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ORIGINAL RESEARCH

Characteristics and Outcomes of Patients With Heart Failure With Reduced Ejection Fraction After a Recent Worsening Heart Failure Event

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BACKGROUND: Contemporary trials of patients with heart failure with reduced ejection fraction (HFrEF) required a recent worsening heart failure (WHF) event for inclusion. We aimed to describe characteristics and outcomes of patients with HFrEF and a recent WHF event at a large tertiary referral center.

METHODS AND RESULTS: We identified adult patients with chronic symptomatic HFrEF (ejection fraction ≤35%) treated at Duke University between January 1, 2009, and December 31, 2018, and applied a set of exclusion criteria to generate a cohort similar to those enrolled in contemporary heart failure trials. Patients were stratified by presence or absence of a recent WHF event, defined as an emergency department visit for heart failure or hospitalization for heart failure in the prior 12 months. Characteristics and outcomes including death and hospitalization were assessed. Of 3867 patients with HFrEF meeting study criteria, 2823 (73.0%) had a WHF event in the prior 12 months. Compared with patients without a WHF event, those with a WHF event were more likely to be under-represented racial and ethnic groups and had lower ejection fraction, a greater burden of comorbidities, and more echocardiographic evidence of cardiac dysfunction. Despite higher use of guideline-directed therapies, patients with a WHF event had higher rates of death (hazard ratio, 2.30; 95% CI, 2.01–2.63), all-cause hospitalization (hazard ratio, 1.56; 95% CI, 1.42–1.71), and heart failure hospitalization (hazard ratio, 1.59; 95% CI, 1.44–1.75) through 5 years compared with those without a recent WHF event.

CONCLUSIONS: WHF events are common in patients with HFrEF and are associated with more advanced disease. Patients with recent WHF have high rates of death and hospitalization, underscoring the need for novel therapies in this large subgroup of patients with HFrEF.

Key Words: heart failure hospitalization ■ heart failure with reduced ejection fraction ■ worsening heart failure event

Heart failure with reduced ejection fraction (HFrEF) is common and is associated with considerable morbidity and mortality.[1] Episodic worsening of symptoms leading to urgent clinic appointments, emergency department (ED) encounters, or hospitalization is widely recognized to be associated with more advanced disease, poor prognosis, and an increase in future resource usage.[2,3] Patients with HFrEF and worsening heart failure (WHF) events have been the focus of several recent clinical trials of new therapeutic agents because of the high rates of subsequent clinical events in this population.[4,5] The exact definition of a WHF event varies slightly between trials, though is generally defined as a patient having signs or symptoms of acute HF requiring escalation of therapy in the outpatient, ED, or inpatient setting.[4,5] We aimed to

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CLINICAL PERSPECTIVE

What Is New?

- Among a diverse population of patients with heart failure with reduced ejection fraction, worsening heart failure events are common, are associated with a higher burden of comorbidities, and are associated with poor outcomes, including high rates of hospitalization and death.

What Are the Clinical Implications?

- Patients with heart failure with reduced ejection fraction and recent worsening heart failure events represent an important, high-risk group that may be of particular interest in the development and implementation of new heart failure therapies.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor neprilysin inhibitor
DUHS	Duke University Health System
HFrEF	heart failure with reduced ejection fraction
WHF	worsening heart failure

assess the prevalence, characteristics, and outcomes of patients with HFrEF and a recent WHF event using data from Duke University Health System (DUHS).

METHODS

Data Sources

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data sources for our analysis included the DUHS electronic health record (EHR) and the Duke Echocardiography Laboratory Database. Data from the DUHS EHR were obtained in May 2020 using a clinical research query tool to search current and legacy EHR systems. Duke Echocardiography Laboratory Database is an internally curated database that includes an array of echocardiographic data elements from all patients who have undergone echocardiography at Duke University Hospital and clinics since 1995. Data from both inpatient and outpatient examinations are collected and stored. Linkage between DUHS EHR and Duke Echocardiography Laboratory Database was achieved by medical record number. Follow-up data were ascertained through December 31, 2019. Hospitalization events were obtained from DUHS EHR data. Death data were obtained using deaths recorded in the DUHS EHR, which included deaths recorded as part of healthcare delivery, deaths reported in the Social Security Administration Death Master File provided through the National Technical Information Service, and from North Carolina death certificates. Duke University institutional review board approval was obtained and consent was waived before the conduct of study activities.

Population

This study was intended to focus on patients with HFrEF, and we therefore used echocardiographic data to derive the cohort. We first derived an "overall HFrEF cohort" by identifying all echocardiograms performed within the DUHS between January 1, 2009, and December 31, 2018. We then identified (1) adult patients (aged >18 but ≤85 years at the time of index echocardiogram) with (2) a left ventricular ejection fraction (LVEF) ≤35%, and (3) 2 separate encounters with a heart failure (HF) *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis code within 18 months before the index echocardiogram (in order to include only patients with chronic symptomatic HFrEF) (Figure 1). A full list of HF diagnosis codes can be found in Table S1.

We excluded patients with (1) estimated glomerular filtration rate <20 mL/min per 1.73 m^2 (based on closest estimated glomerular filtration rate within 18 months before index echocardiogram) or no estimated glomerular filtration rate measured, (2) history of heart transplantation, (3) history of durable ventricular assist device, and (4) patients with EHR inconsistencies (such as date of death before date of echocardiogram).

Patients from the overall HFrEF cohort were then stratified by presence or absence of a recent WHF event. A recent WHF event was defined as either an ED visit or a hospitalization with an *ICD-9* or *ICD-10* diagnosis code consistent with heart failure within 1 year before the index echocardiogram (Table S1). For the primary analysis we included any HF diagnosis associated with the ED visit or hospitalization, whether coded as primary or secondary and whether coded on admission or discharge. As a sensitivity analysis, we restricted the definition of the WHF event to include only primary discharge HF diagnosis codes.

Data Elements and Statistical Analysis

Baseline was defined as the date of index echocardiogram. Variables extracted from the EHR included demographics, comorbidities, vital signs, encounters, diagnosis codes, laboratory data, cardiovascular medications, echocardiographic measurements, and clinical outcome events (death, hospitalization, HF hospitalization). *ICD-9* and *ICD-10* codes for cardiovascular

