glycemic control, risk reduction in kidney disease) or reasons for SGLT2i discontinuation during the trial. As 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 prior to randomization and thus classified as a non-user. We counted the first instance of reporting of drug discontinuation, which might not represent permanent drug discontinuation of an SGLT2i.

Conclusions

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

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Supplemental Materials

Table S1

Figure S1



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Table 1. Baseline Characteristics by Concomitant SGLT2 Inhibitor Use.

	No SGLT2i Use	SGLT2i Use
	n=5,184	n=817
Age	72.1 ± 9.5	71.4 ± 10.5
Women	2412 (46.5%)	320 (39.2%)
<i>Race</i>		
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%)
<i>Region</i>		
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 prior HF Hospitalization	3036 (58.6%)	583 (71.4%)
<i>Recency of Heart Failure Event</i>		
≤7 days from randomization	1031 (19.9%)	188 (23.0%)
>7 days to ≤ 3 months	1657 (32.0%)	371 (45.4%)
>3 months or no index HF event	2496 (48.1%)	258 (31.6%)
Systolic Blood Pressure (mmHg)	129.9 ± 15.1	126.4 ± 16.5
Body Mass Index (kg/m ²)	29.9 ± 6.1	30.0 ± 6.3
Serum Creatinine (mg/dL)	1.1 ± 0.4	1.2 ± 0.4
eGFR (mL/min/1.73m ²)	62.5 ± 19.5	59.6 ± 20.8
eGFR < 60 mL/min/1.73m ²	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
LVEF 40 to <50%	1836 (35.5%)	336 (41.2%)
LVEF 50 to <60%	2308 (44.6%)	366 (44.9%)
LVEF ≥60%	1034 (20.0%)	113 (13.9%)
NT-proBNP (pg/mL)	1014 [438-1907]	1180 [527-2263]
<i>NYHA class</i>		
NYHA Class II	3577 (69.0%)	569 (69.6%)
NYHA Class III	1573 (30.3%)	240 (29.4%)
NYHA Class IV	33 (0.6 %)	8 (1.0 %)
Hypertension	4593 (88.6%)	732 (89.6%)
Diabetes Mellitus	1823 (35.2%)	616 (75.4%)
Atrial Fibrillation on Electrocardiogram	1983 (38.3%)	310 (37.9%)



Prior Stroke	605 (11.7%)	103 (12.6%)
Prior Myocardial Infarction	1314 (25.3%)	227 (27.8%)
β -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%)

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; eGFR = estimated glomerular filtration; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT2i = sodium glucose co-transporter-2 inhibitor; UACR = urine albumin creatinine ratio



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Table 2. Key Outcomes by Concomitant SGLT2 Inhibitor Use.

	No SGLT2i Use (Reference)	SGLT2i Use	Rate Ratio (RR) or Hazard Ratio (HR) (95% CI) Relative to No SGLT2i Use	P-value
	n=5,184	n=817		
CV death and total worsening HF events	1956 Events [15.2/100py]	410 Events [24.2/100py]	RR 1.57 (1.30, 1.88)	<0.001
Total worsening HF events	1533 Events [11.9/100py]	333 Events [19.7/100py]	RR 1.61 (1.31, 1.97)	<0.001
CV death	425 (8.2%) [3.3/100py]	77 (9.4%) [4.6/100py]	HR 1.40 (1.10, 1.79)	0.007
All-cause death	876 (16.9%) [6.8/100py]	137 (16.8%) [8.0/100py]	HR 1.20 (1.00, 1.43)	0.050
Renal composite outcome	112 (2.2%) [1.0/100py]	18 (2.2%) [1.2/100py]	HR 1.31 (0.80, 2.17)	0.284
CV death or first worsening HF event	1126 (21.7%) [9.6/100py]	217 (26.6%) [14.5/100py]	HR 1.45 (1.25, 1.68)	<0.001
CV death or first HF hospitalization	1054 (20.3%) [8.9/100py]	209 (25.6%) [13.8/100py]	HR 1.50 (1.29, 1.74)	<0.001

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; RR = rate ratio; SGLT2i = sodium-glucose-co-transporter-2 inhibitor

