Contemporary outpatient management of patients with worsening heart failure with reduced ejection fraction: Clinical outcome results from the CHART-HF study

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ABSTRACT

Background: Based on available data from randomized clinical trials, patients with heart failure with reduced ejection fraction (HFrEF) and worsening HF events (WHFE) have substantial disease burden and poor outcomes. WHFE clinical outcome data in non-clinical trial patients, more representative of the US clinical practice, has not been demonstrated.

Methods and results: CHART-HF collected data from two complementary, non-clinical trial cohort with HFrEF (LVEF <45 %): 1) 1,000 patients from an integrated delivery network and 2) 458 patients from a nationwide physician panel. CHART-HF included patients with WHFE between 2017 and 2019 followed by an index outpatient cardiology visit ≤6 months, and patients without WHFE in a given year between 2017 and 2019, with the last outpatient cardiology visit in the same year as the index visit. Compared to patients without WHFE (after covariate adjustment, all p < 0.05), patients with WHFE had a greater risk of HF-related hospitalization (hazard ratio [HR]: 1.53–2.40) and next WHFE event (HR: 1.67–2.41) following index visits in both cohorts.

Conclusion: HFrEF patients with recent WHFE consistently had worse clinical outcomes in these non-clinical trial cohorts. Despite advances in therapies, unmet need to improve clinical outcomes in HFrEF patients with WHFE remains.

1. Background

Despite significant therapeutic advances to improve survival and reduce hospitalizations, many patients with heart failure with reduced ejection fraction (HFrEF) face continued disease progression and experience worsening heart failure events (WHFE) requiring subsequent use of intravenous diuretic therapy in the outpatient, inpatient, and emergency department setting [1,2]. Moreover, patients with WHFE have a high comorbidity burden, a higher risk of symptom worsening, worse survival, and greater healthcare costs compared to patients with HFrEF without WHFE [1–5].

The high morbidity and mortality associated with WHFE has prompted an increased focus on including patients with recent WHFE in contemporary clinical trials (VICTORIA [6], GALACTIC-HF [7] and PIONEER-HF [8] for HFrEF, and SOLOIST [9] and EMPULSE [10] for HFrEF and HF with preserved ejection fraction [HFpEF]). Although clinical benefit has been demonstrated for some therapeutics in this trial cohort, outcomes remain unacceptably poor for patients following WHFE. There is an unmet need to better understand WHFE outside of clinical trial cohorts, starting with clinical outcomes.

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To address the gap, CHART-HF used a chart review of patient medical records from an integrated delivery network and medical records from a physician survey to characterize clinical characteristics and outcomes among patients with HFrEF with vs. without WHFE in two representative US clinical practice.

2. Methods

2.1. Study design

The design and patient eligibility criteria for the CHART-HF study have been previously described [11]. Briefly, this study was conducted using a retrospective chart review of electronic medical record (EMR) of HFrEF patients with WHFE (i.e., WHFE cohort) and those without WHFE (i.e., reference cohort) in a given calendar year between January 1, 2017, and December 31, 2019. The study design scheme is illustrated in Fig. 1.

2.2. Patient eligibility

The patient eligibility criteria have been previously described in detail [11]. All patients were required to have 1) an outpatient visit with a cardiologist between January 1, 2017 and December 31, 2019 to serve as the index date, 2) a diagnosis of HF and an LVEF <45 %, as measured

by the most recent assessment within the prior 12 months, 3) age ≥18 years at index date, and 4) available and accessible medical data for ≥12 months following the index date or from the index date to death, whichever occurs first.

Patients in the WHFE cohort were required to have a WHFE within a calendar year between 2017 and 2019, and an associated outpatient visit with a cardiologist ≤6 months following the WHFE (index date), defined as receipt of intravenous diuretics in the inpatient, outpatient, or emergency department setting. The index date was defined as the date of the first outpatient cardiologist visit following the WHFE instead of the date of WHFE to mimic the design of the VICTORIA clinical trial (NCT02861534) where patients were randomized within 6 months after WHFE. In addition, this definition of the index date is easier for chart reviewers to operationalize and more clinically relevant as a decision point than the date of WHFE. Patients in the reference cohort did not have any WHFE within a given calendar year between 2017 and 2019 (the last outpatient cardiologist visit in that calendar year as the index date) and ≤6 months prior to the index date.

The same patient eligibility criteria were applied to selected patients from the two data sources as detailed below.

2.3. Data sources

This study utilized two distinct but complementary data sources.
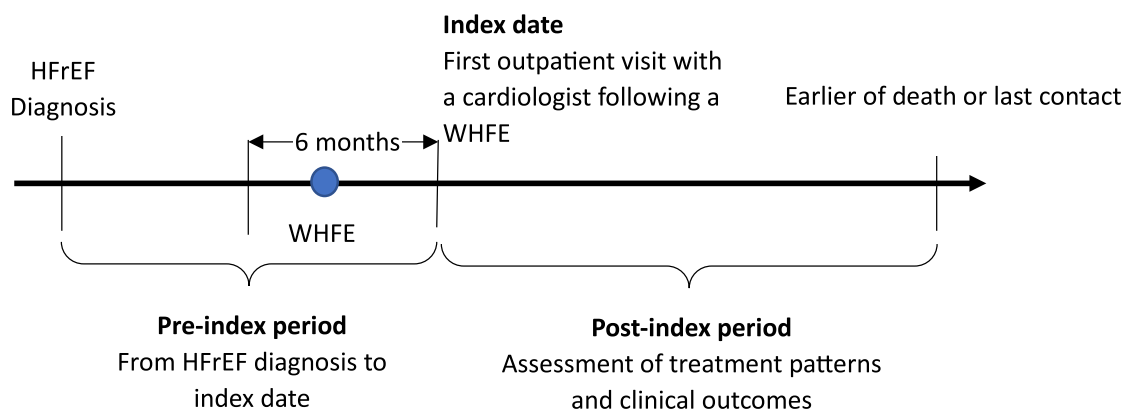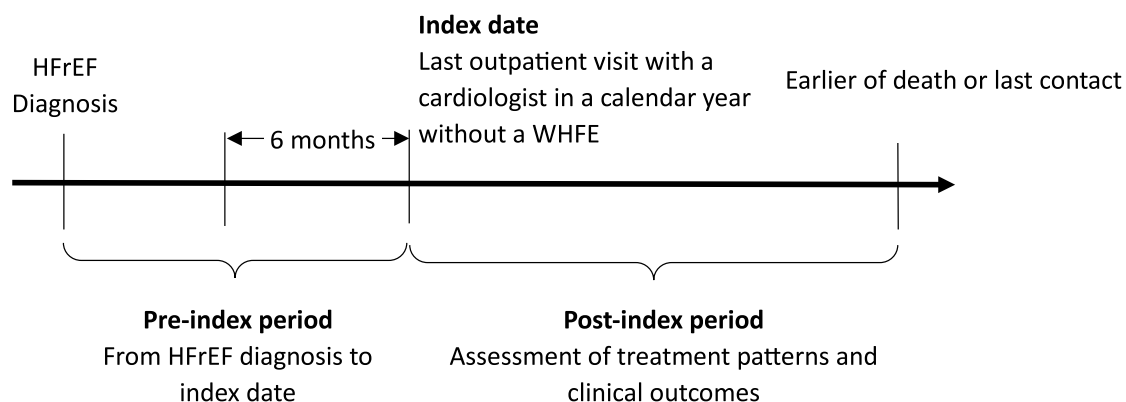