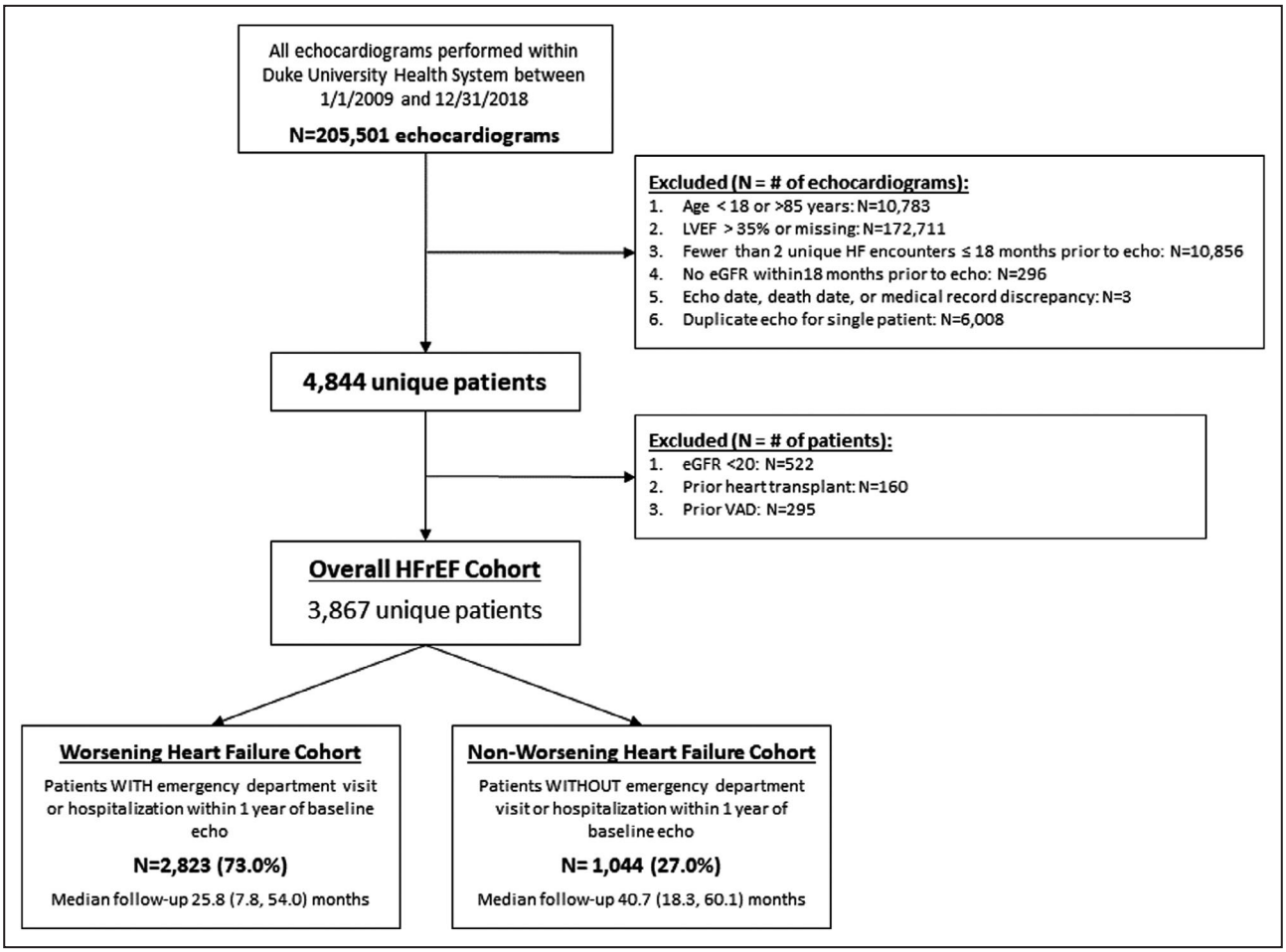

Figure 1. Consolidated Standards of Reporting Trials diagram showing derivation of study population.
eGFR indicates estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

comorbidities are listed in Table S1. *ICD-9* and *ICD-10* codes for additional Charlson and Elixhauser medical comorbidities were derived from a standardized coding algorithm.[6] Baseline comorbidities and medical history were defined based on presence of relevant diagnosis and procedure codes on or within 5 years before the index date. Vital signs were based on the closest measurement on or within 1 year before the index date. Medication use was based on the presence of a relevant prescription order in the EHR on or within 1 year before the index date. Laboratory measures were based on the closest measurement on or within 18 months before the index date.

Baseline characteristics were described for the overall HF cohort and stratified by recent WHF event status. Continuous variables were expressed as median (25th, 75th) and differences between groups were assessed using Wilcoxon rank-sum testing. Categorical variables were expressed as n (%), and differences between groups were assessed using the Pearson chi-square test or Fisher's exact test, as appropriate. For data elements where data were not available for all patients, the number of patients for whom data were available is presented next to the appropriate field.

Outcomes assessed included all-cause death, all-cause hospitalization, HF hospitalization, composite all-cause death or all-cause hospitalization, and composite all-cause death or HF hospitalization. Five-year cumulative incidence curves for first event were estimated using the Kaplan-Meier method for mortality and the composite end point, and the cumulative incidence function for hospitalization end points accounting for death as a competing risk. Cumulative incidence rates with 95% CIs were calculated at 1, 3, and 5 years after index echocardiogram for all-cause death and additionally at 1 month after index echocardiogram for all-cause hospitalization and HF hospitalization. Unadjusted Cox proportional hazards models were used to generate cause-specific hazard ratios (HRs) with 95% CIs and *P* values comparing the 5-year hazard for each outcome by WHF event status. An unadjusted negative binomial regression model using a

recurrent events analysis for all-cause hospitalization and HF hospitalization was used to calculate and compare event rates (events/year) in the WHF event cohort versus the non-WHF event cohort.

The objectives of this study were descriptive. All analyses of the association between a recent WHF and outcomes were univariable and did not attempt to adjust for potential confounders such as comorbidities. No adjustment was made for multiple comparisons, and a nominal 2-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 3867 unique patients with a median (25th, 75th) follow-up of 29.4 (10.4, 59.8) months met study criteria for the "overall HFrEF cohort" (Figure 1). After applying criteria for a recent WHF event, a total of 2823 (73.0%) patients were included in the WHF event cohort (median follow-up, 25.8 [7.8, 54.9] months), and 1044 (27.0%) patients were included in the non-WHF event cohort (median follow-up, 40.7 [18.3, 60.0 months]).

Baseline characteristics for the overall HFrEF cohort as well as the WHF and non-WHF event cohorts are shown in Table 1. Most patients (2752/2823; 97.5%) in the WHF cohort experienced a HF hospitalization during the year prior to index echocardiogram, whereas fewer patients (71/2823; 2.5%) met criteria for the WHF cohort by ED visit alone. The mean±SD number of hospitalizations per patient in the WHF event cohort within 1 year before baseline echocardiogram was 1.8±1.2. Compared with patients without a recent WHF event, patients with a recent WHF event were more likely to be non-White (1219/2806 [43.4%] non-White in the WHF cohort versus 363/1035 [35.1%] non-White in the non-WHF cohort; $P<0.001$), had lower LVEF (1620/2823 [57.4%] with LVEF <25% in the WHF cohort versus 505/1044 [48.4%] with LVEF <25% in the non-WHF cohort; $P<0.001$), and had a greater burden of all examined comorbidities (Table 1). Patients with a recent WHF event were more commonly on cardiovascular medications at the time of the baseline echocardiogram, except for angiotensin receptor neprilysin inhibitors (ARNIs), which was more common in the non-WHF event cohort. Patients in the WHF event cohort were more commonly receiving triple therapy for HFrEF within 1 year of the baseline echocardiogram (defined as concomitant use of a beta blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/ARNI, and mineralocorticoid receptor antagonist). Patients in the WHF event cohort had higher creatinine and blood urea nitrogen, and lower estimated glomerular filtration rate than those without a recent WHF event. Similarly, patients with a WHF event more commonly had elevated levels of brain natriuretic peptide and NT-proBNP (N-terminal pro-B-type natriuretic peptide).

Echocardiographic Characteristics

Measurements from baseline echocardiograms can be found in Table 2. For patients in the WHF cohort, the median (25th, 75th) time between the index echocardiogram and the WHF event was 2 (0, 6) months. Patients in the WHF event cohort were more likely to have evidence of left atrial enlargement and echocardiographic markers of elevated left ventricular filling pressure. Patients in the WHF event cohort also had echocardiographically defined higher right ventricular systolic pressures and more severe mitral regurgitation.

