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Finerenone and Outpatient Worsening Heart Failure With Mildly Reduced or Preserved Ejection Fraction

A Secondary Analysis of the FINEARTS-HF Randomized Clinical Trial

Jonathan W. Cunningham, MD, MPH; Safia Chatur, MD; Brian L. Claggett, PhD; Muthiah Vaduganathan, MD, MPH; Akshay S. Desai, MD, MPH; Pardeep S. Jhund, MD, PhD; Guillermo Llamas Esperón, MD; Carolyn S. P. Lam, MD, PhD; Naoki Sato, MD, PhD; Michele Senni, MD; Sanjiv Shah, MD; Adriaan Voors, MD, PhD; Faiez Zannad, MD; Bertram Pitt, MD; Shelley Zieroth, MD; Meike Brinker, MD; Katja Rohwedder, MD; So-Young Kim, MD; James Lay-Flurrie, MSc; Prabhakar Viswanathan, MBBS, PhD; John J. V. McMurray, MD; Scott D. Solomon, MD

IMPORTANCE Worsening heart failure (HF) is commonly managed in the outpatient setting with adjustments in oral diuretic therapy. The effect of the nonsteroidal mineralocorticoid receptor antagonist finerenone on outpatient worsening HF events in patients with mildly reduced or preserved ejection fraction is unknown.

OBJECTIVE To evaluate the effect of finerenone on outpatient worsening HF events requiring oral diuretic intensification among patients with HF with mildly reduced or preserved ejection fraction.

DESIGN, SETTING, AND PARTICIPANTS This is a secondary analysis of the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF), a global, multicenter randomized clinical trial. Patients had HF and an ejection fraction of 40% or greater. Data analysis was conducted from September 1 to December 10, 2024.

INTERVENTION Participants were randomized 1:1 to finerenone or placebo.

MAIN OUTCOMES AND MEASURES Primary outcome events (cardiovascular death, HF hospitalization, and outpatient urgent HF visit requiring intravenous diuretic therapy) were centrally adjudicated. In this prespecified analysis, outpatient oral diuretic intensification events were defined as initiations of loop or thiazide diuretic or increases in loop diuretic dosage. The risk of all-cause death following each type of worsening HF event (HF hospitalization, urgent HF visit, or outpatient oral diuretic intensification) and the effect of finerenone on outpatient oral diuretic intensification alone or as part of an extended composite outcome with primary outcome events were evaluated.

RESULTS A total of 6001 participants (mean [SD] age, 72.0 [9.6] years; 2732 [46%] female) were enrolled. First worsening HF events included 664 HF hospitalizations, 87 urgent HF visits, and 1250 oral diuretic intensifications. Rates of death were higher following worsening HF: 27.7 (95% CI, 24.3-31.5) per 100 patient-years after HF hospitalization, 13.6 (95% CI, 8.8-21.1) per 100 patient-years after urgent HF visit, and 11.6 (95% CI, 10.2-13.1) per 100 patient-years after outpatient oral diuretic intensification compared with 4.5 (95% CI, 4.2-4.9) per 100 patient-years for patients without worsening HF. Adding outpatient oral diuretic intensification to the primary outcome increased the number of patients experiencing events from 1343 to 2238. Finerenone reduced outpatient oral diuretic intensification alone (hazard ratio [HR], 0.89 [95% CI, 0.80-0.98]; $P = .02$) and in an extended composite outcome that further included cardiovascular death, HF hospitalization, and urgent HF visit (HR, 0.85 [95% CI, 0.78-0.92]; $P < .001$).

CONCLUSIONS AND RELEVANCE Outpatient worsening HF events requiring oral diuretic intensification were common, associated with poor prognosis, and reduced by finerenone in patients with HF with mildly reduced or preserved ejection fraction.

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Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (ssolomon@bwh.harvard.edu).