Fig. 1. Study design scheme.

These two cohorts were uniquely chosen for their ability to explore WHFE, treatment patterns and reasons for changes to medications after WHFE in clinical practice. This paper will focus on the outcomes. In the cohort from an integrated delivery network system, data was from electronic medical record reviewed by research study staff. In the second cohort, the data was from chart review by a nationwide panel of cardiologists. In the integrated delivery network system cohort, a total of 500 patients with WHFE and 500 without WHFE with the most recent index date in each cohort were randomly selected [12–14]. In the physician panel cohort [15–17], cardiologists with significant HFrEF experience were invited to conduct an anonymized chart review of their own patients who met the eligibility criteria. To reduce selection bias, participating cardiologists were asked to select up to 5 eligible patients whose last name started with a randomly selected letter. If no such patients existed, a different randomly selected letter was presented. Participating cardiologists abstracted patient charts using an electronic case report form via a secure online portal. Screening questions were asked to confirm patient eligibility before each chart abstraction. Data entry was assessed for completeness and consistency. When discrepancies were identified, cardiologists would be asked to double check or correct the data entry. Cardiologists were compensated for their time and expertise on abstracting patient charts. Locally reported lab values including BNP or NT-proBNP were recorded.

2.4. Study outcomes

Study outcomes included all-cause death, all-cause hospitalization, HF-related hospitalization, next WHFE, next HF-related hospitalization or cardiovascular death, and next HF-related hospitalization or all-cause death. The study also collected patient baseline demographic and clinical characteristics on index date or most recent timepoint prior to index date and HF treatment prior to and after index date.

2.5. Statistical analysis

Data from the integrated delivery network system and the physician panel cohort were analyzed separately. Most analyses were descriptive in nature. Kaplan-Meier methods were used to analyze time-to-event outcomes. Cox proportional-hazards models were used to analyze the differences in time-to-event outcomes between cohorts when adjusting for patient age, gender, race, smoking status, and use of any HFrEF medications (i.e., beta blocker, ACEI, ARB, ARNI, MRA) on or prior to index date. Simplified parsimonious models were used to maximize sample size while controlling for key factors that might impact outcomes. The proportional hazards assumption was tested by including interaction terms of covariates and a function of survival time in the model. Hazard ratios (HRs) were calculated for specific follow-up time points when violation of the proportional hazard assumption was observed.

3. Results

3.1. Baseline patient characteristics

3.1.1. Integrated delivery network system cohort

The study included 500 patients with WHFE and 500 without WHFE. The mean age at the index date was 68.6 (±13.3) years for patients with WHFE and 68.0 (±13.0) years for patients without WHFE. In both cohorts, 95.2 % of patients were white. More than 70 % of patients had Medicare. Approximately two thirds of the patients were either current or past smokers (Table 1).

The mean time from initial HFrEF diagnosis to index date was 1.5 (±2.4) and 2.7 (±2.5) years among patients with and without WHFE, respectively. The median follow-up time for medication use and clinical outcomes from index date was 1.92 years in the WHFE cohort and 2.01 years in the reference cohort. Among patients with WHFE, the average

Table 1
Patient characteristics on index date.