Clinical Outcomes

Patients with a recent WHF event had a higher cumulative incidence of all-cause mortality at 1-, 3-, and 5-years after baseline echocardiogram (Table 3) as well as a higher hazard for all-cause mortality through 5 years (HR, 2.30; 95% CI, 2.01–2.63; $P<0.001$) than patients in the non-WHF event cohort (Figure 2). In the time-to-first-event analysis, patients with a recent WHF event also had a higher cumulative incidence of all-cause hospitalization and HF hospitalization at 1 month, 1 year, 3 years, and 5 years after baseline echocardiogram, as well as higher hazards for all-cause hospitalization (HR, 1.60; 95% CI, 1.42–1.71; $P<0.001$) and HF hospitalization (HR, 1.59; 95% CI, 1.44–1.75; $P<0.001$) through 5 years (Figure 2). Based on graphical inspection of the cumulative incidence curves, we noted that the HR comparing outcomes by WHF status was higher during the initial follow-up period and attenuated toward the null later during follow-up. Consequently, we interpret our HR estimates as an average effect observed during 5 years of follow-up, and we advise against extrapolating these estimates to studies with longer or shorter follow-up duration.

In the recurrent events analysis, patients with a recent WHF event had higher event rates per year for all-cause hospitalization and HF hospitalization compared with those without a recent WHF event ($P<0.001$ for all) (Table 4).

Sensitivity Analysis

After using a more restrictive definition that requires hospitalization and ED encounters to have a primary discharge diagnosis of acute HF (definitions in Table S1) to be classified as a WHF event, a total of 1668 of 3867 (43.1%) patients were included in the WHF event cohort and 2199 of 3867 (56.9%) patients were included in the non-WHF event cohort (Table S2).

Table 1. Baseline Characteristics, Stratified by Recent Worsening Heart Failure Event Status

Patient characteristics	Overall HFrEF cohort (N=3867)		WHF cohort (N=2823)		Non-WHF cohort (N=1044)		*P* Value
	Result	N	Result	N	Result	N	
Female sex, n (%)	1235 (31.9)	3867	915 (32.4)	2823	320 (30.7)	1044	0.297
Age, y	64 (55–73)	3867	65 (54–73)	2823	64 (55–72)	1044	0.330
BMI, kg/m^2	28.4 (24.5–33.7)	3867	28.2 (24.3–33.7)	2823	28.9 (25.1–33.7)	1044	0.034
Race, n (%)							<0.001
White	2259 (58.8)	3841	1587 (56.6)	2806	672 (64.9)	1035	
Black	1440 (37.5)	3841	1123 (40.0)	2806	317 (30.6)	1035	
Other‡	142 (3.7)	3841	96 (3.4)	2806	46 (4.4)	1035	
Left ventricular ejection fraction, n (%)							<0.001
<25%	2125 (55.0)	3867	1620 (57.4)	2823	505 (48.4)	1044	
≥25	1742 (45.0)	3867	1203 (42.6)	2823	539 (51.6)	1044	
HF hospitalization ≤1 y prior to echo, n (%)	2752 (71.2)	3867	2752 (97.5)	2823	N/A	1044	
HF ED visit ≤1 y prior to echo, n (%)	407 (10.5)	3867	407 (14.4)	2823	N/A	1044	
Comorbidities, n (%)							
Hypertension	3025 (78.2)	3867	2306 (81.7)	2823	719 (68.9)	1044	<0.001
Diabetes mellitus	1608 (41.6)	3867	1248 (44.2)	2823	360 (34.5)	1044	<0.001
CAD	2645 (68.4)	3867	2015 (71.4)	2823	630 (60.3)	1044	<0.001
Prior myocardial infarction	1360 (35.2)	3867	1085 (38.4)	2823	275 (26.3)	1044	<0.001
Hyperlipidemia	2355 (60.9)	3867	1752 (62.1)	2823	603 (57.8)	1044	0.015
Cerebrovascular disease	880 (22.8)	3867	699 (24.8)	2823	181 (17.3)	1044	<0.001
Peripheral vascular disease	1033 (26.7)	3867	814 (28.8)	2823	219 (21.0)	1044	<0.001
Renal disease	1254 (32.4)	3867	1065 (37.7)	2823	189 (18.1)	1044	<0.001
Atrial fibrillation/flutter	1622 (41.9)	3867	1250 (44.3)	2823	372 (35.6)	1044	<0.001
Chronic pulmonary disease	1595 (41.2)	3867	1285 (45.5)	2823	310 (29.7)	1044	<0.001
Vital signs							
Heart rate, bpm	79 (69–90)	3578	80 (70–92)	2571	75 (67–84)	1007	<0.001
Systolic blood pressure, mm Hg	116 (104–130)	3574	116 (104–130)	2566	116 (106–131)	1008	0.124
Cardiovascular therapies, n (%)							
Aspirin	2512 (65.0)	3867	2091 (74.1)	2823	421 (40.3)	1044	<0.001
Statin	2297 (59.4)	3867	1856 (65.7)	2823	441 (42.2)	1044	<0.001
Beta blocker	3154 (81.6)	3867	2480 (87.8)	2823	674 (64.6)	1044	<0.001
ACEI/ARB	2815 (72.8)	3867	2170 (76.9)	2823	645 (61.8)	1044	<0.001
Calcium channel blocker	1103 (28.5)	3867	957 (33.9)	2823	146 (14.0)	1044	<0.001
Any diuretic	3194 (82.6)	3867	2582 (91.5)	2823	612 (58.6)	1044	<0.001
MRA	1649 (42.6)	3867	1292 (45.8)	2823	357 (34.2)	1044	<0.001
ARNI	109 (2.8)	3867	69 (2.4)	2823	40 (3.8)	1044	0.021
Hydralazine	726 (18.8)	3867	654 (23.2)	2823	72 (6.9)	1044	<0.001
Nitrates	681 (17.6)	3867	592 (21.0)	2823	89 (8.5)	1044	<0.001
Triple HFrEF therapy*	1130 (29.2)	3867	913 (32.3)	2823	217 (20.8)	1044	<0.001
CRT ≤5 y of index echo	574 (14.8)	3867	360 (12.8)	2823	214 (20.5)	1044	<0.001
ICD ≤5 y of index echo	1511 (39.1)	3867	1008 (35.7)	2823	503 (48.2)	1044	<0.001

(*Continued*)

Table 1. Continued

Patient characteristics	Overall HFrEF cohort (N=3867)		WHF cohort (N=2823)		Non-WHF cohort (N=1044)		*P* Value
	Result	N	Result	N	Result	N	
Laboratory measures							
Creatinine, mg/dL	1.2 (1.0–1.6)	3867	1.3 (1.0–1.7)	2823	1.1 (0.9–1.4)	1044	<0.001
BUN, mg/dL	20 (14–29)	3764	21 (14–30)	2775	18 (13–24)	989	<0.001
Sodium, mmol/L	138 (136–140)	3767	138 (135–140)	2776	139 (137–140)	991	<0.001
Hemoglobin, g/dL	12.2 (10.6–13.7)	3617	11.8 (10.3–13.4)	2752	13.2 (12.0–14.4)	865	<0.001
eGFR (CKD-EPI)	60 (43–79)	3867	58 (41–78)	2823	65 (50–85)	1044	<0.001
BNP, pg/mL	579 (234–1413)	1036	666 (250–1516)	842	421 (195–1110)	194	0.001
Elevated BNP,† n (%)	782 (75.5)	1036	643 (76.4)	842	139 (71.6)	194	0.169
NT-ProBNP, pg/mL†	3099 (933.0–9463)	3237	3687 (1178–11 349)	2433	1757 (529.0–5438)	804	<0.001
Elevated NT-proBNP, n (%)	2624 (81.1)	3237	2033 (83.6)	2433	591 (73.5)	804	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and WHF, worsening heart failure.

