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Original Article

Worsening Heart Failure and Medication Use in HFrEF: A Finnish Retrospective Registry Study and Patient Survey

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ABSTRACT

Background and Objectives: Understanding worsening heart failure events (WHFEs) and clinical practices in the real world is essential in heart failure (HF) management. The primary objective of this single-center, retrospective, observational study, including a patient survey, was to characterize WHFEs and associated factors during the first year after the incident HF diagnosis in Finnish patients. Secondly, implementation and adherence to guideline-directed medical therapy (GDMT) and mortality during the whole follow-up were assessed.
Methods: Incident HF patients (International Classification of Diseases, 10th Revision: I50) with reduced ejection fraction (HFrEF; <40%) were identified between 2013–2019 from the hospital data lake of Southwest Finland. Clinical characteristics, healthcare resource utilization, medication prescriptions and purchases, and deaths were collected from hospital records and national registers between 2011–2021. A survey was linked with register data for a subgroup of patients. Associations between explanatory factors, WHFEs, and mortality were studied using logistic and Cox regression models.
Results: Among 570 HFrEF patients, 23% (n=133) experienced a WHFE within the first year after the incident diagnosis. During this 1-year period, 85% used angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 90% beta-blockers, and 44% mineralocorticoid receptor antagonists, and >80% of patients were adherent to these medications. WHFEs were associated with higher risk of mortality (hazard ratio [HR], 1.82; 95% confidence interval [CI], 1.31–2.53; p<0.001), whereas adherence was associated with a lower risk of WHFEs (odds ratio, 0.31; 95% CI, 0.20–0.48; p<0.001) and mortality (HR, 0.66; 95% CI, 0.47–0.94; p=0.021) in multivariate models. Quality of life was lower in patients with (n=47) than without WHFEs (n=100).
Conclusions: Improving adherence is crucial for mitigating adverse outcomes in HF.

Keywords: Heart failure; Medication adherence; Registries, Symptom exacerbation; Quality of life

INTRODUCTION

Heart failure (HF) is a complex, progressive clinical syndrome characterized by symptomatic stability of variable durations, punctuated by episodes of worsening symptoms despite background treatment. Worsening heart failure events (WHFEs) are a sign of the disease progressing to a new phase, and the majority of HF patients develop WHFEs during their disease course.[1] WHFEs are associated with increased risk of mortality, hospital admissions, higher healthcare resource use (HCRU), and poor quality of life (QoL), and the main cost driver in HF.[1-4]

Due to their high burden and prognostic impact, prevention of the first and recurring WHFEs is a main target of HF treatment, in addition to improvement of survival, functional capacity, and QoL.[1,5] According to the European Society of Cardiology (ESC) care guidelines, early initiation of guideline-directed medical treatment (GDMT) including beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), and mineralocorticoid receptor antagonists (MRAs) are recommended for all HF patients with reduced left ventricular ejection fraction (LVEF ≤40%; heart failure with reduced ejection fraction [HFrEF]).[5] Diuretics are recommended for patients with signs of congestion. In 2023, the ESC added a recommendation to include sodium-glucose cotransporter-2 (SGLT-2) inhibitors to GDMT for all HF patients regardless of their LVEF and diabetic status.[5,6] Moreover, options such as angiotensin receptor-neprilysin inhibitors (ARNIs) and the oral soluble guanylate cyclase stimulator vericiguat have become available for the treatment of selected HFrEF patients with WHFEs.[6,7] According to the Finnish Current Care Guidelines (2023) ACEIs/angiotensin receptor blockers (ARBs), BBs, SGLT-2 inhibitors and MRAs constitute the cornerstone of HF management.[8] ARNIs can be used instead of ACEIs/ARBs in those HFrEF patients that, despite having the aforementioned treatments, continue to experience troublesome symptoms.

