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Characterization of the Progression from Ambulatory to Hospitalized Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome. Some patients develop elevated filling pressures exclusively during exercise and never require hospitalization, whereas others periodically develop congestion that requires inpatient treatment. The features differentiating these cohorts are unclear.

Methods: We performed a secondary analysis of 7 NIH sponsored multicenter trials of HFpEF (EF 50%, n=727). Patients were stratified by history of HF hospitalization, comparing patients never hospitalized (HFpEF_{NH}) to those with a prior hospitalization (HFpEF_{PH}). Currently hospitalized (HFpEF_{CH}) patients were included to fill the spectrum. Clinical characteristics, cardiac structure, biomarkers, quality of life (QOL), functional capacity, activity levels, and outcomes were compared.

Results: As expected, HFpEF_{CH} (n=338) displayed the greatest severity of congestion, as assessed by NTproBNP levels, edema, and orthopnea. As compared to HFpEF_{NH} (n=109), HFpEF_{PH} (n=280) displayed greater comorbidity burden with more lung disease, renal dysfunction and anemia, along with lower activity levels (accelerometry), poorer exercise capacity (6 minute walk distance and peak exercise capacity), and more orthopnea. Patients with current or prior hospitalization displayed higher rates of future HF hospitalization, but QOL was similarly impaired in all HFpEF patients, regardless of hospitalization history.

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Disclosures: None

Conclusions: A greater burden of non-cardiac organ dysfunction, sedentariness, functional impairment, and higher event rates distinguish patients with HFpEF and prior HF hospitalization from those never hospitalized. Despite lower event rates, quality of life is severely and similarly in patients with no history of hospitalization. These data suggest that the two clinical profiles of HFpEF may require different treatment strategies.

Trial Registration: RELAX trial clinicaltrials.gov Identifier: [NCT00763867](https://clinicaltrials.gov/ct2/show/study/NCT00763867);

NEAT trial clinicaltrials.gov Identifier: [NCT02053493](https://clinicaltrials.gov/ct2/show/study/NCT02053493);

INDIE trial clinicaltrials.gov Identifier: [NCT02742129](https://clinicaltrials.gov/ct2/show/study/NCT02742129);

DOSE trial clinicaltrials.gov Identifier: [NCT00577135](https://clinicaltrials.gov/ct2/show/study/NCT00577135);

CARRESS trial clinicaltrials.gov Identifier: [NCT00608491](https://clinicaltrials.gov/ct2/show/study/NCT00608491);

ROSE trial clinicaltrials.gov Identifier: [NCT01132846](https://clinicaltrials.gov/ct2/show/study/NCT01132846);

ATHENA trial clinicaltrials.gov Identifier: [NCT02235077](https://clinicaltrials.gov/ct2/show/study/NCT02235077).

Keywords

heart failure; HFpEF; quality of life; phenotyping; hospitalization

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) can be defined as a clinical syndrome characterized by symptoms of dyspnea and fatigue that are caused by an inability of the heart to pump blood to the body at a rate commensurate with its needs at rest and during exercise, or to do so only at the expense of high filling pressures.¹ Within this broad definition, there are subgroups of patients that may differ from one another in important ways.² Some experience severe, lifestyle-limiting symptoms related to elevated filling pressure during activity, but never present with congestion that is apparent at rest. Other patients intermittently develop volume retention requiring hospitalization. As compared to the former group, patients with prior hospitalization display greater morbidity and mortality,^{3–5} and may respond differentially to treatment,⁶ but it is unknown what differentiates patients with exercise-induced symptoms from those developing frank congestion that intermittently becomes apparent at rest, necessitating hospitalization.

Over the past decade, there have been 7 multicenter trials conducted within the NIH-sponsored HF Network that recruited patients with HFpEF in the inpatient and ambulatory settings.^{7–13} In this analysis including all patients with HFpEF participating in these trials, we performed a detailed comparison of clinical characteristics, comorbidity burden, cardiac structure and function, biomarkers, quality of life (QOL), functional capacity, activity levels, and outcomes, specifically comparing patients that had never been hospitalized, to those with prior hospitalization, and those with current hospitalization. We hypothesized that even in the compensated setting, patients with prior hospitalization would display greater non-cardiac organ dysfunction and poorer functional capacity as compared to patients with no prior history of HF hospitalization.