*Triple HFrEF therapy defined as concomitant use of beta blocker, ACEI/ARB/ARNI, and MRA.

†Elevated BNP defined as ≥125 or ≥375 pg/mL if history of atrial fibrillation/flutter; elevated NT-proBNP defined as ≥400 or ≥1200 pg/mL if history of atrial fibrillation/flutter.

‡Other race includes Alaskan Native, American Indian, Asian, Multiracial, Native Hawaiian, Other Pacific Islander, 2 or more races, or any other race not listed. Number ranges in parentheses are either interquartile range or mean.

Baseline characteristics of patient cohorts from the sensitivity analysis were slightly different than those from the primary analysis. Compared with the non-WHF event cohort, patients in the WHF event cohort were younger and more likely to be female (Table S2). Compared with the primary analysis, there were less pronounced differences in baseline comorbidities between the cohorts from the sensitivity analysis. Patterns of baseline medication use, cardiovascular device history, baseline laboratory studies, and echocardiographic characteristics were similar between the main analysis and the sensitivity analysis (Tables S2 and S3).

In the sensitivity analysis, patients in the WHF event cohort had higher cumulative incidence of each of the clinical outcomes at all examined time points after index echocardiogram than those from the non-WHF event cohort (Table S4 and Figure S1). Patients in the WHF event cohort had a higher hazard for all-cause death, all-cause hospitalization, and HF hospitalization at 5 years, as well as higher event rates per year in the recurrent events analysis for all-cause hospitalization and HF hospitalization (Table S5). Although the absolute incidence and rates of HF hospitalization during the 5-year follow-up period were lower in the sensitivity analysis than in the main analysis for both the WHF and non-WHF groups, the relative difference between the WHF and non-WHF groups was larger.

DISCUSSION

In DUHS patients with chronic HFrEF undergoing an echocardiogram between 2009 and 2018, 73.0% had a recent WHF event using a broad WHF definition, and 43.1% using a more strict WHF definition. Compared with patients with HFrEF without a recent WHF event, patients with a recent WHF event had a greater burden of comorbidities, higher use of guideline-directed medical therapies, higher levels of negatively prognostic biomarkers, and more significant echocardiographic abnormalities. Despite having higher use of guideline-directed HFrEF therapies, patients with a recent WHF event had significantly higher event rates for all-cause death, all-cause hospitalization, and HF hospitalization than those without a recent WHF event.

These data highlight several important differences between patients with and without recent WHF events. Patients in the recent WHF event cohort had lower LVEF on baseline echocardiogram and higher baseline levels of prognostic biomarkers including creatinine, blood urea nitrogen, brain natriuretic peptide, and NTproBNP. These parameters have been shown to be highly prognostic in patients with HFrEF across a variety of populations, correlating with patient symptom burden and adverse clinical outcomes including hospitalization and death.[7,8] Importantly, these data are both retrospective and observational; thus, causality remains a question

Table 2. Echocardiographic Characteristics, Stratified by Recent WHF Event Status

Characteristic	Overall (N=3867)		WHF cohort (N=2823)		Non-WHF cohort (N=1044)		*P* Value
	Result	N	Result	N	Result	N	
Index echo in-hospital, n (%)	2002 (51.8)	3867	1977 (70.0)	2823	25 (2.4)	1044	<0.001
Left atrial diameter, cm	4.5 (4.0–5.0)	3448	4.6 (4.0–5.0)	2480	4.5 (4.0–5.0)	968	0.028
Left atrial area, cm^2	28.0 (23.5–33.0)	2988	28.0 (24.0–33.0)	2189	27.0 (22.0–32.0)	799	<0.001
Left atrial volume, mL	102.0 (78.0–132.0)	1578	103.0 (79.0–131.0)	1158	101.0 (74.0–133.0)	420	0.451
Left atrial volume index, mL/m^2	45.0 (30.0–60.0)	1041	46.0 (32.0–60.0)	759	41.0 (27.0–58.0)	282	0.022
Left atrial enlargement, n (%)	801 (76.9)	1041	596 (78.5)	759	205 (72.7)	282	0.047
Left ventricular hypertrophy, n (%)	2099 (57.6)	3641	1546 (58.6)	2636	553 (55.0)	1005	0.048
LVH severity, n (%)							0.232
None	1425 (38.4)	3707	1016 (37.7)	2692	409 (40.3)	1015	
Mild	1716 (46.3)	3707	1269 (47.1)	2692	447 (44.0)	1015	
Moderate	566 (15.3)	3707	407 (15.1)	2692	159 (15.7)	1015	
Severe	0 (0.0)	3707	0 (0.0)	2692	0 (0.0)	1015	
Diastolic function class, n (%)							<0.001
Normal	41 (2.0)	2002	25 (1.8)	1371	16 (2.5)	631	
Grade 1	721 (36.0)	2002	420 (30.6)	1371	301 (47.7)	631	
Grade 2	213 (10.6)	2002	145 (10.6)	1371	68 (10.8)	631	
Grade 3	197 (9.8)	2002	150 (10.9)	1371	47 (7.4)	631	
Grade 3–4	772 (38.6)	2002	588 (42.9)	1371	184 (29.2)	631	
Grade 4	58 (2.9)	2002	43 (3.1)	1371	15 (2.4)	631	
E/e′ ratio	16 (12–23)	807	17 (12–23)	552	15 (10–21)	255	0.006
Mitral annulus e′ velocity, cm/s	5.0 (4.0–6.5)	810	5.0 (4.0–6.7)	555	5.0 (4.0–6.5)	255	0.521
Mitral inflow E velocity, cm/s	88 (67–108)	810	92 (71–112)	555	81 (61–101)	255	<0.001
Tricuspid regurgitation velocity	2.9 (2.5–3.2)	2149	2.9 (2.5–3.2)	1624	2.8 (2.4–3.2)	525	<0.001
Mitral regurgitation severity, n (%)							<0.001
None	230 (6.4)	3588	167 (6.4)	2596	63 (6.4)	992	
Trivial	982 (27.4)	3588	643 (24.8)	2596	339 (34.2)	992	
Mild	1319 (36.8)	3588	951 (36.6)	2596	368 (37.1)	992	
Moderate	767 (21.4)	3588	592 (22.8)	2596	175 (17.6)	992	
Severe	290 (8.1)	3588	243 (9.4)	2596	47 (4.7)	992	

Left atrial enlargement defined as left atrial volume index >28 mL/m^2. Left ventricular hypertrophy defined as septal or posterior wall thickness ≥1.1 cm. Diastolic function definitions: Grade 1=E/A reversal, Grade 2=pseudonormalization, Grade 3=reversible restrictive pattern, Grade 3–4=restrictive pattern with indeterminate reversibility, Grade 4=irreversible restrictive pattern. E/e' indicates mitral inflow E velocity to the mitral annulus e' velocity; LV, left ventricle; LVH, left ventricular hypertrophy; and WHF, worsening heart failure.

for future prospective studies. However, these findings do speak to the significance of a recent WHF event as a strong indicator of more advanced disease in a highly vulnerable patient population.