Adherence to GDMT is critical to overall disease management and to decrease adverse outcomes in HF patients.[9,10] Reported medication adherence rates vary widely (10–98%) in HF patients depending on the population and methodology used, and poor adherence to medication is common.[9,11,12] Low adherence was associated with increased hospitalizations and mortality in patients with HFrEF, whereas high adherence was associated with fewer HF symptoms and lower hospitalization rates and mortality.[11-14] Medication adherence is affected by various patient-related factors such as age, multimorbidity, and number of medications used, in addition to other factors related to healthcare services and support available.[12,15]

To evaluate and develop current clinical practices, it is essential to characterize disease outcomes and implementation of care guidelines in the real world. The Finnish healthcare system provides unique features for such studies, as all citizens have equal access to tax-based public healthcare and detailed data on treatment, HCRU, and patient characteristics are recorded in nationwide health registers and data lakes at the university hospitals. In Finland, HF epidemiology, HCRU, and hospitalizations have been previously described utilizing data in one hospital data lake.[16-18] However, a comprehensive picture of treatment implementation, as well as a detailed understanding of factors associated with WHFEs and patients' perspectives are lacking. The primary objective of this single-center, retrospective, observational study combined with a patient survey, was to characterize WHFEs during the first year after the incident HF diagnosis and associated factors in Finnish patients with HFrEF. Secondly, implementation and adherence to GDMT, and mortality during the whole follow-up were assessed.

METHODS

Study population and subgroups

This was a single-center, observational, retrospective study. The study population was identified from the Auria hospital data lake, covering data from the secondary care setting in the Hospital District of Southwest Finland (population base approximately 490,000 individuals), between January 1, 2013 and December 31, 2019 (**Figure 1**). The study population included all incident HF patients in the Auria hospital data lake fulfilling the following criteria: ≥1 HF diagnosis (International Classification of Diseases, 10th Revision [ICD-10]: I50), ≥18 years old at the time of the recording of the first HF diagnosis, and a history without I50 diagnosis for ≥2 years before the first HF diagnosis. The first HF diagnosis recording date was defined as the index date for patients.

The main study population consisted of patients with HFrEF (LVEF ≤40%) (**Figure 1**). The LVEF was extracted from echocardiogram (ECHO) data from the Auria hospital data lake using a new, advanced text mining method as described in a previous study.[16] To be included in the HFrEF cohort, a patient should have LVEF ≤40% based on ECHO measurements at most three months before/after the index date (the closest measurement to the index date was considered). HFrEF patients were further divided into subgroups based on whether or not they developed a WHFE within 1 year after the index date (WHF and nWHF, respectively). A WHFE was defined as a healthcare encounter that occurred in the secondary healthcare unit >7 days after the index date, and 1) started as an emergency room visit and continued (within 24 hours) as an inpatient visit that included an HF diagnosis (ICD-10: I50) as a