	Integrated delivery network system Health System Sample		physician Nationwide Panel Sample	
	Patients with WHFE (n = 500)	Patients without WHFE (n = 500)	Patients with WHFE (n = 226)	Patients without WHFE (n = 232)
Demographics[1]				
Age, years, mean ± SD [median]	68.6 ± 13.3 [69.5]	68.0 ± 13.0 [70]	61.9 ± 11.4 [64.2]	63.0 ± 10.7 [64]
Female, n (%)	144 (28.8 %)	122 (24.4 %)	72 (31.9 %)	88 (37.9 %)
Race, n (%)				
White or Caucasian	476 (95.2 %)	476 (95.2 %)	141 (62.4 %)	154 (66.4 %)
Black or African American	19 (3.8 %)	22 (4.4 %)	71 (31.4 %)	55 (23.7 %)
Asian	3 (0.6 %)	1 (0.2 %)	9 (4.0 %)	12 (5.2 %)
Other/unknown	2 (0.4 %)	1 (0.2 %)	5 (2.2 %)	11 (4.7 %)
Hispanic, n (%)	7 (1.4 %)	7 (1.4 %)	22 (9.7 %)	20 (8.6 %)
Insurance, n (%)				
Commercial	49 (9.8 %)	69 (13.8 %)	96 (42.5 %)	94 (40.5 %)
Medicare	354 (70.8 %)	366 (73.2 %)	106 (46.9 %)	102 (44.0 %)
Medicaid	50 (10.0 %)	32 (6.4 %)	21 (9.3 %)	27 (11.6 %)
Other/unknown	47 (9.4 %)	33 (6.6 %)	3 (1.3 %)	9 (3.9 %)
Smoking status, n (%)				
Current	72 (14.4 %)	58 (11.6 %)	14 (6.2 %)	13 (5.6 %)
Past	251 (50.2 %)	260 (52.0 %)	98 (43.4 %)	102 (44.0 %)
Time from initial HFrEF diagnosis to index date (years)[1]				
Mean ± SD [median]	1.5 ± 2.4 [0.2]	2.7 ± 2.5 [2.0]	1.8 ± 2.5 [1.0]	2.4 ± 3.9 [1.3]
Year of index WHFE, n (%)[2]				
2017	–	–	2 (0.9 %)	–
2018	182 (36 %)	–	10 (4.4 %)	–
2019	318 (64 %)	–	214 (94.7 %)	–
Time from index WHFE to index date (months)				
Mean ± SD [median]	1.5 ± 1.3 [1.0]	–	1.6 ± 1.5 [1.0]	–
Vital signs[3]**, mean ± SD [median]**				
Heart rate	77.0 ± 14.6 [76]	72.6 ± 12.4 [72]	79.9 ± 14.1 [80]	73.7 ± 11.7 [72]
Systolic blood pressure	117.8 ± 15.6 [118]	119.8 ± 16.2 [118]	122.6 ± 17.5 [120]	121.6 ± 17.8 [120]
Weight	193.6 ± 53.1 [186]	201.8 ± 49.9 [200]	195.4 ± 34.6 [192]	189.5 ± 33.0 [190]
BMI	30.0 ± 7.4 [29]	31.1 ± 6.7 [31]	29.9 ± 5.1 [29]	28.9 ± 5.2 [29]
LVEF[3]**, n (%)**				
<20	70 (14.0 %)	24 (4.8 %)	5 (2.2 %)	3 (1.3 %)
20–29	183 (36.6 %)	132 (26.4 %)	38 (16.8 %)	28 (12.1 %)
30–39	167 (33.4 %)	210 (42.0 %)	140 (61.9 %)	126 (54.3 %)
40–44	67 (13.4 %)	116 (23.2 %)	43 (19.0 %)	75 (32.3 %)
NYHA Class[3]**, n (%)**				
Class I	–	–	2 (0.9 %)	9 (3.9 %)
Class II	–	–	76 (33.6 %)	144 (62.1 %)
Class III	–	–	135 (59.7 %)	78 (33.6 %)

Table 1 (*continued*)

	Integrated delivery network system Health System Sample		physician Nationwide Panel Sample	
	Patients with WHFE (n = 500)	Patients without WHFE (n = 500)	Patients with WHFE (n = 226)	Patients without WHFE (n = 232)
Class IV	–	–	13 (5.8 %)	1 (0.4 %)
Lab values[3], mean ± SD [median]				
Potassium, mmol/L	4.3 ± 0.4 [4]	4.4 ± 0.4 [4]	4.3 ± 0.7 [4.2]	4.3 ± 0.4 [4.2]
Sodium[4], mEq/L	139.1 ± 3.4 [139]	140.6 ± 3.1 [141]	135.6 ± 8.8 [136.0]	137.3 ± 5.7 [138.0]
BNP[5], pg/mL	728.0 ± 826.2 [388]	181.7 ± 175.2 [126]	876.9 ± 1064.9 [455.0]	428.2 ± 514.4 [242.0]
NT-proBNP[6], pg/mL	7,014.8 ± 9,758.5 [3,503]	3,305.5 ± 6,574.5 [1,607]	2064.4 ± 3372.9 [960.0]	1081.6 ± 1171.2 [600.0]
By category				
<2,500 pg/mL	150 (38.1 %)	87 (66.9 %)	39 (70.9 %)	45 (90.0 %)
2,500–5,000 pg/mL	82 (20.8 %)	23 (17.7 %)	12 (21.8 %)	4 (8.0 %)
>5,000 pg/mL	162 (41.1 %)	20 (15.4 %)	4 (7.3 %)	1 (2.0 %)
Hemoglobin[7], g/dL	12.5 ± 2.3 [12]	17.3 ± 76.2 [14]	10.1 ± 5.1 [12.0]	10.9 ± 3.9 [12.0]
CKD Stage[8]				
Stage 1 (eGFR ≥90)	0 (0.0 %)	1 (0.2 %)	8 (6.7 %)	11 (8.7 %)
Stage 2 (eGFR 60–89)	254 (50.8 %)	255 (58.8 %)	41 (34.5 %)	48 (38.1 %)
Stage 3 (eGFR 30–59)	203 (40.6 %)	159 (31.8 %)	69 (58.0 %)	64 (50.8 %)
Stage 4 (eGFR 15–29)	36 (7.2 %)	17 (3.9 %)	0 (0.0 %)	3 (2.4 %)
Stage 5 (eGFR <15)	7 (1.4 %)	2 (0.5 %)	1 (0.8 %)	0 (0.0 %)
BUN[9], mg/dL	26.1 ± 15.1 [22]	21.8 ± 11.9 [19]	37.2 ± 68.2 [25.0]	36.6 ± 83.5 [24.0]
Serum creatinine, mg/dL	1.3 ± 0.6 [1]	1.2 ± 0.5 [1]	1.6 ± 2.8 [1.2]	1.3 ± 1.0 [1.2]
HbA1c[10]				
Normal (<5.7 %)	93 (27.3 %)	37 (17.9 %)	10 (14.5 %)	20 (20.6 %)
Pre-diabetes (5.7 %–6.4 %)	87 (25.5 %)	66 (31.9 %)	28 (40.6 %)	35 (36.1 %)
Diabetes (>6.4 %)	161 (47.2 %)	104 (50.2 %)	31 (44.9 %)	42 (43.3 %)
Comorbidities[3], n (%)				
Hypertension	332 (66.4 %)	292 (58.4 %)	145 (64.2 %)	145 (62.5 %)
Coronary artery disease	280 (56.0 %)	287 (57.4 %)	79 (35.0 %)	83 (35.8 %)
Atrial fibrillation	195 (39.0 %)	164 (32.8 %)	66 (29.2 %)	70 (30.2 %)
Peripheral artery disease	114 (22.8 %)	113 (22.6 %)	25 (11.1 %)	17 (7.3 %)
Stroke	62 (12.4 %)	48 (9.6 %)	13 (5.8 %)	7 (3.0 %)
Severe uncorrected valve disease	34 (6.8 %)	17 (3.4 %)	1 (0.4 %)	1 (0.4 %)
COPD/emphysema	107 (21.4 %)	77 (15.4 %)	39 (17.3 %)	36 (15.5 %)
Obstructive sleep apnea	50 (10.0 %)	63 (12.6 %)	26 (11.5 %)	32 (13.8 %)
Depression	48 (9.6 %)	38 (7.6 %)	21 (9.3 %)	27 (11.6 %)
Anxiety disorder	42 (8.4 %)	49 (9.8 %)	17 (7.5 %)	21 (9.1 %)
Diabetes mellitus				
Type 1	–	–	0 (0.0 %)	1 (0.4 %)
Type 2	195 (39.0 %)	157 (31.4 %)	51 (22.6 %)	53 (22.9 %)
Obesity	–	–	49 (21.7 %)	47 (20.3 %)