Table 3. Treatment Effects of Finerenone by Concomitant SGLT2 Inhibitor Use

	No SGLT2i Use		SGLT2i Use		P _{interaction}
	Finerenone n=2610	Placebo n=2574	Finerenone n=393	Placebo n=424	
CV death and total worsening HF events					
Events	907	1049	176	234	
Rate (per 100 pt-yrs)	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 pt-yrs)	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
CV death					
Events (%)	205 (7.9%)	220 (8.5%)	37 (9.4%)	40 (9.4%)	
Rate (per 100 pt-yrs)	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 pt-yrs)	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 endpoint					
Events (%)	67 (2.6%)	45 (1.7%)	8 (2.0%)	10 (2.4%)	
Rate (per 100 pt-yrs)	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
CV death or first worsening HF event					
Events (%)	529 (20.3%)	597 (23.2%)	95 (24.2%)	122 (28.8%)	
Rate (per 100 pt-yrs)	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
CV death or first HF hospitalization					
Events (%)	505 (19.3%)	549 (21.3%)	94 (23.9%)	115 (27.1%)	
Rate (per 100 pt-yrs)	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

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; RR = rate ratio; SGLT2i = sodium-glucose-co-transporter-2 inhibitor

Table 4. Adverse Events and Other Safety Markers of Interest by Concomitant SGLT2 Inhibitor Use.

	No SGLT2i Use		SGLT2i Use	
	Finerenone	Placebo	Finerenone	Placebo
	n=2601	n=2570	n=392	n=423
Any Serious Adverse Events	995 (38.3%)	1042 (40.5%)	162 (41.3%)	171 (40.4%)
Elevated Serum Creatinine \geq 2.5 mg/dl	120 (4.8 %)	78 (3.1 %)	21 (5.5 %)	11 (2.7 %)
Elevated Serum Creatinine \geq 3.0 mg/dl	50 (2.0 %)	29 (1.2 %)	7 (1.8 %)	5 (1.2 %)
Elevated Serum Potassium $>$ 5.5 mmol/liter	358 (14.2%)	176 (7.1 %)	55 (14.5%)	23 (5.6 %)
Elevated Serum Potassium $>$ 6.0 mmol/liter	76 (3.0 %)	39 (1.6 %)	10 (2.6 %)	2 (0.5 %)
Reduced Serum Potassium $<$ 3.5 mmol/liter	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%)

Abbreviations: SGLT2i = sodium-glucose-co-transporter-2 inhibitor

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.



Figure Legends

Figure 1. Treatment Effects of Finerenone on Primary Endpoint by Concomitant SGLT2 Inhibitor Use

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; py = patient-years; SGLT2i = sodium-glucose-co-transporter-2 inhibitor; RR = rate ratio

Absolute rate reductions (ARR) were calculated as the between-arm difference in event rates incorporating all events throughout the duration of the trial.

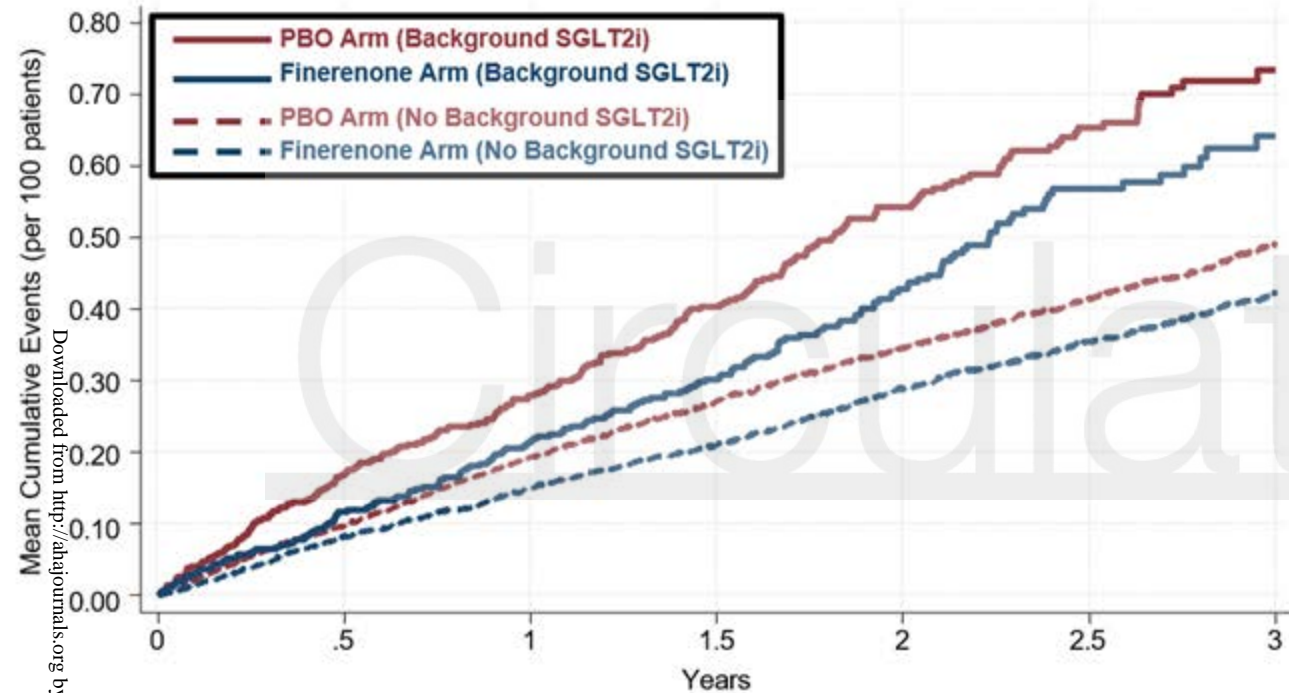
Figure 2. New Initiations and Discontinuations of SGLT2i During Trial Follow-up