METHODS

Outpatient HFpEF trials

The RELAX, NEAT, and INDIE trials were multicenter, randomized placebo-controlled clinical trials conducted in ambulatory HFpEF patients testing sildenafil, isosorbide mononitrate and inhaled inorganic nitrite, respectively.^{7–9} These 3 trials included outpatients with HFpEF diagnosed either following a prior HF hospitalization, or with exercise intolerance and objective evidence of impaired cardiac reserve and high filling pressures. Common and rigorous entry criteria were required to verify the diagnosis of HFpEF in the trials, specifically New York Heart Association (NYHA) class II–IV HF symptoms, left ventricular (LV) ejection fraction (EF) $\geq 50\%$, and objective evidence of HF based upon prior hospitalization, invasive hemodynamics, elevated natriuretic peptide levels, or echocardiographic diastolic dysfunction together with chronic use of a loop diuretic. Participants in RELAX and INDIE were additionally required to display peak oxygen consumption (peak VO_2) at CPET of $\geq 60\%$ and $\geq 75\%$ predicted, respectively, with peak respiratory exchange ratio ≥ 1.0 . Detailed inclusion and exclusion criteria from these trials are included in Supplemental Table 1.

Prior to receipt of study drug, participants in these trials underwent baseline QOL assessment, echocardiography, NTproBNP measurement, cardiopulmonary exercise test (CPET) to assess maximal aerobic capacity (in RELAX and INDIE), 6 minute walk test to assess submaximal exercise performance (in RELAX and NEAT), and accelerometry to quantify the volume of daily activity (in NEAT and INDIE) (details of evaluation of HF severity in supplemental appendix).^{7–9} The current study reports baseline data obtained from these studies, prior to receipt of study medications.

Inpatient HFpEF trials

The DOSE, CARRESS, ROSE and ATHENA trials were multicenter randomized trials conducted in HF patients hospitalized with volume overload (regardless of EF), testing inpatient strategies of continuous/bolus diuretic infusions, ultrafiltration, dopamine/nesiritide and spironolactone (Supplemental Table 2).^{10–13} The current analysis reports baseline data from these studies, prior to receipt of study medications and only includes the subset of patients with HFpEF (EF $\geq 50\%$).

Subject Groups

The primary analysis centers on the comparison of patients from RELAX, INDIE and NEAT trials, stratified as having a prior HF hospitalization (HFpEF_{PH}), or HFpEF with dyspnea on exertion but no prior HF hospitalization (HFpEF_{NH}). To expand the spectrum of analysis to those currently hospitalized (HFpEF_{CH}), we also included subjects enrolled in the acute hospitalization trials DOSE, CARRESS, ROSE and ATHENA. Because the HFpEF_{CH} group did not prospectively undergo the same assessments, and because the hospitalization itself is expected to influence a number of the findings directly, sensitivity analyses with and without this group were performed. Some patients participated in more than one trial. To maintain the assumption of independence, we kept the earliest study enrollment data for these patients and removed them from the study samples from later trials.

Statistical Analysis

Categorical and continuous variables were compared by the Chi square or Fisher's exact test and the *t*-test or Kruskal-Wallis test respectively. We used multivariable generalized linear regression models to assess the association between HF hospitalization history and each outcome variable, adjusted for random effect of clinical trial, age, sex and self-reported white race. For consistent interpretation of the clinical trial effect, pairwise comparisons were estimated using the corresponding contrasts from models with all three hospitalization groups.

We used a multivariable Cox proportional hazards regression model to assess the association between study group and time to HF hospitalization or death. The multivariable Cox model adjusted for clinical trial, age, sex and self-reported white race. The proportional hazards assumption was assessed and found to be valid. Additional details of analytical methods are included in the supplemental appendix.

RESULTS

Study population

Including all 7 studies, there was a total of 1647 patients. Of this, 895 patients with an EF<50% or missing EF data were excluded. In addition, 25 duplicate patients that had been enrolled in more than one study were included only as part of the first study in which they participated (Supplemental Table 3). This results in the final study sample of 727 patients enrolled from the ATHENA (N=88), CARRESS (N=59), DOSE (N=81), ROSE (N=110), INDIE (N=91), NEAT (N=99), and RELAX (N=199) clinical trials.