Table 1 (*continued*)

	Integrated delivery network system Health System Sample		physician Nationwide Panel Sample	
	Patients with WHFE (n = 500)	Patients without WHFE (n = 500)	Patients with WHFE (n = 226)	Patients without WHFE (n = 232)
Chronic kidney disease	163 (32.6 %)	129 (25.8 %)	43 (19.0 %)	42 (18.1 %)
Medications used[11], n (%)				
Beta blocker	393 (78.6 %)	371 (74.2 %)	183 (81.0 %)	198 (85.3 %)
ACEI	191 (38.2 %)	182 (36.4 %)	99 (43.8 %)	131 (56.5 %)
MRA	74 (14.8 %)	106 (21.2 %)	91 (40.3 %)	101 (43.5 %)
ARNI	21 (4.2 %)	78 (15.6 %)	70 (31.0 %)	56 (24.1 %)
ARB	52 (10.4 %)	65 (13.0 %)	43 (19.0 %)	50 (21.6 %)
Hydralazine	–	–	12 (5.3 %)	10 (4.3 %)
Digoxin/digitoxin	–	–	11 (4.9 %)	9 (3.9 %)
Loop diuretics	–	–	12 (5.3 %)	5 (2.2 %)
Thiazide diuretics	–	–	6 (2.7 %)	9 (3.9 %)
Ivabradine	–	–	2 (0.9 %)	2 (0.9 %)
Surgical and procedural history, n (%)				
Implantable cardioverter-defibrillator	123 (24.6 %)	205 (41.0 %)	38 (16.8 %)	49 (21.1 %)
Biventricular pacemaker	22 (4.4 %)	26 (5.2 %)	20 (8.8 %)	18 (7.8 %)
Prior percutaneous coronary intervention	8 (1.6 %)	11 (2.2 %)	36 (15.9 %)	45 (19.4 %)
Coronary artery bypass grafting	72 (14.4 %)	80 (16.0 %)	8 (3.5 %)	19 (8.2 %)
Valve replacement	27 (5.4 %)	27 (5.4 %)		
Aortic valve	–	–	2 (0.9 %)	0 (0.0 %)
Mitral valve	–	–	0 (0.0 %)	1 (0.4 %)
Transcatheter mitral valve repair	0 (0.0 %)	0 (0.0 %)	2 (0.9 %)	0 (0.0 %)
Implantable cardiovascular hemodynamic monitoring device	0 (0.0 %)	0 (0.0 %)	1 (0.4 %)	3 (1.3 %)

Abbreviations: ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin-receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; HbA1c: Hemoglobin A1C; HF: heart failure; HfrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: *N*-terminal-pro hormone BNP; NYHA: New York Heart Association; SD: standard deviation; WHFE: worsening heart failure event.

Notes:

[1] Date of initial HfrEF diagnosis was based on clinical syndrome of HF..

[2] Date of index WHFE was the most recent WHFE prior to the index date..

[3] Assessed at the index date or at the most recent prior assessment within 12 months before index date..

[4] For the WHFE cohort and without WHFE cohort, there were 154 and 154 patients with data available for the physician panel, respectively..

[5] For the WHFE cohort and without WHFE cohort, there were 76 and 68 patients with data available for the physician panel, respectively, and 6 and 4 patients for the Integrated delivery network system, respectively..

[6] For the WHFE cohort and without WHFE cohort, there were 55 and 50 patients with data available for the physician panel, respectively, and 384 and 130 patients for the the integrated delivery network system, respectively..

[7] For the WHFE cohort and without WHFE cohort, there were 154 and 158 patients with data available for the physician panel, respectively..

[8] For the WHFE cohort and without WHFE cohort, there were 119 and 126 patients with data available for the physician panel, respectively..

[9] For the WHFE cohort and without WHFE cohort, there were 146 and 162 patients with data available for the physician panel, respectively..

[10] For the WHFE cohort and without WHFE cohort, there were 69 and 97 patients with data available for the physician panel, respectively, and 341 and 207 patients for the the integrated delivery network system, respectively.

[11] Hydralazine, digoxin/digitoxin, loop diuretics, thiazide diuretics, and ivabradine were only assessed for the physician panel.

time from index WHFE to index date was 1.5 (±1.3) months. Patients with WHFE had higher natriuretic peptide levels (BNP) (mean 728 vs. 182 pg/mL) and NT-proBNP (7,015 vs. 3,306 pg/mL), higher rates of chronic comorbidities, and less often had an implantable cardioverter-defibrillator (24.6 % vs. 41.0 %) than patients without WHFE (Table 1).