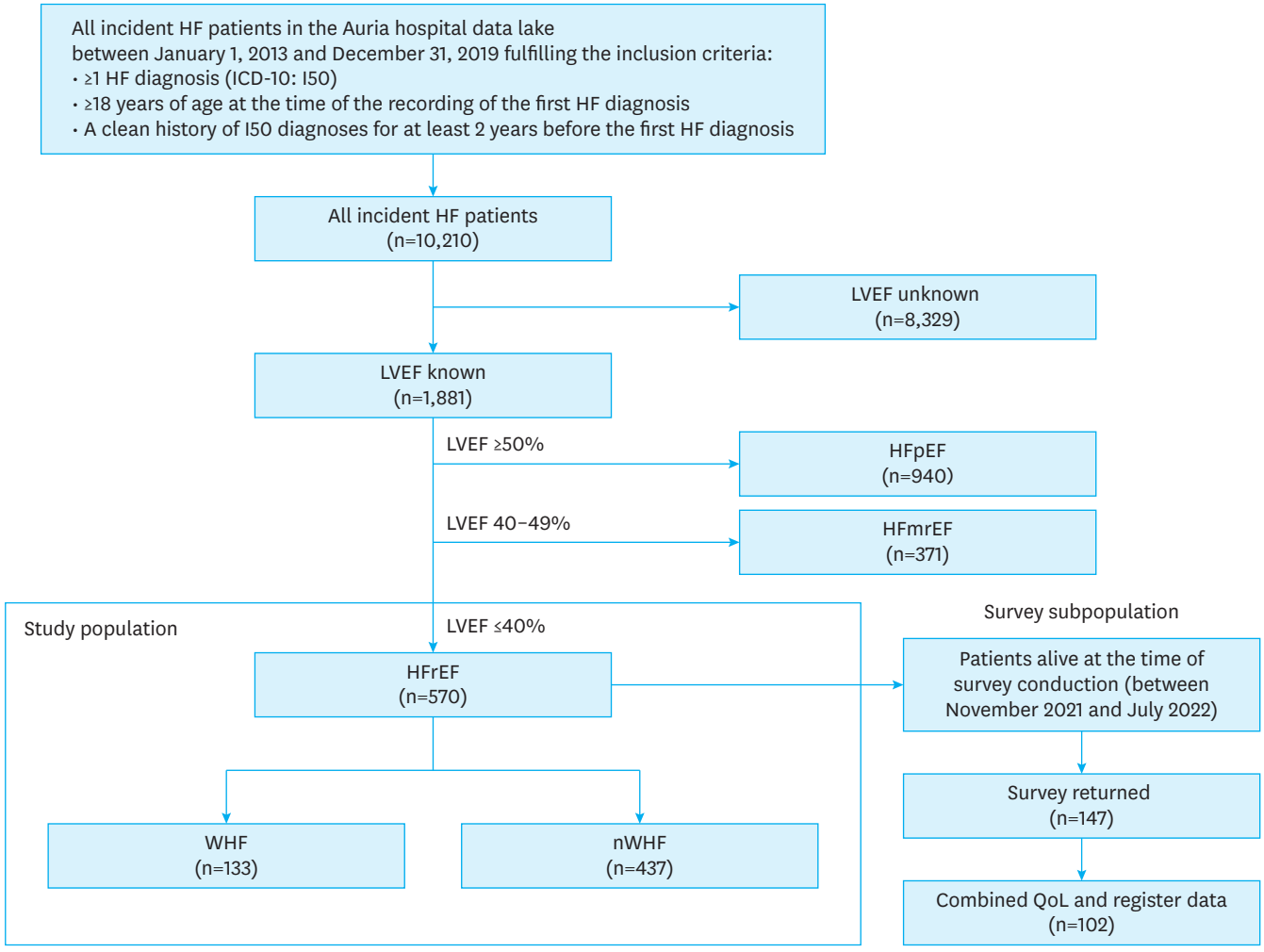

Figure 1. Formation of the main study population and the survey subpopulation.
The main study population is patients with HFrEF.
HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD-10 = International Classification of Diseases, 10th Revision; LVEF = left ventricular ejection fraction; nWHF = patients without WHFE during the first year after the index date; WHF = patients with WHFE during the first year after the index date; WHFE = worsening heart failure event; QoL = quality of life.

primary or secondary diagnosis, and/or 2) included an intravenous administration of furosemide (Anatomic Therapeutic Chemical [ATC] code: C03CA01) or levosimendan (C01CX08) at the cardiology department and an HF diagnosis (ICD-10: I50) as a primary or secondary diagnosis.

In addition, a separate survey subgroup consisted of HFrEF patients who replied to the patient survey (described below).

Registry data collection

Data for the identified patients were collected from January 1, 2011 until December 31, 2020 or death, whichever occurred first (a minimum of 2 years of baseline data and a maximum 8 years of follow-up). Data on demographic and clinical characteristics including ICD-10 diagnoses, laboratory measurements, secondary care HCRU, and medications administered and prescribed at the hospital were collected from the Auria hospital data lake. Supplementary data on medications prescribed elsewhere than at the hospital, and on all prescribed medication purchases, were collected from the Prescription Centre by the Social Insurance Institution of Finland (Kela) and supplementary data on diagnoses (ICD-10) from the Register of Primary Health Care Visits (Avohilmo) by the Finnish Institute for Health and Welfare (THL). Data on dates and causes of death was collected from The Causes of Death Register by Statistics Finland. Individual-level data from different register data sources and patient survey were linked by using social security numbers (SSNs).