Another important feature of this analysis is the finding that patients with recent WHF events have higher rates of death and hospitalization than those without a recent WHF event despite higher use of guideline-directed HFrEF therapies. The reason behind this finding is likely in part explained by disproportionately more advanced disease in the recent WHF event cohort. Although we do not have access to data describing symptom burden in our patient populations, one may also reasonably assume that the non-WHF cohort contains some proportion of patients with minimally symptomatic HFrEF, thus partially explaining lower rates of medical therapy use in this population as many HFrEF therapies are only indicated in symptomatic patients.[9] Clinical inertia may also contribute, as patients in the non-WHF cohort are more "clinically stable," and thus clinicians are less likely to escalate therapy.[10] One peculiar finding is the slightly higher prevalence of ARNI use in the non-WHF event cohort (3.8%) compared with the WHF event cohort (2.4%; *P*=0.021 for difference between groups), a finding that opposes the trend demonstrated by all other guideline-directed medical therapies. Notably, this finding does not persist in the sensitivity analysis that employs a much stricter definition for WHF event, in which ARNI use is similar between cohorts. Furthermore, the very low use of

Table 3. Cumulative Incidence Rates (95% CIs) for Clinical Outcomes at Prespecified Time Points After Baseline Echocardiogram, Stratified by Recent WHF Event Status

Clinical outcome	Time from baseline echo	WHF cohort		Non-WHF cohort	
		N	Incidence	N	Incidence
All-cause mortality	1 y	710	25.6 (24.0–27.2)	70	7.0 (5.5–8.7)
	3 y	1117	43.3 (41.3–45.3)	183	20.7 (18.1–23.5)
	5 y	1312	55.1 (52.8–57.1)	260	33.0 (29.6–36.5)
All-cause hospitalization	1 mo	397	14.1 (12.8–15.4)	101	9.7 (8.0–11.6)
	1 y	1364	49.1 (47.2–51.0)	358	35.3 (32.4–38.3)
	3 y	1688	63.0 (61.1–64.9)	522	54.6 (51.3–57.8)
	5 y	1791	69.0 (67.1–70.9)	599	67.0 (63.5–70.2)
HF hospitalization	1 mo	376	13.3 (12.1–14.6)	92	8.8 (7.2–10.6)
	1 y	1299	46.7 (44.9–48.6)	331	32.7 (29.8–35.6)
	3 y	1625	60.6 (58.7–62.5)	487	50.1 (47.7–54.2)
	5 y	1736	67.1 (65.1–68.9)	569	64.0 (60.5–67.3)
All-cause death/hospitalization	1 y	1742	62.6 (60.8–64.4)	392	38.7 (35.7–41.7)
	3 y	2151	80.3 (78.6–81.8)	583	61.3 (58.0–64.4)
	5 y	2281	87.9 (86.4–89.2)	679	76.7 (73.4–79.6)
All-cause death/HF hospitalization	1 y	1685	60.6 (58.7–62.4)	366	36.1 (33.2–39.1)
	3 y	2103	78.5 (76.8–80.1)	553	58.2 (54.8–61.3)
	5 y	2243	86.6 (85.1–88.0)	656	74.5 (71.1–77.5)

Data presented as N with event; cumulative incidence rate (95% CI). HF indicates heart failure; and WHF, worsening heart failure.

ARNI among our study population, likely attributable to the bulk of the study period occurring before approval of ARNI for treatment of HFrEF and subsequent slow adoption of this therapy,[11] makes it difficult to interpret the significance of this finding. The high event rates for death and hospitalization in the recent WHF cohort despite the use of guideline-directed therapy suggests a significant unmet need for new effective therapies to reduce morbidity and mortality in patients with HFrEF.

Although DUHS is a large, academic, quaternary cardiovascular referral and heart transplant center, patients from this analysis are reasonably representative of other broad populations from prospective HF registries. The CHAMP-HF (Change the Management of Patients With Heart Failure) registry is a multicenter registry of ≈150 US sites enrolling patients with chronic HFrEF.[12] Patients in the overall HFrEF cohort from our analysis are similar to those from the CHAMP-HF registry with respect to age, sex distribution, body mass index, LVEF, renal function (by estimated glomerular filtration rate), and use of HF medical therapies.[13] One notable difference is the higher proportion of Black patients in our study population (38% in our population versus 16% in CHAMP-HF), which may make DUHS patients more representative of unselected patients in general practice. Patients from the main analysis had much higher rates of HF hospitalization within 1 year before baseline echocardiogram (71% in our population versus 38% in CHAMP-HF), though HF hospitalizations within 1 year of baseline using the more strict sensitivity analysis definition (42.0%) was similar. An analysis of patients with HFrEF and a history of HF hospitalization from the GWTG-HF (Get With The Guidelines–Heart Failure) registry reveals similar findings, with DUHS patients and registry patients having similar rates of guideline-directed HF therapy use (albeit with higher mineralocorticoid use in DUHS patients).[14]

In patients in the recent WHF event cohort, the vast majority (2752/2823; 97.5%) experienced a HF hospitalization within 1 year before the index echocardiogram, with a small minority of patients (407/2823; 14.4%) having experienced an ED visit for HF that did not lead to hospital admission. Among those who experienced a HF hospitalization as their WHF event, the mean number of hospitalizations within 1 year of the baseline echocardiogram was 1.8±1.2. Notably among patients in the recent WHF cohort, there was a total of 2942 DUHS ED visits for HF within 1 year of the baseline echocardiogram, with 2345 (79.7%) of these ED visits leading to hospital admission. These findings are in keeping with prior reports suggesting a high rate of hospitalization and resource usage among patients with HFrEF.[15] Strategies to improve outpatient management of patients with HFrEF aimed at reducing hospitalization burden have been proposed and implemented with varying degrees of success.[16]

A unique feature of this analysis is the description of baseline echocardiographic parameters obtained in patients with and without a recent WHF event. In