At the end of the index visit, 80.6 %, 39.8 %, 10.6 %, 4.6 %%, and 18.4 % of patients with WHFE and 74.6 %, 36.4 %, 14.2 %, 15.8 %, and 22.4 % of patients without WHFE used beta blocker, ACEI, ARB, ARNI, and MRA, respectively. Triple therapy was used by 13.6 % of patients with WHFE and 16.8 % of those without WHFE, with 14.2 % of patients with WHFE and 13.8 % of patients without WHFE not receiving any HFrEF medications.

3.1.2. Physician panel cohort

A total of 238 cardiologists from the nationwide panel participated and reviewed medical charts of 458 patients with HFrEF, including 226 with WHFE and 232 without WHFE. About 42.4 % of the cardiologists were HF specialists, 7.1 % were electrophysiologists, and the remaining half were neither. Most cardiologists were from the Northeast (32.4 %) or the South (32.8 %), and practice in an academic institution (39.5 %) or private setting (37.8 %). These cardiologists had experience treating HF (17.1 ± 8.2 years).

The mean (± standard deviation) age at the index date was 61.9 (±11.4) years for patients with WHFE and 63.0 (±10.7) years for patients without WHFE. Over 60 % of patients were White, and 31.4 % of the WHFE cohort and 23.7 % of the cohort without WHFE were Black. About 40 % of patients had commercial insurance, while slightly over 40 % had Medicare. About half of the patients were either current or past smokers (Table 1).

The mean time from initial HFrEF diagnosis to index date was 1.8 (±2.5) years in the WHFE cohort and 2.4 (±3.9) years in the cohort without WHFE. Treatment use and clinical outcomes in the 12-month follow-up period after index date were collected. Among patients with WHFE, the mean time from index WHFE to index date was 1.6 (±1.5) months. Compared to patients without WHFE, patients with WHFE were more likely to be NYHA class III or IV (65.5 % vs. 34.0 %), tended to have higher BNP (877 vs. 428 pg/mL) and NT-proBNP (2,064 vs. 1,082 pg/mL). The prevalence of comorbidities was similar between cohorts (Table 1).

At the end of the index visit, 84.5 %, 42.5 %, 15.0 %, 42.9 %, and 50.0 % of patients in the WHFE cohort and 87.9 %, 54.3 %, 20.7 %, 33.2 %, and 50.9 % of patients without WHFE used beta blocker, ACEI, ARB, ARNI, and MRA, respectively. Triple therapy was used by 42.0 % of patients with WHFE and 43.5 % of those without WHFE, with 6.1 % of patients with WHFE and 5.6 % of patients without WHFE not receiving any HFrEF medications.

Compared to patients from the integrated delivery network system cohort, patients from the physician panel were younger, more racially diverse, had lower rates of current or past smoking, lower rates of chronic comorbidities, higher LVEF, lower NT-proBNP, and more likely to receive HFrEF guideline-directed medical treatments.

3.2. Clinical outcomes

3.2.1. All-cause death and all-cause hospitalizations

The incidence rate of all-cause death was 28.2 and 13.4 per 100 patient years in the WHFE and reference cohort, respectively, in the integrated delivery network system cohort and 1.5 and 1.2 per 100

patient years, respectively, in the physician panel. Patients with WHFE had a greater risk of all-cause death than patients without WHFE in the integrated delivery network system cohort during the follow-up period after adjustment (HR 2.08, 95 % CI [1.58, 2,74], p < 0.001). There was no statistically significant difference in all-cause mortality between those with and without WHFE in the physician panel (HR 1.32, p = 0.61) (Table 2; Fig. 2).

The incidence rate of all-cause hospitalization was 126.1 and 52.3 per 100 patient years in the WHFE and reference cohort, respectively, in the integrated delivery network system cohort. Patients with WHFE had a greater risk of all-cause hospitalization than those without WHFE during the follow-up period (HR 2.21, 95 % CI [1.86, 2.62], p < 0.001). The HR varied over time and was 4.65, 4.14, 3.68 and 3.55 at 3 months, 6 months, 12 months, and 15 months follow-up, respectively. The median time to all-cause hospitalization was shorter in patients with WHFE than those without WHFE (4.7 months vs 17.6 months) (Table 2; Fig. 2). All-cause hospitalization was not collected from the physician panel.

3.2.2. HF-related hospitalization and next WHFE

The incidence rate of HF-related hospitalization was 82.7 and 32.3 per 100 patient years in the WHFE and reference cohort, respectively, in the integrated delivery network system cohort and 45.9 and 29.6 per 100 patient years, respectively, in the physician panel. The incidence rate of subsequent WHFE was 101.1 and 38.4 per 100 patient years in the WHFE and reference cohort, respectively, in the GHS and 51.5 and 30.0 per 100 patient years, respectively, in the physician panel.

In both integrated delivery network system cohort and physician panel, patients with WHFE had a greater risk of HF-related hospitalization (integrated delivery network system cohort: HR 2.40, 95 % CI [1.97, 2.92], p < 0.001; physician panel: HR 1.53, 95 % CI [1.10, 2.15], p < 0.05) and next WHFE (integrated delivery network system cohort: HR 2.41, 95 % CI [2.00, 2.90], p < 0.001; physician panel: HR 1.67, 95 % CI [1.20, 2.33], p < 0.01) than patients without WHFE during the follow-up period (Table 2; Fig. 3). The HRs of HF-related hospitalization and next WHFE varied over time in the integrated delivery network system cohort and stratified results showed that the HRs of HF-related hospitalization for patients with vs. without WHFE were 6.64, 5.75, 4.98, and 4.75 at 3 months, 6 months, 12 months, and 15 months follow-up, respectively. The HRs of next WHFE for patients with vs. without WHFE in the integrated delivery network system cohort were 7.73, 6.52, 5.51 and 5.22 at 3 months, 6 months, 12 months, and 15 months follow-up, respectively.