Patients with heart failure (HF) experience periods of stability interrupted by episodes of worsening symptoms and volume retention requiring diuresis.[1,2] Hospitalization for worsening HF is associated with high subsequent risk for rehospitalization and death and therefore has traditionally been included as an outcome in clinical trials of HF therapies.[3-5] Financial incentives and patient preferences are increasingly moving care for worsening HF to the outpatient or even telehealth setting.[6] Outpatient worsening HF events treated with intravenous loop diuretic have been shown to also predict poor prognosis and have therefore been added to clinical trial primary composite outcomes, but they have proven to be rare (<15% the rate of HF hospitalization).[7-9]

Initiation or increase in the dosage of oral diuretics occurs far more frequently than intravenous treatment. In previous trials, this was associated with a 2.5- to 3-fold greater risk of subsequent mortality compared with stable outpatients, which was similar to outpatient intravenous diuretic administration, although less than HF hospitalization.[10,11] Oral diuretic intensification may be an early marker of worsening HF, identifying patients with high absolute benefit from programs to manage congestion or optimize guideline-directed medical therapy. It remains unknown whether the type of diuretic change (loop or thiazide) or the degree of dosage intensification influences subsequent prognosis.

The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) compared the nonsteroidal mineralocorticoid receptor antagonist finerenone with placebo in patients with HF with mildly reduced or preserved ejection fraction who were using either a loop or thiazide diuretic at baseline.[12-14] Finerenone reduced the primary outcome of total worsening HF events (hospitalization or urgent HF visit requiring intravenous diuretic) and cardiovascular (CV) death by 16%. Outpatient oral diuretic intensification—defined as initiations or increases in the dosage of loop diuretics or initiation of thiazide diuretics—was a prespecified exploratory outcome in the FINEARTS-HF trial. In this study, we investigated the frequency and prognostic significance of worsening HF events treated with hospitalization, outpatient intravenous diuretic administration, or oral diuretic intensification as well as the effect of finerenone on the risk for these events.

Key Points

Question Does the nonsteroidal mineralocorticoid receptor antagonist finerenone reduce outpatient worsening heart failure (HF) events requiring oral diuretic intensification among patients with HF with mildly reduced or preserved ejection fraction?

Findings In this secondary analysis of a randomized clinical trial that included 6001 participants, outpatient oral diuretic intensification events were common and associated with greater risk of subsequent death compared with stable outpatients. Finerenone reduced outpatient oral diuretic intensifications by 11%.

Meaning Finerenone may prevent outpatient worsening HF in patients with mildly reduced or preserved ejection fraction.

Methods

Study Design and Participants

The FINEARTS-HF trial was a global, multicenter, parallel-group, double-blind, randomized clinical trial comparing the nonsteroidal mineralocorticoid receptor antagonist finerenone with placebo in patients with symptomatic HF and left ventricular ejection fraction of 40% or greater. The design, baseline characteristics, and primary results of the trial have been previously published.[12-14] Key inclusion criteria included evidence of structural heart disease, elevated plasma natriuretic peptide levels, and use of a loop or thiazide diuretic for at least 30 days prior to randomization. Potential participants using any mineralocorticoid receptor antagonist within 30 days of randomization or continuously (≥90 days) in the 12 months before screening were excluded from the trial. The dosage of finerenone was 20 mg or 40 mg daily depending on baseline kidney function. The study protocol was approved by an ethics committee or institutional review board at each individual site and is available in Supplement 1. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. The current study is a prespecified secondary analysis. All participants provided written informed consent. Data analysis was conducted from September 1 to December 10, 2024.

Clinical End Points

The primary outcome of the FINEARTS-HF trial was a composite of CV death and total worsening HF events, which included both unplanned hospitalizations for HF and urgent visits for HF treated with intravenous loop diuretic. Primary outcome events were adjudicated from participant medical records by a central clinical end point committee.

Outpatient oral diuretic intensification events were identified from medication records, without review of participant medical records. Information on the medication dosage, start date, and stop date was reported by individual sites. Medications were reviewed at every study visit, and any changes to concomitant medication use were reconciled and documented by each site investigator. Loop diuretic daily dosages were converted to furosemide dose equivalents; bumetanide, 1 mg, torsemide, 20 mg, and ethacrynic acid, 100 mg, were considered equivalent to 80 mg of oral furosemide. Oral diuretic intensification was defined as initiation of loop diuretic in patients who were not using one at baseline, an increase in loop diuretic dosage above both the previous and randomization dosages, or initiation of thiazide diuretic. Dosing frequencies including other and as needed were not considered in analysis of diuretic dosage increases because the total daily dosage could not be defined. Analysis of worsening HF events inclusive of initiation of intensification of oral therapy for HF was prespecified in the FINEARTS-HF trial's academic statistical analysis plan (Supplement 1). In a sensitivity analysis, thiazide initiation events were excluded because they may have occurred