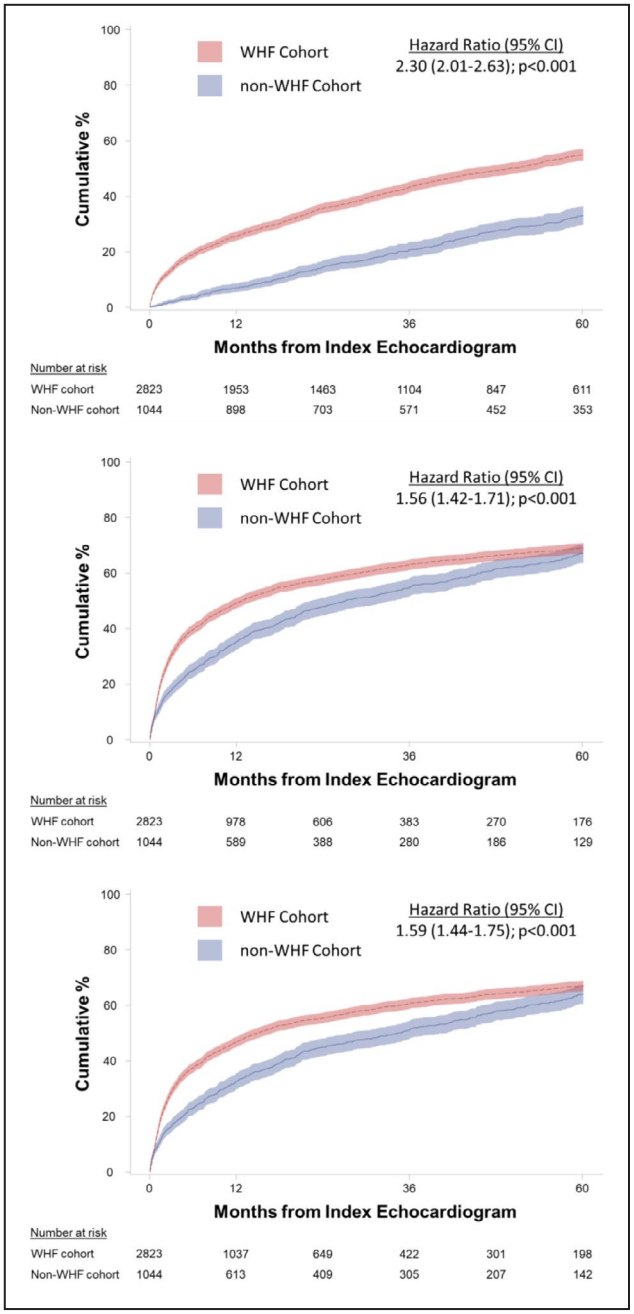

Figure 2. Five-year cumulative incidence curves for all-cause mortality (top), all-cause hospitalization (middle), and heart failure hospitalization (bottom) stratified by recent WHF event status, including hazard ratios with 95% CIs.
WHF indicates worsening heart failure.

both the primary analysis and the sensitivity analysis, patients in the recent WHF event cohort were found to have echocardiographic parameters suggestive of a greater degree of adverse cardiac remodeling and dysfunction than those in the non-WHF event cohort. These included left ventricular hypertrophy, left atrial enlargement, more severe diastolic dysfunction, higher tricuspid regurgitation velocities (ie, higher pulmonary pressures), and more severe mitral regurgitation. Each of these parameters is known to be of prognostic significance in patients with HFrEF.[17,18] The difference in severity of mitral regurgitation between groups is an interesting finding, particularly with the 2-fold higher percentage of patients with severe mitral regurgitation in the recent WHF event cohort (9.4%) compared with the non-WHF event cohort (4.7%). Studies have suggested that cardiac resynchronization therapy and transcatheter mitral valve repair in select patients with severe mitral regurgitation and symptomatic HFrEF may confer benefits in both quality of life and mortality.[19] The proportions of such patients likely to benefit from these therapies in our study population is not known.

Table 4. Association Between Recent WHF Event Status and Recurrent Hospitalization Events Through 5 Years of Follow-Up

Clinical outcome	WHF cohort events/ patient-year	Non-WHF cohort events/ patient-year	Rate ratio (95% CI)	*P* Value
All-cause hospitalization	1.45	0.78	1.85 (1.66, 2.06)	<0.001
HF hospitalization	1.31	0.68	1.91 (1.71, 2.14)	<0.001

HF indicates heart failure; and WHF, worsening heart failure.

Limitations

Data from this analysis are observational, retrospective, and are derived from a single academic medical center, and therefore are subject to the usual biases of such studies. We observed a statistically significant difference in the distribution of races between the WHF and non-WHF cohorts; however, our analysis did not collect data describing social determinants of health. We believe that additional data exploring this important finding would be best suited for a dedicated analysis. We are unable to obtain data describing changes in medical therapies over time, which has important implications on prognosis and clinical outcomes in both cohorts. Use of ARNI and sodium glucose transporter 2 inhibitors in our population is minimal given the study time period. While ARNI has been shown to have consistent benefits in patients with and without recent WHF events,[20] the differential effect of sodium glucose transporter 2 inhibitors is unknown. These data describe encounters only within the DUHS system; thus, WHF events before the baseline echocardiogram as well as ED visits and hospitalizations during study follow-up occurring outside of the DUHS system are not captured. Finally, patient-centered metrics such as functional class, symptom burden, and quality of life were not assessed in our analysis.

CONCLUSIONS

A high proportion of patients with chronic symptomatic HFrEF have experienced a recent WHF event. Patients with WHF events have a higher burden of comorbidities and have more echocardiographic abnormalities than patients without recent WHF events. Over 5 years of follow-up, death and hospitalization are more common in patients with recent WHF events despite guideline-directed medical therapy use; thus, new and effective treatments are needed to reduce clinical events in this vulnerable patient population. These data underscore the critical need for novel therapies in this vulnerable patient population.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 and ICD-10 definitions for comorbidities and acute heart failure events.

Heart Failure ICD-9 (diagnosis)	
4280 Congestive heart failure, unspecified	42822 Chronic systolic heart failure
42820 Systolic heart failure, unspecified	42823 Acute on chronic systolic heart failure
42821 Acute systolic heart failure	4289 Heart Failure, unspecified
Heart Failure ICD-10 (diagnosis)	
I50.20 Unspecified systolic (congestive) heart failure	I13.0 HF due to HTN and CKD
I50.21 Acute systolic (congestive) heart failure	I13.1 Hypertensive heart and CKD without HF
I50.22 Chronic systolic (congestive) heart failure	I13.10 Hypertensive heart and CKD 1-4 without HF
I50.23 Acute on chronic systolic (congestive) heart failure	I13.11 Hypertensive heart and CKD 5 without HF
I50.83 High output heart failure	I13.2 HF due to HTN and CKD 5
I50.84 End stage heart failure	I97.13 HF following surgery
I50.89 Other heart failure	I09.81 Rheumatic HF
I50.9 Heart failure, unspecified	I42.1 Obstructive HCM
I11.0 HF due to HTN	I42.2 Other HCM
Hyperlipidemia ICD-9	
2720 Pure hypercholesterolemia	2724 Other and unspecified hyperlipidemia
2722 Mixed hyperlipidemia	
Hyperlipidemia ICD-10	
E7800 Pure hypercholesterolemia, unspecified	E784 Other hyperlipidemia
E7801 Familial hypercholesterolemia	E785 Hyperlipidemia, unspecified
E782 Mixed hyperlipidemia	
Atrial Fibrillation/Flutter ICD-9	
427.31 Atrial fibrillation	427.32 Atrial flutter
Atrial Fibrillation/Flutter ICD-10	
I48.X Atrial fibrillation and flutter	I48.9X Unspecified atrial fibrillation and flutter
Coronary Artery Disease ICD-9	
410.X Acute myocardial infarction	411.X Other acute and subacute forms of ischemic heart disease
412.X Old myocardial infarction	414.X Other forms of chronic ischemic heart disease
413.X Angina pectoris	
Coronary Artery Disease ICD-10	
I20.X Angina pectoris, unspecified	I23.X Certain current complications following acute myocardial infarction
I21.X Acute myocardial infarction	I24.X Acute coronary thrombosis not resulting in myocardial infarction
I22.X Subsequent myocardial infarction	I25.X Chronic ischemic heart disease
Acute Heart Failure Event ICD-9	
4280 Congestive heart failure, unspecified	42823 Acute on chronic systolic heart failure
42820 Systolic heart failure, unspecified	4289 Heart Failure, unspecified
42821 Acute systolic heart failure	7823 Edema

42822 Chronic systolic heart failure	27669 Other fluid overload
Acute Heart Failure Event ICD-10	
I50.20 Unspecified systolic (congestive) heart failure	I13.11 Hypertensive heart and CKD 5 without HF
I50.21 Acute systolic (congestive) heart failure	I13.2 HF due to HTN and CKD 5
I50.22 Chronic systolic (congestive) heart failure	I97.13 HF following surgery
I50.23 Acute on chronic systolic (congestive) heart failure	I09.81 Rheumatic HF
I50.83 High output heart failure	I42.1 Obstructive HCM
I50.84 End stage heart failure	I42.2 Other HCM
I50.89 Other heart failure	E87.70 Fluid overload, unspecified
I50.9 Heart failure, unspecified	E87.79 Other fluid overload
I11.0 HF due to HTN	R60.0 Localized edema
I13.0 HF due to HTN and CKD	R60.1 Generalized edema
I13.1 Hypertensive heart and CKD without HF	R60.9 Edema, unspecified
I13.10 Hypertensive heart and CKD 1-4 without HF	

Table S2. Baseline characteristics from the sensitivity analysis, stratified by recent worsening heart failure event status.