3.2.3. Composite outcome measures

The incidence rate of next HF-related hospitalization or cardiovascular death was 46.6 and 30.3 per 100 patient years in the WHFE and reference cohort, respectively, in the physician panel. Patients with WHFE had a greater risk of next HF-related hospitalization or cardiovascular death than those without WHFE during the follow-up period (HR 1.53, 95 % CI [1.10, 2.14], p < 0.05). Risk of next HF-related hospitalization or cardiovascular death was not assessed in the integrated delivery network system cohort due to lack of cause of death information (Table 2).

The incidence rate of HF-related hospitalization or all-cause death was 100.2 and 41.1 per 100 patient years in the WHFE and reference cohort, respectively, in the integrated delivery network system cohort and 47.2 and 30.3 per 100 patient years, respectively, in the physician panel. In both the integrated delivery network system cohort and physician panel, patients with WHFE had a greater risk of next HF-related hospitalization or all-cause death than patients without WHFE during the follow-up period (integrated delivery network system cohort: HR 2.28, 95 % CI [1.91, 2.73], p < 0.001; physician panel: HR 1.55, 95 % CI [1.11, 2.17], p < 0.01). The HR varied over time in the integrated delivery network system cohort and were 5.31, 4.69, 4.14, and 3.97 at 3 months, 6 months, 12 months, and 15 months follow-up, respectively (Table 2).

Table 2

Hazard ratio of clinical outcomes among patients with versus without worsening heart failure event.

	Integrated delivery network system Health System Sample			Physician panel Nationwide Panel Sample		
	Hazard Ratio[a]	95 % CI	P-Value[b]	Hazard Ratio[a]	95 % CI	P-Value[b]
All-cause death	2.08	(1.58, 2.74)	<0.001 *	1.32	(0.45, 3.83)	0.61
All-cause hospitalization	2.21	(1.86, 2.62)	<0.001 *			
HF-related Hospitalization	2.40	(1.97, 2.92)	<0.001 *	1.53	(1.10, 2.15)	<0.05*
Next WHFE	2.41	(2.00, 2.90)	<0.001 *	1.67	(1.20, 2.33)	<0.01*
HF-related hospitalization or cardiovascular death	–	–	–	1.53	(1.10, 2.14)	<0.05*
HF-related hospitalization or all-cause death	2.28	(1.91, 2.73)	<0.001 *	1.55	(1.11, 2.17)	<0.01*

Abbreviations: CI: confidence interval; HF: heart failure; HfrEF: heart failure with reduced ejection fraction; WHFE: worsening heart failure event.
Notes.
[a] A hazard ratio greater than 1 indicates that patients with a worsening heart failure event have a higher risk of having the event than patients without a worsening heart failure event patients, while a hazard ratio less than 1 indicates that patients have a lower risk of having the event. The models adjusted for age, gender, race, smoking status, and use of any HFrEF medications (i.e., beta blocker, ACEI, ARB, ARNI, MRA) on or prior to index date.
[b] P-values <0.05 are indicated with one asterisk ("*").
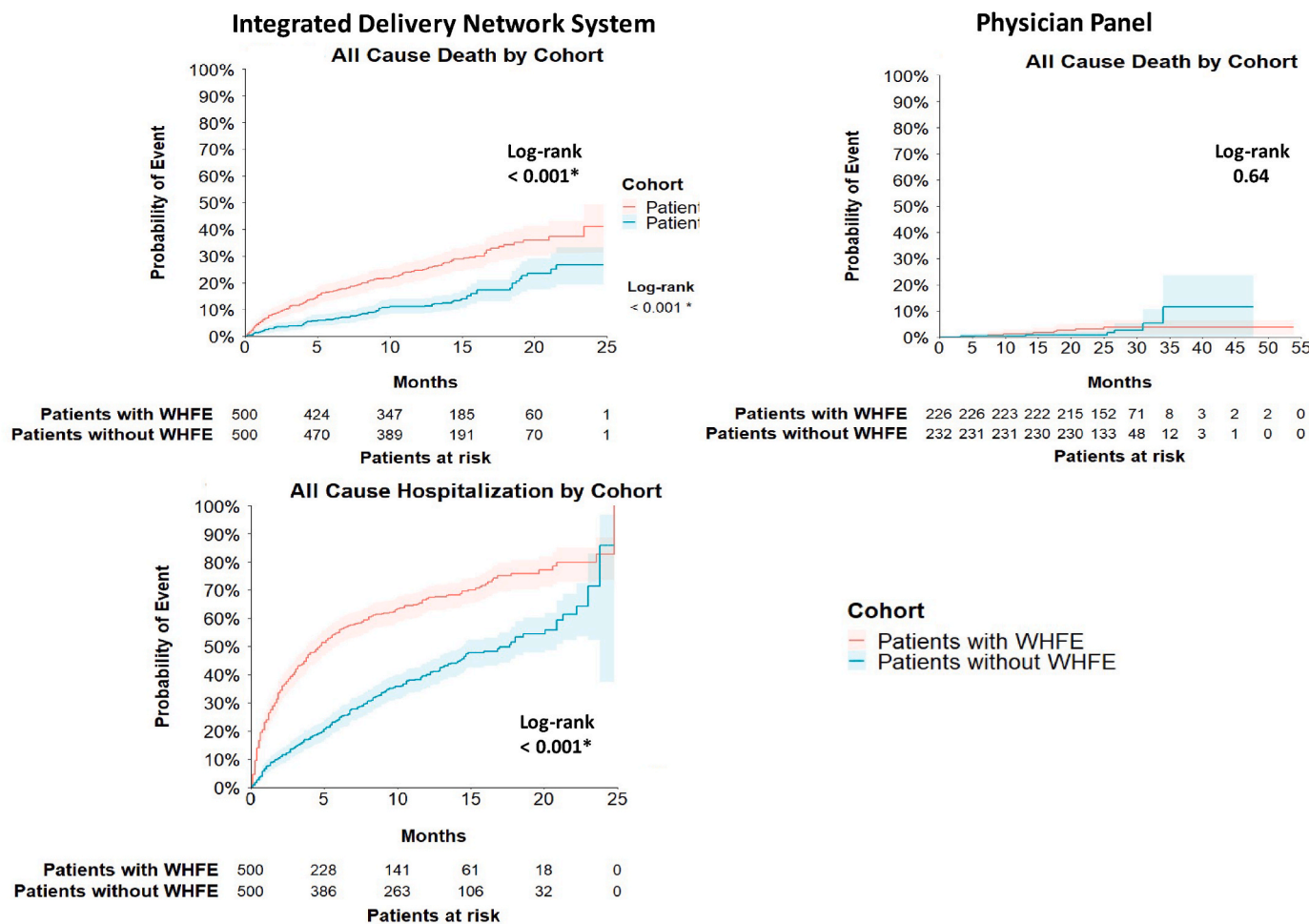
Fig. 2. Cumulative incidence of all-cause mortality and hospitalization outcomes by cohort.