From these 727 patients, there were 280 who had never been hospitalized for HF (HFpEF_{NH}), 109 ambulatory patients with prior HF hospitalization (HFpEF_{PH}) and 338 patients recruited while currently hospitalized with HF (HFpEF_{CH}).

Hospitalized vs Ambulatory HFpEF

HFpEF_{CH} patients were older, more likely to be non-white, and more likely to be men ($p<0.001$ for all). Therefore, all subsequent analyses were adjusted for age, sex and race, and trial in which they participated (Table 1, Supplemental Table 4). As expected based upon the fact that this group was actively decompensated at the time of evaluation, the HFpEF_{CH} group displayed the highest NTproBNP levels, and more dramatic clinical evidence of congestion, including greater prevalence of rales, orthopnea, S3 gallop, and edema. HFpEF_{CH} patients had the lowest EF, along with higher prevalence of prior myocardial infarction, worse renal function and physical examination evidence of more severe right-sided heart failure (ascites, hepatomegaly, and jugular venous distension; Supplemental Table 4). Notably there was a higher burden of atrial fibrillation in HFpEF_{CH}. Comorbidity burden was greatest among HFpEF_{CH} patients, with higher prevalence of chronic obstructive pulmonary disease, diabetes, kidney disease, anemia, prior stroke and pacemaker implantation (Figure 1, Table 1, Supplemental Table 4).

Impact of Prior Hospitalization among Ambulatory HFpEF

Because there are important differences in the degree of congestion, as well as end-organ function, that are specifically related to the decompensated state itself (either as cause or consequence), additional analyses focused on comparisons between patients who were not evaluated at the time of hospitalization based upon the absence or presence of prior hospitalization (i.e. HFpEF_{NH} and HFpEF_{PH}).

The principle differences between ambulatory HFpEF_{NH} and HFpEF_{PH} patients was the presence of greater non-cardiac comorbidity burden, with more impaired renal function in HFpEF_{PH} (higher cystatin C, lower estimated glomerular filtration rate), more anemia, lower hemoglobin, greater prevalence of chronic lung disease, and higher loop diuretic requirement (Table 2). Despite worse renal function and a significantly higher prevalence of orthopnea in the HFpEF_{PH} group, there was no difference in clinical signs of volume overload/right heart failure (edema, JVP elevation, ascites), or in NTproBNP levels. There were no significant differences in age, sex, ethnicity, vital signs, body mass index or NYHA functional class. Similar to differences observed when including HFpEF_{CH} patients, there was a trend for greater prevalence of atrial fibrillation and diabetes in HFpEF_{PH} (Table 2).

Activity Levels, Functional Capacity, and Quality of Life

Peak oxygen consumption (peak VO₂), submaximal exercise performance (6 minute walk distance) and daily activity levels (average daily accelerometry units) were all impaired to a greater extent in HFpEF_{PH} compared to HFpEF_{NH} (Table 3, Figure 2). Despite these differences, quality of life was similarly impaired in HFpEF_{PH} and HFpEF_{NH}.

Cardiac Structure and Function

In contrast to measures of functional capacity, cardiac structure and function measured by echocardiography at rest was similar in ambulatory patients with and without prior hospitalization (Table 3). Specifically, LVEF was numerically identical in HFpEF_{PH} and HFpEF_{NH}, and the two groups displayed similar magnitude of left atrial enlargement, impairment in diastolic relaxation, elevation in filling pressures estimated by the E/e' ratio, and similar elevation in estimated pulmonary artery pressure.

Outcomes

As expected, outcomes were markedly worse in HFpEF_{CH} compared to the other groups (Supplemental Table 5). However, even after excluding these patients and considering only ambulatory patients with HFpEF, the 160 day cumulative incidence of HF hospitalization or death was more than 4-fold higher in HFpEF_{PH} compared to HFpEF_{NH} (Figure 3). This higher risk remained significant after adjustment for clinical trial and demographics (Table 4).