	WHF cohort (N=1668)		non-WHF cohort (N=2199)		P-Value
Patient Characteristics	**Result**	**N**	**Result**	**N**	
Female	569 (34.1%)	1668	666 (30.3%)	2199	0.012
Age (years)	64 (53, 72)	1668	65 (56, 73)	2199	<.001
BMI (kg/m^2)	28.3 (24.2, 34.1)	1612	28.5 (24.8, 33.5)	2135	0.717
Race					<.001
White	856 (51.7%)	1656	1403 (64.2%)	2185	
Black	746 (45.0%)	1656	694 (31.8%)	2185	
Other	54 (3.3%)	1656	88 (4.0%)	2185	
Left Ventricular Ejection Fraction					<.001
< 25%	1060 (63.5%)	1668	1065 (48.4%)	2199	
≥25	608 (36.5%)	1668	1134 (51.6%)	2199	
HF Hospitalization ≤1 year prior to echo	1624 (97.4%)	1668	N/A	2199	
HF ED visit ≤1 year prior to echo	130 (7.8%)	1668	N/A	2199	
Comorbidities					
Hypertension	1330 (79.7%)	1668	1695 (77.1%)	2199	0.048
Diabetes	713 (42.7%)	1668	895 (40.7%)	2199	0.201
CAD	1123 (67.3%)	1668	1522 (69.2%)	2199	0.211
Prior myocardial infarction	576 (34.5%)	1668	784 (35.7%)	2199	0.470
Hyperlipidemia	972 (58.3%)	1668	1383 (62.9%)	2199	0.004
Cerebrovascular disease	396 (23.7%)	1668	484 (22.0%)	2199	0.204
Peripheral vascular disease	411 (24.6%)	1668	622 (28.3%)	2199	0.011
Renal disease	675 (40.5%)	1668	579 (26.3%)	2199	<.001
Atrial Fibrillation/Flutter	710 (42.6%)	1668	912 (41.5%)	2199	0.495
Chronic Pulmonary Disease	802 (48.1%)	1668	793 (36.1%)	2199	<.001
Vital Signs					
Heart rate (bpm)	82 (71, 93)	1517	76 (68, 87)	2061	<.001
Systolic blood pressure (mmHg)	114 (102, 129)	1515	117 (106, 131)	2059	<.001
Cardiovascular Therapies					
Aspirin	1186 (71.1%)	1668	1326 (60.3%)	2199	<.001
Statin	1028 (61.6%)	1668	1269 (57.7%)	2199	0.014
Beta Blocker	1445 (86.6%)	1668	1709 (77.7%)	2199	<.001
ACEi/ARB	1263 (75.7%)	1668	1552 (70.6%)	2199	<.001
Calcium Channel Blocker	515 (30.9%)	1668	588 (26.7%)	2199	0.005
Any Diuretic	1566 (93.9%)	1668	1628 (74.0%)	2199	<.001
MRA	876 (52.5%)	1668	773 (35.2%)	2199	<.001
ARNI	50 (3.0%)	1668	59 (2.7%)	2199	0.558
Hydralazine	403 (24.2%)	1668	323 (14.7%)	2199	<.001
Nitrates	370 (22.2%)	1668	311 (14.1%)	2199	<.001
Triple HFrEF Therapy*	605 (36.3%)	1668	525 (23.9%)	2199	<.001
CRT ≤5 years of index echo	212 (12.7%)	1668	362 (16.5%)	2199	0.001
ICD ≤5 years of index echo	592 (35.5%)	1668	919 (41.8%)	2199	<.001
Laboratory Measures					
Creatinine (mg/dL)	1.3 (1.0, 1.7)	1668	1.2 (0.9, 1.5)	2199	<.001
BUN (mg/dL)	22 (15, 32)	1636	19 (13, 26)	2128	<.001
Sodium (mmol/L)	138 (135, 140)	1636	138 (136, 140)	2131	<.001
Hemoglobin(g/dL)	11.8 (10.4, 13.3)	1623	12.5 (10.9, 13.9)	1994	<.001
eGFR (CKD-Epi)	57 (41, 75)	1668	63 (46, 83)	2199	<.001
BNP (pg/mL)	774 (285, 1723)	528	461 (203, 1148)	508	<.001
Elevated BNP#	417 (79.0%)	528	365 (71.9%)	508	0.008
NT-ProBNP (pg/mL)	3864 (1355, 11818)	1480	2443 (698, 7644)	1757	<.001
Elevated NT-proBNP#	1268 (85.7%)	1480	1356 (77.2%)	1757	<.001

	WHF cohort (N=1668)	non-WHF cohort (N=2199)	P-Value

*Triple HFrEF therapy defined as concomitant use of beta blocker, ACEi/ARB/ARNI, and MRA

#Elevated BNP defined as ≥125pg/mL or ≥375pg/mL if history of atrial fibrillation/flutter; Elevated NT-proBNP defined as ≥400pg/mL or ≥1200pg/mL if history of atrial fibrillation/flutter

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CAD = coronary artery disease; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; ED = emergency department; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro b-type natriuretic peptide.

Table S3. Echocardiographic characteristics from the sensitivity analysis, stratified by recent worsening heart failure event status.

	WHF cohort (N=1668)		non-WHF cohort (N=2199)		P-Value
Characteristic	**Result**	**N**	**Result**	**N**	
Index echo in-hospital	1268 (76.0%)	1668	734 (33.4%)	2199	<.001
Left atrial diameter (cm)	4.6 (4.1, 5.1)	1489	4.5 (3.9, 5.0)	1959	<.001
Left atrial area (cm^2)	29 (24, 34)	1338	27 (23, 32)	1650	<.001
Left atrial volume (mL)	106 (81, 133)	722	99 (75, 130)	856	0.001
Left atrial volume index (mL/m^2)	49 (35, 62)	437	41 (27, 57)	604	<.001
Left atrial enlargement	356 (81.5%)	437	445 (73.7%)	604	0.003
Left ventricular hypertrophy	880 (55.9%)	1575	1219 (59.0%)	2066	0.058
LVH severity					0.255
None	624 (39.3%)	1586	801 (37.8%)	2121	
Mild	737 (46.5%)	1586	979 (46.2%)	2121	
Moderate	225 (14.2%)	1586	341 (16.1%)	2121	
Severe	0 (0.0%)	1586	0 (0.0%)	2121	
Diastolic function class					<.001
Normal	16 (2.0%)	794	25 (2.1%)	1208	
Grade 1	187 (23.6%)	794	534 (44.2%)	1208	
Grade 2	72 (9.1%)	794	141 (11.7%)	1208	
Grade 3	89 (11.2%)	794	108 (8.9%)	1208	
Grade 3-4	402 (50.6%)	794	370 (30.6%)	1208	
Grade 4	28 (3.5%)	794	30 (2.5%)	1208	
E/e' ratio	18 (13, 25)	305	16 (11, 21)	502	<.001
Mitral annulus e' velocity (cm/s)	5.0 (4.0, 6.6)	307	5.0 (4.0, 6.5)	503	0.864
Mitral inflow E velocity (cm/s)	92 (74, 114)	307	84 (64, 104)	503	<.001
Tricuspid regurgitation velocity	2.9 (2.6, 3.3)	1023	2.8 (2.4, 3.2)	1126	<.001
Mitral regurgitation severity					<.001
None	76 (5.0%)	1529	154 (7.5%)	2059	
Trivial	314 (20.5%)	1529	668 (32.4%)	2059	
Mild	561 (36.7%)	1529	758 (36.8%)	2059	
Moderate	394 (25.8%)	1529	373 (18.1%)	2059	
Severe	184 (12.0%)	1529	106 (5.1%)	2059	