4. Discussion

The CHART-HF study used electronic medical record data from two different sources to characterize the clinical characteristics and clinical outcomes of patients with HFrEF with and without WHFE in two representative US clinical practices. The study collected data from real-world clinical practices where clinics are not purposefully enrolled in quality improvement initiatives as in PINNACLE, or in the setting of clinical trials where eligibility criteria select for patients with higher background use of and increased adherence to guideline-directed medical therapy [3]. The study sample in CHART-HF generally reflect

patients seen at most US cardiology clinics. The physician panel provided a representative patient sample with over 30 % non-white, 40 % commercially insured, and 40 % from academic institutions.

Consistent with the prior literature mostly based on clinical trial populations, our study found that patients with WHFE had worse outcomes, including higher risks of HF-related and all-cause hospitalization, next WHFE, and mortality even after adjusting for age, gender, race, smoking status, as well as use of any guideline directed medications on or prior to index date. Particularly, the 1-year mortality rate of patients with WHFE in the integrated delivery network system cohort aligns with two prior studies using US military EMR data and Canadian
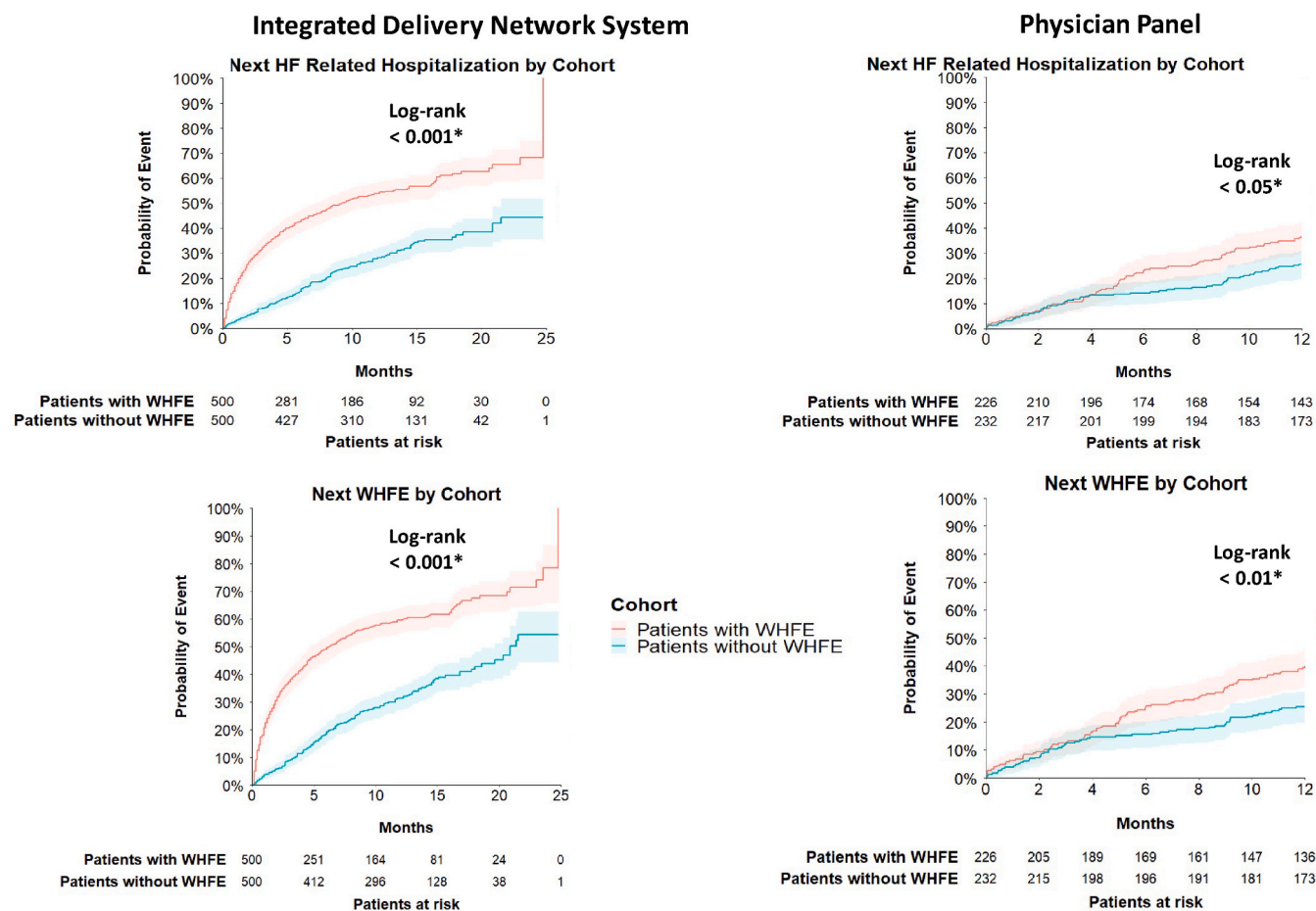
Fig. 3. Cumulative incidence of heart failure outcomes by cohort.