Table 1. Baseline Characteristics by First Worsening Heart Failure (HF) Event

Characteristic	No worsening HF event (n = 3763)	Outpatient oral diuretic intensification (n = 1250)	Urgent HF visit (n = 87)	HF hospitalization (n = 664)	CV death (n = 237)	*P* value
Age, mean (SD), y	71.0 (9.6)	73.9 (9.5)	75.2 (9.4)	73.5 (9.7)	71.8 (9.3)	<.001
Sex, No. (%)						
Female	1697 (45.1)	593 (47.4)	35 (40.2)	308 (46.4)	99 (41.8)	.32
Male	2066 (54.9)	657 (52.6)	52 (59.8)	356 (53.6)	138 (58.2)	
Race, No. (%)[a]						
Asian	600 (15.9)	217 (17.4)	17 (19.5)	131 (19.7)	31 (13.1)	.05
Black	53 (1.4)	18 (1.4)	1 (1.1)	15 (2.3)	1 (0.4)	
White	2997 (79.6)	982 (78.6)	67 (77.0)	489 (73.6)	200 (84.4)	
Other[b]	113 (3.0)	33 (2.6)	2 (2.3)	29 (4.4)	5 (2.1)	
Geographic region, No. (%)						
Asian	587 (15.6)	216 (17.3)	17 (19.5)	131 (19.7)	32 (13.5)	<.001
Eastern Europe	1847 (49.1)	453 (36.2)	17 (19.5)	205 (30.9)	128 (54.0)	
Latin America	421 (11.2)	104 (8.3)	8 (9.2)	78 (11.7)	30 (12.7)	
North America	272 (7.2)	96 (7.7)	16 (18.4)	73 (11.0)	14 (5.9)	
Western Europe, Oceania, or other	636 (16.9)	381 (30.5)	29 (33.3)	177 (26.7)	33 (13.9)	
Any previous hospitalization for heart failure, No. (%)	2110 (56.1)	778 (62.2)	62 (71.3)	524 (78.9)	145 (61.2)	<.001
Time since heart failure event at randomization, No. (%)						
≤7 d	671 (17.8)	329 (26.3)	15 (17.2)	156 (23.5)	48 (20.3)	<.001
>7 d to 3 mo	1268 (33.7)	372 (29.8)	40 (46.0)	275 (41.4)	73 (30.8)	
>3 mo or no index event	1824 (48.5)	549 (43.9)	32 (36.8)	233 (35.1)	116 (48.9)	
Systolic blood pressure, mean (SD), mm Hg	129.5 (14.8)	130.0 (16.4)	130.3 (17.7)	127.2 (16.2)	129.5 (14.2)	.003
BMI, mean (SD)	29.8 (5.9)	30.1 (6.2)	30.5 (6.6)	30.3 (6.8)	30.0 (6.8)	.30
eGFR, mean (SD), mL/min/1.73 m^2	64.7 (19.5)	58.0 (19.1)	55.8 (18.4)	56.0 (20.1)	61.0 (19.0)	<.001
Left ventricular ejection fraction, mean (SD), %	52.5 (7.7)	53.3 (8.1)	51.6 (8.4)	52.0 (7.7)	51.1 (7.8)	<.001
NT-proBNP, median (IQR), pg/mL	851 (376-1619)	1305 (559-2395)	1645 (905-2974)	1702 (916-3164)	1433 (746-2553)	<.001
NYHA functional class, No. (%)						
II	2764 (73.5)	778 (62.3)	63 (72.4)	396 (59.6)	145 (61.2)	<.001
III	983 (26.1)	455 (36.4)	24 (27.6)	262 (39.5)	89 (37.6)	
IV	16 (0.4)	16 (1.3)	0	6 (0.9)	3 (1.3)	
Medical history, No. (%)						
Hypertension	3312 (88.0)	1120 (89.6)	78 (89.7)	604 (91.0)	211 (89.0)	.18
Type 2 diabetes	1462 (38.9)	509 (40.7)	44 (50.6)	312 (47.0)	112 (47.3)	<.001
Atrial fibrillation on ECG at baseline	1320 (35.1)	541 (43.3)	33 (37.9)	297 (44.7)	102 (43.0)	<.001
Stroke	414 (11.0)	144 (11.5)	15 (17.2)	102 (15.4)	33 (13.9)	.007
Myocardial infarction	997 (26.5)	272 (21.8)	25 (28.7)	161 (24.2)	86 (36.3)	<.001
Medication use, No. (%)						
β-Blocker	3232 (85.9)	1019 (81.5)	77 (88.5)	571 (86.0)	196 (82.7)	.003
Angiotensin-converting enzyme inhibitor	1424 (37.8)	410 (32.8)	27 (31.0)	201 (30.3)	93 (39.2)	<.001
Angiotensin receptor blocker	1333 (35.4)	449 (35.9)	27 (31.0)	215 (32.4)	78 (32.9)	.43
Angiotensin receptor neprilysin inhibitor	316 (8.4)	90 (7.2)	9 (10.3)	81 (12.2)	17 (7.2)	.004
Calcium channel blocker	1250 (33.2)	433 (34.6)	27 (31.0)	195 (29.4)	63 (26.6)	.04
Sodium-glucose cotransporter 2 inhibitor	484 (12.9)	170 (13.6)	16 (18.4)	117 (17.6)	30 (12.7)	.01
Loop diuretic	3226 (85.7)	1068 (85.4)	84 (96.6)	647 (97.4)	214 (90.3)	<.001
Thiazide diuretic	584 (15.5)	153 (12.2)	13 (14.9)	51 (7.7)	30 (12.7)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