Survey data collection and linkage with registry data

In addition to the retrospective register data, patient survey data were collected for those HFrEF patients who were alive at the time of survey conduction (November 2021 to July 2022; **Figure 1**). A generic QoL survey (EQ-5D-5L) and questions on physical functioning based on the New York Heart Association (NYHA) classification system were sent in paper format.[19,20] The Heart Center personnel at the Turku University Hospital sent, collected, and digitalized the survey data. Findata (the Finnish Health and Social Data Permit Authority) linked the survey and registry data using SSNs. SSNs were replaced by study identification numbers (SID) before analyses, and all analyses were performed using pseudonymized data on Findata's secure remote access data processing environment.

Descriptive variables

Laboratory values for the WHF group were collected from the closest measurement a minimum of 1 month and a maximum of 1 year before the WHFE (**Supplementary Figure 1**). The choice of this period of time was based on the aim to characterize the clinical status of the patients during the follow-up period before the development of WHFE and to assess whether clinical factors are predictive of WHFE. For the nWHF group, laboratory data were collected correspondingly from the closest measurement a minimum of 1 month and a maximum of 1 year before the end of the 1st follow-up year or death, whichever occurred first. Diagnoses of comorbid conditions (ICD-10) were collected using all data available before a WHFE (WHF group) or the end of the 1st follow-up year/death (whichever occurred first, nWHF group). A multicomorbidity index was defined as a count of distinct ICD-10 codes with 3-digit accuracy. Similarly, a polypharmacy index was defined as a count of distinct ATC codes with 4-digit accuracy.

The total number of WHFEs and the mean number of WHFEs during the 1st follow-up year and the follow-up were analyzed in the WHF subgroup. To address HCRU associated with WHFEs, all healthcare visits (classified by the visit type: inpatient, >24 hours visit; emergency room; intensive care) were analyzed from the period between the first (i.e., the date of fulfilling the criteria of WHFE) and last healthcare visit during the WHFE. Healthcare encounters within <7 days apart were considered to be associated with the same WHFE, i.e., the last encounter was defined as the last visit which was a maximum of 7 days after the previous visit.

The use of pharmacological treatments was assessed based on purchases of reimbursable prescription drugs from community pharmacies. The medication groups were based on ATC classification codes: ACEIs (ATC: C09AA02, C09AA03, C09AA04, C09AA05)/ARBs (ATC: C09CA01, C09CA06, C09CA03); BBs (ATC: C07AB07, C07AG02, C07AB02, C07AB12); and MRAs (ATC: C03DA01, C04DA04). Medication use during the follow-up was assessed by follow-up year starting from the index date until the 5th follow-up year. Medication use was defined as ≥1 drug purchase during the respective follow-up year.

Adherence to HF medications was evaluated using a maximum of 2 years of data preceding the event (the first WHFE, death, or 1 year of follow-up, whichever came first) (**Supplementary Figure 1**). For each ATC group, the 1-year adherence assessment period started from the earliest purchase within this evaluation period and ended at WHFE (WHF group) or the end of the 1st follow-up year or death, whichever occurred first (nWHF group). Within this evaluation period, adherence was calculated as the number of 3-month windows with a refill purchase divided by the total number of time windows.[21]

Adherence was presented by the ATC group level (ACEIs/ARBs, BBs, MRAs, based on ATC codes described above), and in the models as a minimum of adherences over all ATC groups. For sensitivity analysis, a model with an alternative adherence definition was performed. In this analysis, adherence was defined as the number of purchased prescriptions divided by the total number of prescriptions (proportion of purchased vs. prescribed medications). For example, if a patient had 10 prescriptions in the evaluation period and has purchased medication at least once for 7 of these prescriptions, the prescribed versus purchased adherence was 70%.

The main adherence definition was categorized as 0–74% (non-adherent) and 75–100% (adherent), based on the observed association with WHFE. In the sensitivity analysis, adherence was categorized as 0–59% (non-adherent) versus 60–100% (adherent). The cutoff-points were based on observed data, as a priori categories for these definitions were not available.

Outcome measures

The primary outcome measure was the incidence of a WHFE (binary variable: yes/no) during the 1st year of follow-up. The secondary outcome was all-cause mortality during the whole follow-up. Additionally, the proportion of cardiovascular deaths were evaluated based on ICD codes I20–I79 as the primary or secondary cause of death.