British Columbia health care utilization databases, which report 1-year mortality rates of 27–34 % after a HF hospitalization [18,19]. It is important to note that about 75–80 %, 55–66 %, and 18–22 % of patients in the integrated delivery network system cohort and 85–88 %, 81–83 %, and 50 % of patients in the physician panel were on beta blocker, ACEI/ARB/ARNI, and MRA, respectively, on index date. Among patients from the integrated delivery network system cohort, those with WHFE had at least 2-fold greater risk of all-cause death, HF-related hospitalization, another WHFE, and all-cause hospitalization compared to those without WHFE. The additional risks of all-cause hospitalization, HF-related hospitalization, and subsequent WHFE experienced by patients with WHFE vs. those without were even greater immediately after the WHFE. The decrease in risk for the aforementioned clinical outcomes over time may be due to survival bias or patient disease stabilization over time in the follow-up period after acute WHFE. Our real-world, U.S.-based clinical practice data suggests that despite advances in therapies targeting patients with HFrEF with WHFE, there remains unmet need to improve outcomes in this high-risk patient population. Comparing between cohorts, HFrEF patients with WHFE had lower LVEF, more advanced NYHA class, and more comorbidities on their index date compared to patients without WHFE, as observed in the PINNACLE registry data [20]. In addition, patients with WHFE also had higher natriuretic peptide levels than patients without WHFE on and prior to index date. These clinical characteristics could potentially help identify HFrEF patients at high risk for WHFE.

Patients included in CHART-HF had worse clinical outcomes compared to those in the clinical trials. For example, 29.6 % of patients in the placebo arm in the VICTORIA trial had a HF-related hospitalization over a median of 10.8 months follow-up [6]. In CHART-HF, 36.7 % of patients with WHFE from the physician panel and 50.4 % of patients with WHFE from the integrated delivery network system cohort had a HF-related hospitalization during the 12 months follow-up. Compared to the trial population, patients from the physician panel were younger (61.9 vs. 67.2 years) but more likely to be NYHA Class III or IV (65.5 % vs. 40.6 %). While patients from the integrated delivery network system cohort were more similar to the trial population, they were slightly older (68.6 vs. 67.2 years), more frequently White (95.2 % vs. 64.1 %), and had slightly higher BMI (30.0 vs. 27.9). The worse clinical outcomes in real-world clinical practice could be attributed to more comorbidities and advanced disease in a less selective population. In addition, patients in clinical trials are more likely to be treated according to guidelines, have improved adherence, are tightly surveilled, and have a lower attrition risk, leading to better outcomes compared to patients who are not enrolled in trials. For example, the mean time from the index WHFE to next cardiologist visit in our study was 1.5–1.6 months, while the general best practice recommends a follow-up within 7 days after a WHFE event. Overall, our study findings of poor clinical outcomes among patients with WHFE highlight the need for increased use of guideline-directed medical therapy, more timely patient follow-up, and greater adoption of cardiac resynchronization therapy in real-world clinical practice. Our study also confirms the decades-long poor prognosis among patients with HF [21]. In advanced HF patients, mechanical circulatory support, transplant, palliative care or hospice care should be considered.

The study also found higher rates of hospitalizations, next WHFE, and mortality among patients from the integrated delivery network system cohort than those from the physician panel. Compared to patients from the physician panel, patients from the integrated delivery

network system cohort were older and sicker as evidenced by increased burden of comorbidities and clinical biomarkers of HF on the index date. In addition, the differences in clinical outcomes could also be related to differences in treatment, health insurance status, and access to health care. The integrated delivery network system cohort provides care to people in rural areas. Based on treatment patterns evaluated in CHART-HF, patients from the integrated delivery network system cohort were also less likely to receive guideline-directed medical treatment than patients from the physician panel, although 13%–32 % of the study population who had LVEF >40 % might not be subject to the same treatment guidelines. However, differences in treatment patterns observed may be due to differences in data collection and/or reporting bias (i.e., EMR vs. chart extraction). EMR data from the integrated delivery network system cohort might not capture medications filled outside of network. Nonetheless, higher rates of hospitalizations and mortality observed in the integrated delivery network system cohort underscore the need to better understand predictors of WHFE and how to incorporate them into secondary preventive strategies (e.g., adequate guideline-directed medical treatments) for patients with HFrEF.

This study has several limitations. First, the integrated delivery network system cohort is a regional health care provider in central, south-central, and northeastern Pennsylvania and southern New Jersey. Patients from this system were more homogeneous and less representative of the general patient population in the US. To partially address this limitation, we included patient medical charts extracted by cardiologists from the physician nationwide panel. While the geographic location and race/ethnicity of patients from the physician nationwide panel were more diverse, the patient sample was smaller and may be subject to selection bias. While the participating cardiologists received instructions on how to randomly select patients from their practice, the possibility of selection bias cannot be ignored as clinicians may recall specific patients more easily because of more consistent follow-up or more events. The smaller differences in clinical outcomes between patients with and without WHFE observed among patients from the physician panel may be partially attributed to the selection bias towards patients with better outcomes by cardiologists from the panel. Second, the identification of patients, disease characteristics, and treatments were limited by the availability and accuracy of data in the medical record. As information in patients' medical charts were not primarily collected for research purposes, detailed data were lacking for some study measures and outcomes. Relatedly, the extent of information documented in charts varied across patients. Third, results from the physician survey were subject to the completeness and quality of the data entered by clinicians. However, such limitations should be mitigated by established policies by the physician panel where the quality of data is closely monitored, with underperformance resulting in removal from the physician panel. Nonetheless, it is possible that cardiologists participating in the physician nationwide panel may not be fully representative of all US cardiologists. Finally, we did not account for the medication changes that might or might not have taken effect after index visit.

5. Conclusions

In conclusion, HFrEF patients with recent WHFE had worse clinical outcomes irrespective of the setting where they were treated. Despite advances in therapies targeting patients with HFrEF with WHFE, there is still great need to improve the prognosis of this high-risk patient population. Patients with recent WHFE may need additional resources and novel treatment strategies following WHFE.

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CRediT authorship contribution statement

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