[a] Race was included in the analysis for reporting transparency and for readers to assess generalizability of results. Race was determined by the participant based on fixed categories.

[b] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, or not reported.

Table 2. Risk of Death After Worsening Heart Failure (HF) Events[a]

First worsening HF event	Patients, No.	Subsequent death rate, No./100 patient-years (95% CI)
HF hospitalization	664	27.7 (24.3-31.5)
Urgent HF visit	87	13.6 (8.8-21.1)
Outpatient oral diuretic intensification	1250	11.6 (10.2-13.1)
Loop diuretic initiation	343	11.9 (9.5-14.9)
Loop diuretic dosage increase	736	12.3 (10.4-14.4)
Thiazide diuretic initiation	171	8.2 (5.6-12.2)
No worsening HF event	4000	4.5 (4.2-4.9)

[a] Rates of death are calculated beginning at the time of the first worsening HF event for patients who experienced worsening HF and from randomization for patients who did not experience worsening HF.

in response to hypertension rather than worsening HF. A separate sensitivity analysis required that outpatient oral diuretic intensifications be sustained for at least 30 days.

Statistical Analysis

Baseline characteristics of patients who had a first worsening HF event of hospitalization, urgent HF visit, or oral diuretic intensification or who did not experience worsening HF were described using frequency with percentage for categorical variables and mean with SD or median with IQR for continuous variables. In a landmark analysis, we evaluated rates of all-cause mortality following the first nonfatal worsening HF event (hospitalization for HF, urgent HF visit, or outpatient oral diuretic intensification) compared with patients who did not experience a worsening HF event. Among patients with oral diuretic intensification, we assessed rates of subsequent death after each type of intensification event (loop diuretic initiation, loop diuretic dosage increase, or thiazide diuretic initiation). Next, we determined the effect of finerenone vs placebo on time to first outpatient oral diuretic intensification and an extended composite outcome further including CV death, HF hospitalization, and urgent HF visit using Kaplan-Meier curves and a Cox proportional hazards model. Treatment effect estimates were stratified by region and ejection fraction dichotomized at 60%, as prespecified in the FINEARTS-HF trial. Statistical analyses were performed using Stata version 16.0 statistical software (StataCorp LLC).

Results

Clinical Profiles of Patients Experiencing Worsening HF Events

Among 6001 patients in the FINEARTS-HF trial (mean [SD] age, 72.0 [9.6] years; 2732 [46%] female), 664 (11%) experienced a first worsening HF event of HF hospitalization, 87 (1%) had an urgent HF visit with intravenous loop diuretic administration, and 1250 (21%) had oral diuretic intensification. CV death without an intercurrent worsening HF event occurred in 237 (4%), and 3763 patients (63%) did not experience a worsening HF event or CV death. The median (IQR) time to first worsening HF event was 146 (30-393) days for outpatient oral diuretic intensifications, 221 (103-466) days for urgent HF visits, and 309 (113-616) days for HF hospitalizations. Baseline characteristics according to first worsening HF event are shown in **Table 1**. Patients who experienced worsening HF events were older and had higher incidences of recent HF events, lower estimated glomerular filtration rates, and higher baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) levels than patients who did not experience worsening HF. Comparing the types of worsening HF events, patients who first experienced outpatient oral diuretic intensification had less severe baseline characteristics than patients who experienced an urgent HF visit or HF hospitalization. For example, the median (IQR) baseline NT-proBNP level 1305 (559-2395) pg/mL in patients who experienced outpatient oral diuretic intensification compared with 1645 (905-2974) pg/mL for urgent HF visit and 1702 (916-3164) pg/mL for HF hospitalization.