DISCUSSION

This analysis of 727 rigorously phenotyped patients with HFpEF reveals a graded increase in multisystem organ dysfunction across the spectrum of patients ranging from those never hospitalized to previously and actively hospitalized for congestion. As compared to HFpEF

patients that never been hospitalized, patients with HFpEF and a history of hospitalization displayed worse renal function, and greater prevalences of anemia and chronic lung disease, indicating poorer non-cardiac organ system reserve, but cardiac function was similar. Patients with prior HF hospitalization were more sedentary, with reduced activity levels and more severely impaired submaximal and peak exercise capacity. Similar to prior studies, event rates for HF hospitalization or death were significantly increased in patients with prior hospitalization, but despite these previously documented differences in clinical outcomes, disease severity assessed by functional class and patient reported QOL were similarly depressed in patients with or without prior HF hospitalization. These data provide important new insights into the factors that distinguish between, or may promote progression from, a phenotype of predominant exercise-induced symptoms to frank congestion, emphasizing the importance of dysfunction in non-cardiac organ systems including the kidneys, lungs, and skeletal muscle that coexist with cardiac dysfunction in HFpEF to increase risk of HF hospitalization (Figure 4). While event rates are lower in non-hospitalized patients, QOL is equally and severely impaired in this cohort, suggesting that therapies to reduce hospitalization alone may not be sufficient to improve clinical status in patients that do not require inpatient treatment.

Fluid retention, renal dysfunction and HF hospitalization in HFpEF

Hospitalization for volume overload is a watershed moment in the natural history of HFpEF that is associated with an increased risk of subsequent rehospitalization and adverse outcomes.^{3, 4, 14} It has been hypothesized that comorbidity driven intrinsic renal dysfunction may be a major driver to the tendency towards fluid retention in HF, including HFpEF.^{15–22} However, direct evidence for this hypothesis has been lacking and it remains unclear what causes the fluid retention that leads to a HF hospitalization in HFpEF. Quantifying renal reserve in HF patients is complex in the setting of volume overload, given the reversible impairment in renal function that often accompanies congestion.^{23, 24}

In the current study, renal function was most severely impaired in the currently hospitalized HFpEF cohort, possibly explained in part by acute perturbations related to decompensation. But even when evaluated in the stable, compensated setting, patients with HFpEF and prior HF hospitalization displayed poorer renal function and higher diuretic requirements than those never hospitalized, suggesting a central role for kidney dysfunction in the tendency to salt and fluid retention and volume overload in these patients. The increased diuretic requirements in the prior hospitalized group suggest a greater tendency to sodium retention that may be additive with the differences in glomerular filtration rate observed. The higher prevalence of atrial fibrillation may also suggest a role for left atrial dysfunction and atrial dysrhythmia in the transition to the volume overloaded decompensated HF state in HFpEF.²⁵

Impact of Anemia

Anemia may contribute to peripheral vasodilation, renal hypoperfusion and fluid retention leading to decompensation, and worsening anemia is a known precipitant of HF hospitalization regardless of ejection fraction.^{15, 26} Like renal function, anemia was greatest in currently hospitalized patients. While this may be explained in part by hemodilution, the prevalence of anemia was greater even among apparently compensated ambulatory patients

with prior hospitalization as compared to no hospitalization, supporting a role in promoting disease progression. This finding is also notable since sodium glucose co-transporter-2 inhibitors have been shown to decrease HF hospitalization in patients at risk for HFpEF,²⁷ an effect which appears to be at least in part mediated by increases in hematocrit,²⁸ which are driven not only by diuretic hemoconcentration, but also by an independent increase in erythropoietin and red cell mass.²⁹ These drugs therefore may be of particular interest in patients with HFpEF who have been previously hospitalized with HF particularly in the setting of anemia.

Pulmonary Disease and HF hospitalization in HFpEF

Chronic lung disease was over two-fold more common in HFpEF patients with prior HF hospitalization. There is increasing recognition of pulmonary reserve limitations in HFpEF,^{30, 31} and superimposed COPD has been associated with a greater impact on outcomes in HFpEF compared to HFrEF, suggesting a syndrome-specific interaction.³² Loss of intrinsic lung reserve from COPD, or potentially, impairments in pulmonary function caused by HF that may be confused with COPD, may compromise tolerance to elevated left sided filling pressures and lung congestion to heighten ventilatory drive and inefficiency.³¹ This could then lead to more exaggerated symptoms for any degree of hemodynamic perturbation, lowering the threshold to admit patients for inpatient management of HF symptoms.