Survey subpopulation and variables

The survey subpopulation was further divided into subgroups based on whether they had a WHFE during the last 3 follow-up years (January 1, 2018 to December 31, 2020) before the survey conduction. Moreover, a separate subgrouping was performed

based on the adherence (adherent vs. non-adherent) evaluated for the survey population using most recent available register data from January 1, 2019 to December 31, 2020.

Data on the patients' physical functioning capacity, based on NYHA classification (I, II, and III–IV) and QoL based on EQ-5D-5L visual analog scale (VAS) scores, were collected for the survey population. Furthermore, all 49 survey questions were screened to find possible factors associated with low adherence in HFrEF patients.

Statistical analyses

In all descriptive analyses, continuous variables were reported by mean ± standard deviation, median (1st and 3rd quartiles). Categorical variables were reported by number and proportion (%). Results that concern only 1 to 5 patients are either not presented at all (e.g., for summary statistics of continuous variables), or as "1–5" for categorical variables. The comparison of medication adherence between the subgroups was performed using the t-test.

A logistic regression model with a binary outcome of whether or not patients had a WHFE during the 1st year of follow-up was used to assess the factors associated with WHFE. Variables selected for the model were based on previous literature on factors shown to be associated with hospitalizations in HFrEF patients.[16] The association between all-cause mortality and explanatory factors (age group, sex, WHF, total adherence, and polypharmacy and multimorbidity indexes) was assessed using a Cox regression model.

The associations between the register-based adherence and all survey variables were evaluated by comparing the distributions of answers across adherent and non-adherent patients using a chi-squared test of significance.

Statistical analyses were conducted using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). All p values were 2-tailed and $p<0.05$ was considered statistically significant; p values between 0.05 and 0.1 were treated as suggestive.

Ethical considerations

The data permit for the register data was granted by the Finnish Health and Social Data Permit Authority Findata. A study permit was applied for from the Hospital District of Southwest Finland, allowing identification of the study population and contacting of patients for the survey. No ethical evaluation was required for the survey according to the regulations of the Hospital District of Southwest Finland. Informed consent was asked from the patients to link the survey and register data. The investigation conforms with the principles outlined in the Declaration of Helsinki.

RESULTS

Clinical characteristics of WHF and nWHF patients

Altogether 10,210 patients with HF were identified from the register. Of the patients with a reliable LVEF value available (derived by text-mining algorithm) within 3 months from the index date (18.4%, n=1,881), 30.3% (n=570) were included in the main study population of HFrEF patients, whereas 50.0% (n=940) had heart failure with preserved ejection fraction (HFpEFP, LVEF ≥50%;), and 19.7% (n=371) had heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%) (**Figure 1**). Of the HFrEF patients, 23.3% (n=133) were included in the WHF subgroup and 76.7% (n=437) in the nWHF subgroup.

Demographic and clinical characteristics for the WHF and nWHF subgroups are presented in **Table 1**, **Supplementary Tables 1** and **2**. Patients in the WHF subgroup were on average older (mean age 70.2±13.4 years) than in the nWHF subgroup (mean age, 67.8±12.3 years). The mean levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) were higher for the WHF (6,710±6,600 ng/L) compared to the nWHF subgroup (3,800±6,400 ng/L). Of the comorbidities, type 2 diabetes (33.8% vs. 27.0%), myocardial infarction (29.3% vs. 22.0%), chronic kidney disease (30.1% vs. 24.5%), and anemia (10.5% vs. 3.0%) were more often observed in the WHF subgroup than in the nWHF subgroup, respectively (**Supplementary Table 2**).

Characterization of WHFEs

In the WHF subgroup, a total of 308 WHFEs occurred during the whole follow-up period (**Table 2**). The mean number of WHFEs was 1.5±0.9 during the first year and 2.3±2.1 during the whole follow-up. An emergency room visit was coincident with 91.9% (n=283) of the WHFEs, and an intensive care visit with 7.1% (n=22). A total of 91.6% (n=282) of the WHFEs were inpatient stays, with a mean number of 6.0±6.8 inpatient days.