Prognosis After Worsening HF Events

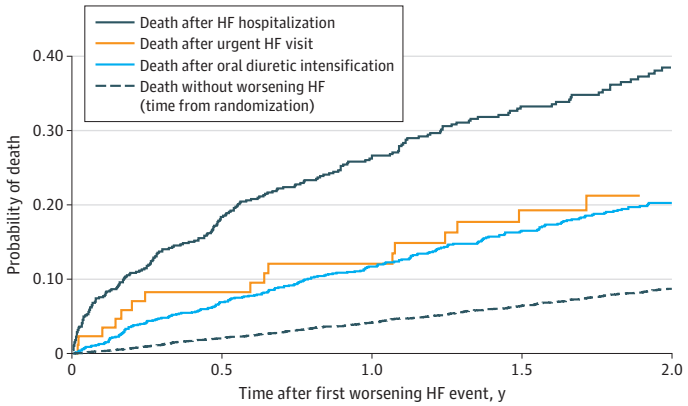
Worsening HF events of all types were associated with elevated rates of subsequent all-cause death (**Table 2** and **Figure 1**). The rate of subsequent death was highest following HF hospitalization (27.7 [95% CI, 24.3-31.5] events per 100 patient-years). Outpatient worsening HF events—oral diuretic intensification (11.6 [95% CI, 10.2-13.1] per 100 patient-years) and urgent HF visit (13.6 [95% CI, 8.8-21.1] per 100 patient-years)—were associated with subsequent death rates that were similar to each other, lower than HF hospitalization, and greater than patients who did not experience any HF event (4.5 [95% CI, 4.2-4.9] per 100 patient-years).

Among the 1250 first oral diuretic intensification events, 736 (59%) were loop diuretic dosage increases, 343 (27%) were loop diuretic initiations, and 171 (14%) were thiazide diuretic initiations. Rates of death were similar following loop diuretic initiation (11.9 [95% CI, 9.5-14.9] per 100 patient-years) and loop diuretic dosage increase (12.3 [95% CI, 10.4-14.4] per 100 patient-years) and were lower following thiazide diuretic initiation (8.2 [95% CI, 5.6-12.2] per 100 patient-years). Most loop diuretic dosage increases (412 [56%]) were to exactly double the previous furosemide equivalent dose; 169 (23%) were less than double, and 155 (21%) were greater than double. Most thiazide diuretic initiations (108 [63%]) involved hydrochlorothiazide; metolazone initiations accounted for only 12 worsening HF events (7% of thiazide initiations) (eTable in Supplement 2). Overall, these results indicate that changes in loop diuretic therapy were associated with 2- to 3-fold greater risk of subsequent death regardless of route (intravenous or oral).

Effect of Finerenone on Outpatient Worsening HF

There were 756 outpatient oral diuretic intensification events in the finerenone group, compared with 832 in the placebo group. Finerenone reduced first outpatient oral diuretic intensification events by 11% (HR, 0.89 [95% CI, 0.80-0.98]; $P = .02$) (**Table 3** and **Figure 2**). Addition of outpatient oral diuretic intensification to the primary outcome of CV death, HF hospitalization, or urgent HF visit increased the number of patients experiencing an event from 1343 to 2238. Finerenone re-

Figure 1. Risk of Death After First Worsening Heart Failure Event



No. at risk

Death after HF hospitalization	664	481	360	231	148
Death after urgent HF visit	87	73	64	52	37
Death after oral diuretic intensification	1246	1091	938	725	555
Death without worsening HF (time from randomization)	6001	4905	4408	3852	3161

The timescale for patients with first worsening heart failure (HF) events is the time after the first worsening HF event; the timescale for patients without worsening HF is the time from randomization.