Abbreviations: CI = confidence interval; HR = hazard ratio; SGLT2i = sodium-glucose-co-transporter-2 inhibitor



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CV Death and Total Worsening HF Events



SGLT2i Subgroup (n=817):

RR 0.83; 95% CI 0.60-1.16

ARR 4.7 per 100py

No SGLT2i Subgroup (n=5,184):

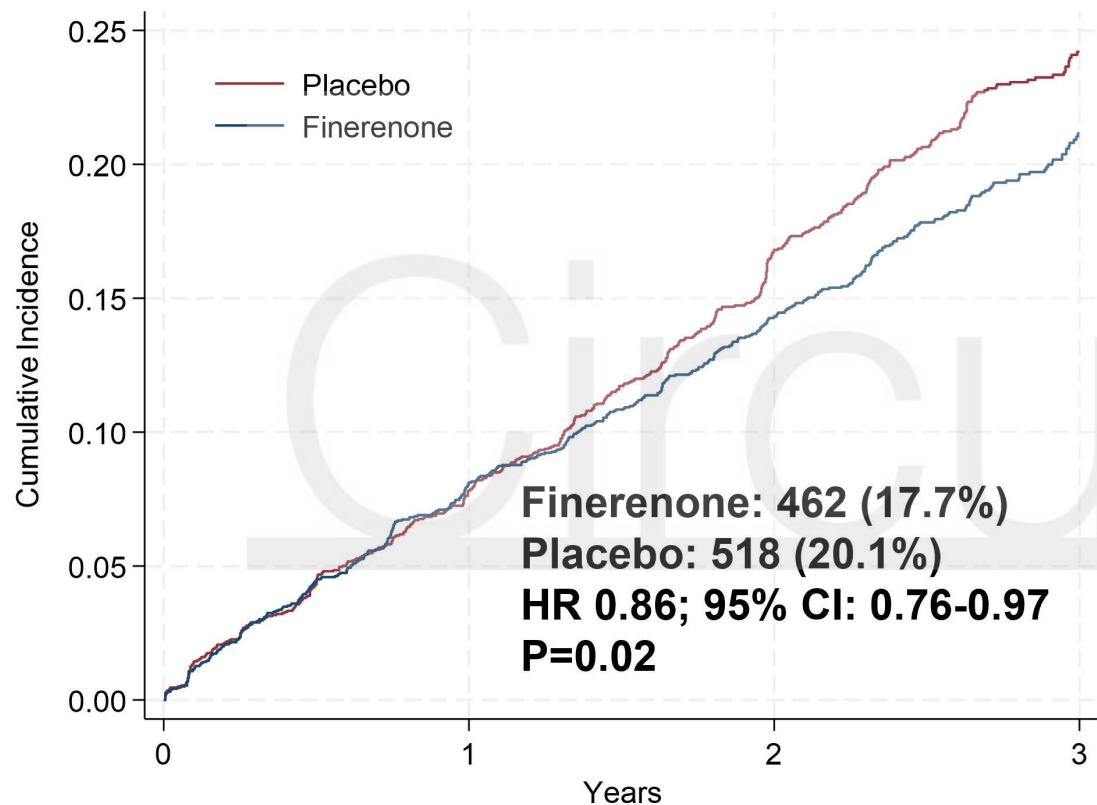
RR 0.85; 95% CI 0.74-0.98

ARR 2.5 per 100py

$p_{\text{interaction}} = 0.76$

Heart
Association.

New Initiations of SGLT2i During Trial (among 5,184 participants without baseline use)



Discontinuations of SGLT2i During Trial (among 817 participants with baseline use)