Medication use and adherence in the WHF and nWHF subgroups

A majority of the HFrEF patients used ACEIs/ARBs (85.3%, n=486) and BBs (90.2%, n=514), and 43.9% (n=250) used MRAs during the 1st follow-up year (**Table 3**). The use of these medication groups decreased after the 1st year, most remarkably the use of ACEIs/ARBs. The decrease in medication use was more pronounced for patients in the WHF than nWHF subgroup: the use of ACEIs/ARBs decreased from 89.5% (n=119) in the first year to 68.3% (n=69) in the second year in WHF patients, and from 84.0% (n=367) to 77.6% (n=305) in nWHF patients. In general, the use of SGLT-2 inhibitors and ARNIs was rare during the study period of 2013–2020 (percentage of users <10% per follow-up year).

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Table 1. Description of demographic and clinical characteristics for WHF and nWHF patients

Characteristics	WHF (n=133)	nWHF (n=437)
Age at the diagnosis (years)		
Missing values	0	0
Mean ± SD	70.2±13.4	67.8±12.3
Median (Q1–Q3)	71.0 (61.1–80.9)	68.5 (60.0–76.9)
Sex		
Missing values	0	0
Female	32 (24.1%)	109 (24.9%)
Male	101 (75.9%)	328 (75.1%)
BMI (kg/m^2)		
Missing values	16	94
Mean ± SD	28.1±6.0	28.5±5.7
Median (Q1–Q3)	26.7 (24.0–31.4)	27.7 (24.4–31.9)
Diastolic blood pressure (mmHg)		
Missing values	32	112
Mean ± SD	74.9±12.2	75.8±14.6
Median (Q1–Q3)	73.8 (66.0–81.9)	74.7 (67.0–82.5)
Systolic blood pressure (mmHg)		
Missing values	32	112
Mean ± SD	125.1±16.9	127.8±19.0
Median (Q1–Q3)	122.3 (112.5–134.4)	125.5 (114.3–140.0)
CRP (mg/L)		
Missing values	34	213
Mean ± SD	29.3±34.5	25.9±29.7
Median (Q1–Q3)	14.8 (6.2–37.9)	13.0 (4.4–37.5)
Creatinine (μmol/L)		
Missing values	21	39
Mean ± SD	111.7±63.3	102.6±52.8
Median (Q1–Q3)	97.5 (78.5–125.2)	92.5 (80.8–109.7)
eGFR-EPI (mL/min/1.7)		
Missing values	21	39
Mean ± SD	72.3±22.9	76.5±21.9
Median (Q1–Q3)	76.4 (56.0–89.0)	81.3 (61.5–90.9)
NT-proBNP (ng/L)		
Missing values	38	130
Mean ± SD	6,709.7±6,602.4	3,795.7±6,404.2
Median (Q1–Q3)	4,746.7 (2,295.0–9,365.5)	1,640.0 (852.8–3,893.8)
Potassium (mmol/L)		
Missing values	23	40
Mean ± SD	4.1±0.3	4.2±0.3
Median (Q1–Q3)	4.1 (3.9–4.3)	4.2 (4.0–4.4)
Polypharmacy index		
Missing values	0	0
Mean ± SD	6.5±2.6	5.9±2.2
Median (Q1–Q3)	7.0 (4.0–8.0)	6.0 (5.0–7.0)
Multicomorbidity index		
Missing values	0	0
Mean ± SD	16.9±9.3	15.1±8.5
Median (Q1–Q3)	14.0 (11.0–21.0)	13.0 (9.0–19.0)

Values are presented from the most recent measurement to a minimum of 1 month and a maximum of 1 year before the event date, defined as i) WHFE (WHF patients), or ii) the end of the 1st follow-up year or death, whichever occurred first (nWHF patients). A multicomorbidity index and polypharmacy index are based on all data available before the event date. Categorical variables were reported by number and proportion (%).
BMI = body mass index; CRP = C-reactive protein; eGFR-EPI = estimate glomerular filtrate rate calculated using Chronic Kidney Disease Epidemiology Collaboration; NT-proBNP = N-terminal pro B-type natriuretic peptide; nWHF = patients without WHFE during the first year after the index date; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHF = patients with WHFE during the first year after the index date; WHFE = worsening heart failure event.