Table 3. Treatment Effect of Finerenone Compared With Placebo on First Worsening Heart Failure (HF) Events

Outcome	Events, No.[a]		HR (95% CI)[b]	*P* value
	Finerenone	Placebo		
CV death	242	260	0.93 (0.78-1.11)	.41
HF hospitalization	450	514	0.86 (0.76-0.97)	.02
Urgent HF visit	73	113	0.63 (0.47-0.85)	.002
Outpatient oral diuretic intensification	756	832	0.89 (0.80-0.98)	.02
CV death, HF hospitalization, or urgent HF visit	624	719	0.84 (0.76-0.94)	.002
CV death, HF hospitalization, urgent HF visit, or outpatient oral diuretic intensification	1049	1189	0.85 (0.78-0.92)	<.001

Abbreviations: CV, cardiovascular; HR, hazard ratio.

[a] Event counts refer to first events only.

[b] HRs compare finerenone with placebo using a Cox proportional hazards model.

duced the risk of this extended composite outcome by 15% (HR, 0.85 [95% CI, 0.78-0.92]; *P* < .001). There was no significant interaction between finerenone treatment and either age or left ventricular ejection fraction greater than or equal to 50% for either outcome. A sensitivity analysis excluding thiazide diuretic initiation from the definition of outpatient oral diuretic intensification showed a similar reduction in outpatient oral diuretic intensification (HR, 0.90 [95% CI, 0.81-0.995]; *P* = .04) and the extended composite outcome (HR, 0.86 [95% CI, 0.79-0.93]; *P* = 001).

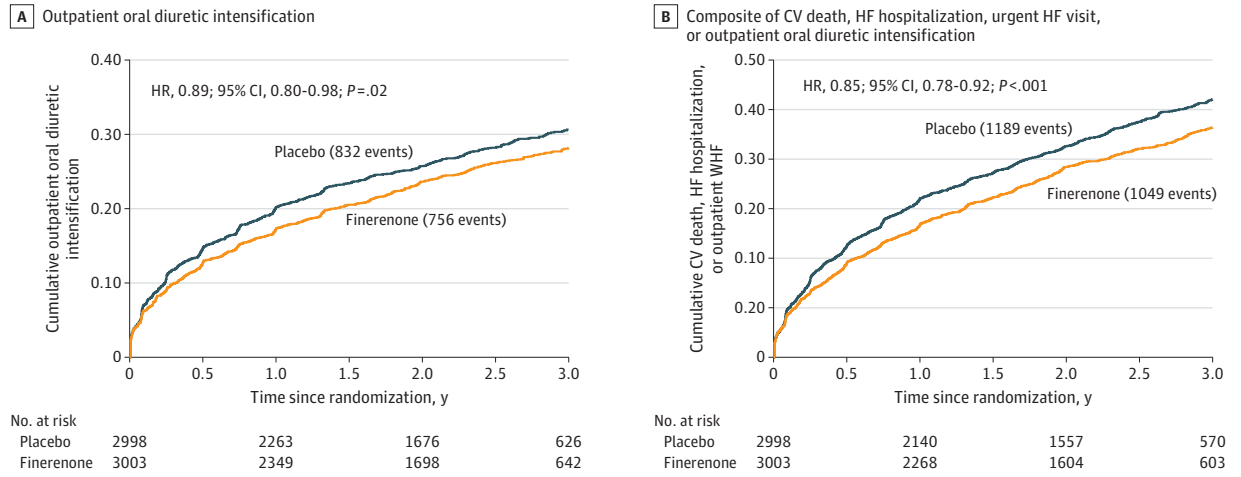
Sensitivity Analysis Requiring Sustained Oral Diuretic Intensification

A sensitivity analysis in which outpatient oral diuretic intensification events were required to be sustained for at least 30 days demonstrated similar results. By this definition, 1372 patients experienced outpatient oral diuretic intensification, which was 14% fewer than in the primary analysis, as expected for a more stringent definition. The rate of death following sustained outpatient oral diuretic intensification events was 11.2 (95% CI, 9.8-12.8) per 100 patient-years, which was similar to the death rate of 11.6 (95% CI, 10.2-13.1) per 100 patient-years for the primary analysis. Finerenone reduced sustained outpatient oral diuretic intensification by 15% (HR, 0.85 [95% CI, 0.76-0.95]; *P* = .003) and the extended composite outcome by 16% (HR, 0.84 [95% CI, 0.77-0.91]; *P* < .001).