Left atrial enlargement defined as left atrial volume index >28mL/m^2

Left ventricular hypertrophy defined as septal or posterior wall thickness ≥1.1cm.

LV = left ventricle, LVH = left ventricular hypertrophy

Diastolic function definitions: Grade 1 = E/A reversal, Grade 2 = pseudonormalization, Grade 3 = reversible restrictive pattern, Grade 3-4 = restrictive pattern with indeterminate reversibility, Grade 4 = irreversible restrictive pattern

Table S4. Cumulative incidence rates (95% confidence intervals) for clinical outcomes at pre-specified time points after baseline echocardiogram from the sensitivity analysis, stratified by recent worsening heart failure event status.

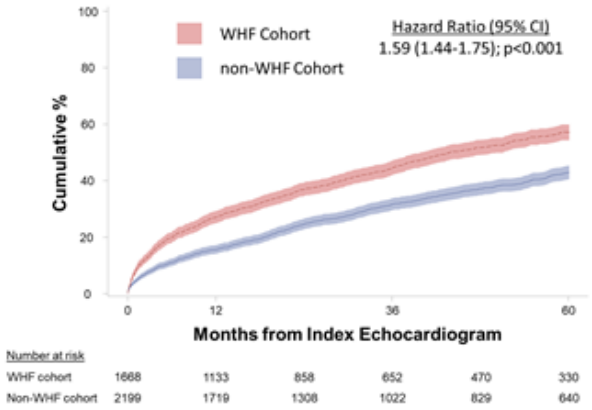
Clinical Outcome	Time From Baseline Echo	WHF cohort		Non-WHF cohort	
		N	Incidence	N	Incidence
All-Cause Mortality	1 year	336	15.6 (14.1, 17.2)	444	27.1 (24.9, 29.3)
	3 years	616	31.7 (29.6, 33.8)	684	44.5 (42.0, 47.1)
	5 years	763	42.9 (40.5, 45.4)	809	57.2 (54.3, 59.9)
All-Cause Hospitalization	1 month	258	11.7 (10.4, 13.1)	240	14.4 (12.8, 16.1)
	1 year	852	39.6 (37.5, 41.7)	870	53.0 (50.5, 55.4)
	3 years	1154	56.5 (54.3, 58.7)	1056	66.3 (63.9, 68.6)
	5 years	1273	65.6 (63.3, 67.8)	1117	72.3 (69.9, 74.6)
HF Hospitalization	1 month	104	4.7 (3.9, 5.7)	117	7.0 (5.9, 8.3)
	1 year	400	18.6 (17.0, 20.3)	543	33.1 (30.8, 35.4)
	3 years	603	30.0 (28.0, 32.1)	714	45.5 (43.0, 48.0)
	5 years	718	38.8 (36.5, 41.2)	773	51.5 (48.9, 54.1)
All-Cause Death/Hospitalization	1 year	1040	48.3 (46.2, 50.4)	1094	66.5 (64.2, 68.8)
	3 years	1416	69.4 (67.3, 71.5)	1318	82.7 (80.6, 84.5)
	5 years	1569	81.1 (79.0, 83.0)	1391	89.8 (87.9, 91.4)
AC-Death/HF-Hospitalization	1 year	651	30.2 (28.3, 32.2)	844	51.4 (48.9, 53.8)
	3 years	1011	50.6 (48.3, 52.8)	1097	69.8 (67.4, 72.1)
	5 years	1181	63.6 (61.2, 66.0)	1192	79.4 (77.0, 81.6)

Data presented as N with event; cumulative incidence rate (95% confidence interval)

Table S5. Association between recent worsening heart failure event status and recurrent hospitalization events through 5-years of follow-up from the sensitivity analysis.

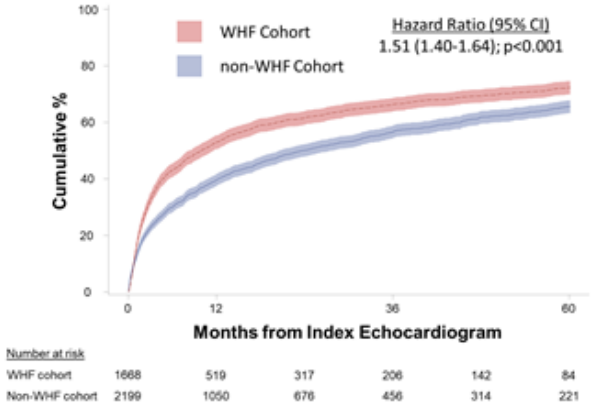
Clinical Outcome	WHF cohort Events/patient-year	Non-WHF cohort Events/patient-year	Rate Ratio with 95% CI	P-Value
All Cause Hospitalization	1.63	0.98	1.67 (1.51, 1.85)	<.001
HF Hospitalization	0.66	0.32	2.06 (1.78, 2.38)	<.001

Figure S1. Five-year cumulative incidence curves for all-cause mortality (TOP), all-cause hospitalization (MIDDLE), and heart failure hospitalization (BOTTOM) from the sensitivity analysis stratified by recent WHF event status, including hazard ratios with 95% confidence intervals.



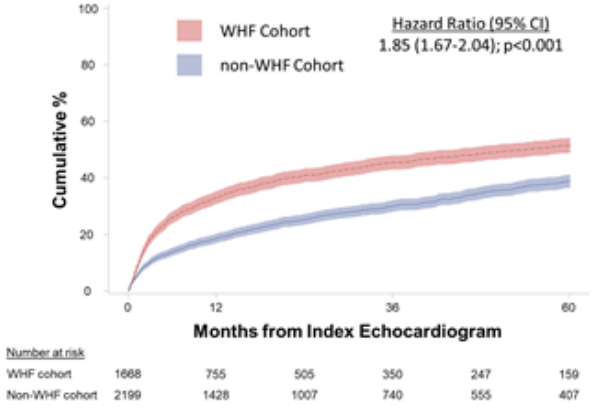
Number at risk

WHF cohort	1668	1133	858	652	470	330
Non-WHF cohort	2199	1719	1308	1022	829	640



Number at risk

WHF cohort	1668	519	317	206	142	84
Non-WHF cohort	2199	1050	676	456	314	221



Number at risk

WHF cohort	1668	755	505	350	247	159
Non-WHF cohort	2199	1428	1007	740	555	407