Role of Functional Impairment and Inactivity

HFpEF patients with prior HF hospitalization also displayed greater sedentariness and functional impairments (both submaximal and peak exercise capacity). Sedentariness is associated with systemic inflammation^{33, 34} and accelerated cellular aging^{35, 36} and may contribute to the greater multisystem non-cardiac dysfunction we observed in HFpEF patients prone to HF hospitalization. Decreased physical activity levels in HFpEF have been associated with incident HF hospitalization, supporting a potential causal role.³⁷ In addition to greater functional impairments prevalent in elderly or obese HFpEF patients, sedentariness reduces resiliency and reserve to deal with multiple physiological stressors that could potentially trigger decompensation,³⁸ including non-HF related hospitalizations. However, reverse causation remains another plausible explanation for impaired functional reserve and activity and the results of ongoing randomized trials are eagerly awaited.^{39, 40}

Relationship of Hospitalization with Outcomes

The current data confirm and extend upon secondary analyses from published trials that revealed greater risk for repeat HF hospitalization amongst patients with prior hospitalization.³⁻⁶ However, there are relevant differences between the HF network trials included in this study and these earlier trials in that patients in the previous trials were required to either demonstrate either prior HF-hospitalization, overt congestion or else other indicators such as elevated natriuretic peptide levels which indirectly excludes many patients with obesity related HFpEF. In the HF Network trials, patients with natriuretic peptides below the threshold typically used to diagnose HF and no prior HF hospitalization were included, provided that definitive hemodynamic evidence of HFpEF had been documented.⁷⁻⁹ Despite these differences in entry criteria, the findings in regards to outcomes are in agreement with prior studies in regards to outcome.³⁻⁶ A review of prior clinical trials of

HFpEF reveals marked heterogeneity in included patients when stratified by prior HF hospitalization status, and many trials do not report the results stratified by this phenotype (Supplemental Table 6).

HFpEF Patients That are Never Hospitalized

A substantial proportion of HFpEF patients present with symptoms of exercise intolerance associated with limited cardiac reserve during stress with elevated filling pressures with exertion.¹ Estimates from community based studies suggest that this subtype of HFpEF without hospitalization (sometimes termed ACC/AHA stage C1) may be even more common than patients with prior hospitalization (stage C2).⁴¹ In the largest HFpEF trial to date (PARAGON-HF), approximately half of the included patients had no prior HF hospitalization.^{6, 42}

The current study provides the first robust multicenter functional and phenotypic characterization of these relatively distinct subsets of clinical HFpEF. Functional capacity was better in the HFpEF_{NH} cohort compared to HFpEF_{PH}, but this group still displayed substantial and clinically relevant impairments in exercise performance. Importantly, despite the 4-fold lower risk of HF hospitalization observed in the HFpEF_{NH} group, NYHA functional class and quality of life were similarly impaired. There may be temptation to conclude that new treatments are not a high priority for this cohort of patients with low rates of “hard events”, but the current findings including similar reductions in quality of life and severe functional impairment emphasize the massive public health importance for identifying effective treatments for this large cohort of patients with HFpEF that do not require hospitalization.

Limitations

This was a secondary analysis of completed randomized clinical trials and is therefore prone to type 1 error. Given the exploratory nature of the analyses, no correction was made for multiple hypothesis testing. Due to differing end points and assessments as performed in the 7 included trials, not all variables are available in all patients studied. Although these data support cross sectional differences in these two clinical profiles of HFpEF, we cannot address the natural history or potential transition from one form to the other. It remains unknown whether these two groups of HFpEF patients represent the same disease process at different stages of disease, or fundamentally different clinical phenotypes. Future longitudinal cohort studies are indicated to answer these important questions. Formal quantification of the degree of valvular regurgitation was not performed and requires further study.

Conclusions

Compared to ambulatory HFpEF patients with exercise intolerance but no prior HF hospitalization, HFpEF patients with a history of HF hospitalization display a greater comorbidity burden with worse renal function, COPD and anemia along with higher event rates and worse functional capacity. Despite these differences, QOL was similarly impaired in ambulatory HFpEF patients with no prior HF hospitalization, with better but still severely depressed functional capacity. These data suggest that these two clinical profiles of HFpEF

may require different treatment strategies. Therapies optimizing non-cardiac organ function hold promise together with cardiac-specific interventions to prevent HF hospitalizations in HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HFpEF	Heart Failure with preserved Ejection Fraction
HF	Heart Failure
HFpEF_{PH}	HFpEF with prior HF hospitalization
HFpEF_{NH}	HFpEF never hospitalization for HF
HFpEF_{CH}	HFpEF currently hospitalized