Discussion

In this analysis of patients with HF with mildly reduced or preserved ejection fraction enrolled in the FINEARTS-HF trial, outpatient worsening HF events were common, associated with poor prognosis, and reduced by the nonsteroidal mineralocorticoid receptor antagonist finerenone. Outpatient oral diuretic intensification was common, occurring in 21% of patients. Despite the absence of central adjudication or requirement of symptoms or signs of worsening HF, oral diuretic intensification was associated with a rate of subsequent death that was at least double that of stable outpatients and similar to centrally adjudicated urgent HF visits requiring intravenous therapy. Finerenone decreased the risk of oral diuretic intensification alone and as part of an extended composite outcome including CV death and worsening HF events. These results support the use of outpatient oral diuretic intensification as an early marker of worsening HF and indicate that the benefit of finerenone in decreasing worsening

Figure 2. Effect of Finerenone on Outpatient Worsening Events Alone and Combined With the Primary Outcome



A, Cumulative incidence of outpatient oral diuretic intensification alone with finerenone vs placebo. B, Cumulative incidence of an extended primary composite outcome including cardiovascular (CV) death, heart failure (HF) hospitalization, urgent HF visit with intravenous therapy, or outpatient oral diuretic intensification. HR indicates hazard ratio.

HF events in patients with HF with mildly reduced or preserved ejection fraction extends to the outpatient setting.

Our findings are consistent with and extend previous work demonstrating that outpatient oral diuretic intensification events are common and associated with poor prognosis in patients with chronic HF. The Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial,[11] which enrolled a similar patient population with HF with mildly reduced or preserved ejection fraction, found a 2- to 3-fold greater risk of death after outpatient oral diuretic intensification compared with stable outpatients, which is consistent with the FINEARTS-HF trial. In the patients with HF with reduced ejection fraction, the relative increase in risk of death following outpatient oral diuretic intensification was at least as strong, approximately 3-fold in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial[10] and 4- to 5-fold in the Prospective Comparison of ARNI [angiotensin receptor neprilysin inhibitor] With ACEI [angiotensin-converting enzyme inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[7] Consistent findings across multiple trials and ejection fraction groups reinforce that outpatient oral diuretic intensification is an early marker of worsening HF with prognostic value.

The definition of outpatient oral diuretic intensification that best identifies worsening HF remains uncertain; our results support including loop diuretic initiations or dosage increases regardless of duration. The current standardized definition of outpatient worsening HF requires that the change in oral diuretic be either a sustained doubling of the loop diuretic dosage or initiation of combination diuretic therapy (most commonly with a thiazide), and it was designed to be used in conjunction with adjudication of HF symptoms and signs.[15] In our study, loop diuretic initiations or dosage increases were associated with greater risk of subsequent death compared with thiazide initiations. While adding a thiazide such as metolazone to a loop diuretic is an evidence-based strategy to treat diuretic resistance,[16] thiazide initiations in our study were driven by hydrochlorothiazide, which is commonly used to treat hypertension and may not represent worsening HF. Metolazone initiation was rare. Limiting the definition of oral diuretic intensification to loop diuretics, or loop diuretics and metolazone, may ensure specificity for worsening HF in the absence of central medical record review. A sensitivity analysis requiring diuretic intensification events to be sustained for at least 30 days showed similar results; this requirement did not clearly identify patients with higher risk for subsequent death.

Since outpatient oral diuretic intensification events are common and occur earlier than urgent HF visits or HF hospitalizations, their inclusion within clinical trial primary composite outcomes has the potential to decrease the sample size or duration of follow-up needed to complete an event-driven trial. Recent trials have included urgent HF visits with intravenous diuretic administration in primary composite outcomes to capture worsening HF regardless of location of care.[9,12,17-19] However, since urgent HF visits are rare, their impact on HF trials has been modest. Outpatient oral diuretic intensification events serve the same purpose and are associated with similar subsequent prognosis and decreases in self-reported health status,[11] but they could have much greater impact because they are greater than 10 times more common. Adding outpatient oral diuretic intensification to the primary composite outcome in the FINEARTS-HF trial increased the number of first events by 67%, from 1343 to 2238, suggesting the potential for the broader composite to decrease the sample size or duration of trials by at least one-third. Outpatient oral diuretic intensification events were modifiable by both dapagliflozin and finerenone.[11]