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Figure 1 - Comorbidity burden across HFpEF phenotypes

Increasing comorbidity burden across HFpEF hospitalization phenotypes (NH- Never hospitalized, PH-Prior hospitalized, CH-Current hospitalized)

Figure 2 - Functional status and Exercise capacity in ambulatory HFpEF phenotypes stratified by hospitalization status

Worse exercise capacity, activity levels and 6 minute walk distance in ambulatory HFpEF patients with prior hospitalization

Figure 3- Risk of HF hospitalization stratified by HF hospitalization phenotype
Increasing risk of HF hospitalization and death with prior or current hospitalization for HFpEF, compared to ambulatory HFpEF patients that had never been hospitalized

Figure 4- Possible interplay between ambulatory and hospitalized HFpEF

Transition from ambulatory HFpEF with dyspnea on exertion to hospitalized HFpEF is associated with increasing comorbidity burden with greater renal dysfunction, anemia and lung disease, along with inactivity and decreased functional capacity. Despite differences in HF hospitalization risk, quality of life was equally impaired in both groups.

Table 1:**Patient Characteristics by HF Hospitalization History**

	HFpEF_{pH+CH} (Ever hospitalized) (N=447)	HFpEF_{NH} (Never hospitalized) (N=280)	p value[*]
Demographics and Biomarkers			
Age, years	72 (62, 80)	69 (62, 76)	0.006
White race: n (%)	359 (80%)	254 (91%)	<0.001
Female sex: n (%)	188 (42%)	153 (55%)	<0.001
Body mass index, kg/m ²	34 (28, 41)	34 (29, 39)	0.055
Ejection fraction, %	58 (55, 64)	61 (56, 66)	0.003
Creatinine, mg/dL	1.5 (1.1, 1.9)	1.1 (0.9, 1.4)	0.019
Cystatin C, mg/L [N]	1.8 (1.4, 2.2) [330]	1.2 (1.0, 1.6) [199]	0.002
eGFR, mL/min/1.73m ²	47 (36, 60)	62 (48, 79)	0.008
NT-proBNP, pg/mL	2323 (917, 4566)	380 (104, 982)	<0.001
Hemoglobin, g/dL [N]	11.3 (10.0, 12.9) [355]	13.1 (12.2, 14.1) [280]	<0.001
Symptoms; Physical Exam			
NYHA functional class III/IV: n/N (%)	344 / 420 (82%)	150 / 280 (54%)	<0.001
Orthopnea: n/N (%)	279 / 338 (82%)	134 / 268 (50%)	<0.001
Systolic blood pressure, mmHg	122 (112, 138)	126 (118, 138)	0.075
Diastolic blood pressure, mmHg	65 (58, 74)	70 (64, 80)	<0.001
Heart rate, bpm	72 (64, 81)	68 (62, 78)	<0.001
Rales present: n (%)	206 (46%)	7 (2%)	<0.001
Ascites: n/N (%)	64 / 342 (19%)	0 / 279 (0%)	-
Hepatomegaly: n/N (%)	53 / 330 (16%)	4 / 276 (1%)	<0.001
Jugular venous pressure elevation: n/N (%)	270 / 344 (79%)	104 / 274 (38%)	<0.001
Peripheral edema present: n/N (%)	300 / 357 (84%)	163 / 280 (58%)	<0.001
S3 auscultation: n/N (%)	35 / 353 (10%)	8 / 279 (3%)	0.050
Medical History/Comorbidities			
Atrial fibrillation/flutter: n (%)	269 (60%)	122 (44%)	0.002
Chronic kidney disease stage 3/4: n (%)	334 (75%)	131 (47%)	0.006
COPD: n (%)	133 (30%)	35 (13%)	<.001
Diabetes: n (%)	230 (52%)	99 (35%)	0.006
Hypertension: n (%)	395 (88%)	235 (84%)	0.35
Prior Myocardial infarction: n (%)	84 (19%)	29 (10%)	0.015
Prior Stroke: n (%)	56 (13%)	15 (5%)	0.007
Anemia: n/N (%)	246 / 106 (69%)	82 / 280 (29%)	<0.001
Medications			
ACE inhibitor/ARB: n/N (%)	226 / 446 (50.7%)	177 / 280 (63.2%)	0.009
Aldosterone antagonist: n/N (%)	79 / 446 (17.7%)	54 / 280 (19.3%)	0.72
Beta-blocker: n/N (%)	333 / 446 (74.7%)	191 / 280 (68.2%)	0.32
Calcium channel blocker: n/N (%)	140 / 446 (31.4%)	93 / 280 (33.2%)	0.18
Digoxin: n/N (%)	48 / 446 (10.8%)	18 / 280 (6.4%)	0.22