On the other hand, outpatient oral diuretic intensification is not as clinically meaningful an end point as HF hospitalization or death. Reductions in oral diuretic intensification with finerenone and sodium-glucose cotransporter 2 inhibitors may be perceived as reflecting diuretic effects rather than a true clinical benefit in reducing risk of worsening HF. The SUMMIT trial comparing tirzepatide with placebo in patients with HF with preserved ejection fraction included outpatient oral diuretic intensification in the primary composite end point but also required adjudicated symptoms and signs of worsening HF.[20] This approach may help to capture worsening HF events regardless of setting while maintaining specificity for clinically meaningful events. The potential value of centrally adjudicated outpatient worsening HF events must be weighed against the effort and cost required for adjudication.

Finally, our results provide further support that finerenone reduces worsening HF events in patients with HF with mildly reduced or preserved ejection fraction. The primary results of the FINEARTS-HF trial showed that finerenone reduced the prespecified primary outcome of cardiovascular death and total worsening HF events by 16%, with a similar reduction in first events. We now show that finerenone also reduced the clinically meaningful outcome of outpatient oral diuretic intensification by 11% and an extended composite including the primary outcome by 15%. These results indicate that the benefits of finerenone extend to reductions in outpatient worsening HF.

Limitations

Several limitations must be acknowledged. Outpatient oral diuretic intensification events were ascertained from concomitant medication data, without central adjudication or consideration of the participant's symptoms or signs of HF. Medication data may have been reported inaccurately or inconsistently by individual sites. We applied stringent criteria to identify outpatient oral diuretic intensification events only when medications were clearly reported, which may have led to underestimation of the number of events. As-needed dosing was not included in analysis of loop diuretic dosage increases. Increases in mineralocorticoid receptor antagonist therapy have been included in some definitions of outpatient oral diuretic intensification but were excluded from this study because the dosing of finerenone (a mineralocorticoid receptor antagonist) was protocol driven and continuous use of other mineralocorticoid receptor antagonists for longer than 14 days was prohibited.

Conclusions

In patients with HF with mildly reduced or preserved ejection fraction, outpatient oral diuretic intensification events were common and associated with elevated risk of subsequent death that was similar to adjudicated urgent HF visits requiring intravenous therapy. These results support the use of outpatient oral diuretic intensification as a clinically relevant, early marker of worsening HF. Finerenone decreased the risk of oral diuretic intensification alone and as part of an extended composite outcome including CV death, HF hospitalizations, and urgent HF visits. Reductions in worsening HF events with finerenone in patients with HF with mildly reduced or preserved ejection fraction appear to extend to the outpatient setting.

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Author Affiliations: Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Cunningham, Claggett, Vaduganathan, Desai, Solomon); Massachusetts General Hospital, Harvard Medical School, Boston (Chatur); University of Glasgow, Glasgow, Scotland, United Kingdom (Jhund, McMurray); Hospital Cardiológica Aguascalientes, Aguascalientes, Mexico (Llamas Esperón); National Heart Centre Singapore and Duke-National University of Singapore, Singapore (Lam); Kawaguchi Cardiovascular and Respiratory Hospital, Saitama, Japan (Sato); University of Milano-Bicocca ASST Papa Giovanni XXIII Hospital, Bergamo, Italy (Senni); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah); University of Groningen, Groningen, the Netherlands (Voors); University of Lorraine, Nancy, France (Zannad); University of Michigan, Ann Arbor (Pitt); Section of Cardiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada (Zieroth); Research and Development, Pharmaceuticals, Bayer, Berlin, Germany (Brinker, Rohwedder, Kim, Lay-Flurrie, Viswanathan).

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Concept and design: Cunningham, Chatur, Vaduganathan, Lam, Voors, Zannad, Kim, Lay-Flurrie, Solomon.
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Drafting of the manuscript: Cunningham.
Critical review of the manuscript for important intellectual content: Chatur, Claggett, Vaduganathan, Desai, Jhund, Llamas Esperón, Lam, Sato, Senni, Shah, Voors, Zannad, Pitt, Zieroth, Brinker, Rohwedder, Kim, Lay-Flurrie, Viswanathan, McMurray, Solomon.
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