* Adjusted for age, sex, self-reported white race, and random effect of clinical trial

Abbreviations: HFpEF_{NH} -HFpEF Never hospitalization, HFpEF_{PH} -HFpEF prior hospitalized, HFpEF_{CH} -HFpEF currently hospitalized, Q1 = 1st quartile; Q3 = 3rd quartile; eGFR = estimated glomerular filtration rate (MDRD formula); NT-proBNP = N-terminal prohormone of brain natriuretic peptide; oxygen saturation;

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Table 2:

Comorbidity burden and markers of congestion in Ambulatory HFpEF stratified by prior HF hospitalization status

	HFpEF _{PH} (N=109)	HFpEF _{NH} (N=280)	p value [*]
Age, years	67 (59, 74)	69 (62, 76)	0.13
White race: n (%)	93 (85%)	254 (91%)	0.17
Female sex: n (%)	49 (45%)	153 (55%)	0.08
Laboratory Results			
BUN, mg/dL [N]	25 (19, 35) [101]	21 (16, 28) [249]	0.27
Creatinine, mg/dL	1.2 (1.0, 1.6)	1.1 (0.9, 1.4)	0.09
Cystatin C, mg/L [N]	1.4 (1.1, 1.8) [88]	1.2 (1.0, 1.6) [199]	0.007
eGFR, mL/min/1.73m ²	57 (42, 70)	62 (48, 79)	0.008
NT-proBNP, pg/mL	486 (180, 1256)	380 (104, 982)	0.79
Potassium, mEq/L [N]	4.3 (3.9, 4.7) [103]	4.3 (4.0, 4.7) [263]	0.87
Sodium, mEq/L [N]	139 (137, 141) [103]	140 (139, 142) [262]	0.13
Hemoglobin, g/dL [N]	12.9 (11.8, 13.9) [106]	13.1 (12.2, 14.1) [280]	0.048
cGMP, pmol/L	95 (68, 135)	112 (73, 165)	0.76
Comorbidities			
Atrial fibrillation/flutter: n (%)	56 (51%)	122 (44%)	0.07
Chronic obstructive pulmonary disease: n (%)	28 (26%)	35 (13%)	0.003
Depression: n (%)	30 (28%)	81 (29%)	0.85
Diabetes: n (%)	53 (49%)	99 (35%)	0.08
Hypertension: n (%)	97 (89%)	235 (84%)	0.22
Anemia: n/N (%)	44 / 106 (42%)	82 / 280 (29%)	0.03
Loop diuretic (furosemide equivalent): n (%)	93 (85%)	190 (68%)	0.001
Pacemaker: n (%)	14 (13%)	30 (11%)	0.38
Physical Exam/Symptoms/Vital Signs			
Body mass index, kg/m ²	35 (28, 42)	34 (29, 39)	0.30
Systolic blood pressure, mmHg	128 (114, 140)	126 (118, 138)	0.59
Diastolic blood pressure, mmHg	70 (62, 78)	70 (64, 80)	0.41
Heart rate, bpm	70 (62, 78)	68 (62, 78)	0.88
NYHA functional class III/IV: n/N (%)	53 / 109 (49%)	150 / 280 (54%)	0.35
Jugular venous pressure elevation: n/N (%)	44 / 106 (42%)	104 / 274 (38%)	0.54
Orthopnea: n/N (%)	69 / 105 (66%)	134 / 268 (50%)	0.017
Peripheral edema: n/N (%)	62 / 109 (57%)	163 / 280 (58%)	0.86
Medications			
ACE inhibitor/ARB: n/N (%)	72 / 109 (66.1%)	177 / 280 (63.2%)	0.77
Aldosterone antagonist: n/N (%)	21 / 109 (19.3%)	54 / 280 (19.3%)	0.57
Beta-blocker: n/N (%)	86 / 109 (78.9%)	191 / 280 (68.2%)	0.045
Calcium channel blocker: n/N (%)	28 / 109 (25.7%)	93 / 280 (33.2%)	0.10
Digoxin: n/N (%)	8 / 109 (7.3%)	18 / 280 (6.4%)	0.96

* Adjusted for age, sex, self-reported white race, and random effect of clinical trial

Table 3:

Cardiac structure, functional reserve and quality of life in Ambulatory HFpEF stratified by prior HF hospitalization status

	HFpEF _{PH} (N=109)	HFpEF _{NH} (N=280)	p value*
Echocardiographic Structure/Function			
Ejection fraction, %	61 (57, 66)	61 (56, 66)	0.92
Left atrial volume index, cc/m ² [N]	42 (33, 55) [57]	41 (31, 54) [161]	0.86
Left ventricular diastolic dimension, cm [N]	4.7 (4.3, 5.2) [72]	4.6 (4.3, 5.1) [176]	0.86
Left ventricular mass index, g/m ² [N]	85 (64, 107) [69]	73 (62, 91) [173]	0.12
Medial e', m/s [N]	0.06 (0.04, 0.08) [81]	0.06 (0.05, 0.08) [197]	0.72
Medial E/e' ratio [N]	15 (12, 25) [79]	14 (10, 20) [190]	0.25
PASP, mmHg [N]	39 (34, 51) [44]	38 (31, 48) [124]	0.39
Exercise Capacity/Accelerometry			
Activity from 7 am to 9 pm, AAU [N]	4510 (3396, 6368) [31]	5382 (3834, 8333) [141]	0.026
Peak VO ₂ , mL/min/kg [N]	12 (10, 14) [89]	13 (11, 16) [200]	0.004
6-minute walk distance, m [N]	279 (212, 362) [88]	332 (261, 396) [209]	0.003
Quality of Life			
KCCQ overall summary score: median (Q1, Q3) [N]	54 (40, 73) [40]	54 (41, 72) [150]	0.75
KCCQ physical limitation score: median (Q1, Q3) [N]	58 (44, 84) [40]	58 (42, 75) [150]	0.54
KCCQ total symptom score: median (Q1, Q3) [N]	55 (33, 80) [40]	55 (45, 74) [150]	0.77
KCCQ quality of life score: median (Q1, Q3) [N]	50 (33, 67) [40]	50 (33, 75) [149]	0.94
KCCQ social limitation score: median (Q1, Q3) [N]	59 (31, 75) [40]	58 (35, 83) [148]	0.88
MLHFQ total score: median (Q1, Q3) [N]	44 (25, 63) [83]	43 (29, 62) [192]	0.91

* Adjusted for age, sex, self-reported white race, and random effect of clinical trial

Abbreviations: AAU = arbitrary accelerometer units BUN = blood urea nitrogen; cGMP = cyclic guanosine monophosphate; CPET = cardiopulmonary exercise test; eGFR = estimated glomerular filtration rate (MDRD formula); KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PASP = pulmonary artery systolic pressure; VO₂ = oxygen consumption volume.

Table 4:

Association of HF Hospitalization History (Previously Hospitalized vs. Never Hospitalized) with Time to HF Hospitalization or Death – Ambulatory Groups

HFpEF_{PH} vs HFpEF_{NH}						
Outcome	160-Day Cumulative Incidence (95% CI)^[1]		Unadjusted^[2]		Adjusted^[3]	
	Never Hosp.	Previously Hosp.	Hazard Ratio (95% CI)^[4]	P-value	Hazard Ratio (95% CI)^[4]	P-value
HF Hospitalization or Death	0.05 (0.02, 0.09)	0.17 (0.11, 0.27)	4.2 (1.9, 9.4)	<.001	3.4 (1.5, 7.7)	0.003
Death ^[5]	0.02 (0.00, 0.05)	0.00 (0.00, 0.00)	-	-	-	-
HF Hospitalization	0.03 (0.01, 0.07)	0.17 (0.11, 0.27)	6.1 (2.5, 4.8)	<.001	4.8 (1.9, 11.9)	<.001

Abbreviations: CI = confidence interval.

^[1] Kaplan-Meier estimate.

^[2] Stratified by clinical trial.

^[3] Adjusted for age, gender, and self-reported white race, and stratified by clinical trial.

^[4] Estimated ratio in the hazard rate of the outcome occurring for previously hospitalized vs. never hospitalized

^[5] No previously hospitalized patients died during the study, so confidence intervals and p-values were not computed.