Over 80% of patients were adherent to all studied medication groups. Of the patients in the WHF subgroup, 69.6% (n=80), 71.8% (n=84), and 62.5% (n=20) were adherent to ACEIs/ARBs, BBs, and MRAs, respectively (**Table 4**). In the nWHF subgroup, the respective patient proportions were 90.1% (n=346), 89.4% (n=355), and 86.5% (n=173). In the multivariate model adjusted for sex and age group, medication adherence was associated with a significantly lower risk of WHFEs (odds ratio [OR], 0.31;

Table 2. Healthcare resource use related to WHFE for patients with HFrEF

Variable	1st event (n=133)	2nd event (n=74)	3rd event (n=38)	4th event (n=23)	>4th event (n=40)	All (n=308)
Inpatient (>24 hours) visit during the WHFE						
No	7 (5.3%)	9 (12.2%)	1–5	1–5	1–5	26 (8.4%)
Yes	126 (94.7%)	65 (87.8%)	33–37	18–22	35–39	282 (91.6%)
Inpatient days/WHFE						
Mean ± SD	6.8±7.9	5.0±5.4	5.9±6.5	4.6±3.9	6.2±6.7	6.0 (6.8)
Median (Q1–Q3)	5.0 (2.0–8.0)	3.0 (1.0–7.8)	3.5 (1.0–7.8)	5.0 (1.0–7.0)	3.0 (2.0–7.5)	4.0 (1.0–8.0)
Emergency room visit* during the WHFE						
No	22 (16.5%)	1–5	1–5	0 (0.0%)	0 (0.0%)	25 (8.1%)
Yes	111 (83.5%)	69–73	33–37	23 (100.0%)	40 (100.0%)	283 (91.9%)
Intensive care visits						
No	117 (88.0%)	69–73	33–37	23 (100.0%)	35–39	286 (92.9%)
Yes	16 (12.0%)	1–5	1–5	0 (0.0%)	1–5	22 (7.1%)

The summaries include patients who had a WHFE during the first year of follow-up and are presented stratified by the sequential number of WHFE over the whole follow-up period (i.e., not only over the first year of follow-up). For categorical variables, results that concern one to five patients are presented as "1–5", and a range of five is also presented for the other category of the same variable. Categorical variables were reported by number and proportion (%).
HFrEF = heart failure with reduced ejection fraction; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHFE = worsening heart failure event.
*Emergency room visit was defined according to the Finnish healthcare recording system that specifies a visit to be acute care.

Table 3. Description of HF medication use in patients with HFrEF from the 1st to the 5th year of follow-up

Variable	Strata	Year 1	Year 2	Year 3	Year 4	Year 5
No. of patients	All	570	494	386	305	206
	nWHF	437	393	315	251	176
	WHF	133	101	71	54	30
ACEIs/ARBs	All	486 (85.3%)	374 (75.7%)	290 (75.1%)	228 (74.8%)	150 (72.8%)
	nWHF	367 (84.0%)	305 (77.6%)	241 (76.5%)	191 (76.1%)	131 (74.4%)
	WHF	119 (89.5%)	69 (68.3%)	49 (69.0%)	37 (68.5%)	19 (63.3%)
BBs	All	514 (90.2%)	414 (83.8%)	324 (83.9%)	257 (84.3%)	173 (84.0%)
	nWHF	388 (88.8%)	331 (84.2%)	264 (83.8%)	211 (84.1%)	147 (83.5%)
	WHF	126 (94.7%)	83 (82.2%)	60 (84.5%)	46 (85.2%)	25 (83.3%)
MRAs	All	250 (43.9%)	195 (39.5%)	147 (38.1%)	115 (37.7%)	76 (36.9%)
	nWHF	195 (44.6%)	156 (39.7%)	123 (39.0%)	98 (39.0%)	63 (35.8%)
	WHF	55 (41.4%)	39 (38.6%)	24 (33.8%)	17 (31.5%)	13 (43.3%)
ARNIs	All	25 (4.4%)	27 (5.5%)	17 (4.4%)	15 (4.9%)	14 (6.8%)
	nWHF	18 (4.1%)	19 (4.8%)	12–16	10–14	9–13
	WHF	7 (5.3%)	8 (7.9%)	1–5	1–5	1–5
SGLT-2 inhibitors	All	15 (2.6%)	18 (3.6%)	13 (3.4%)	13 (4.3%)	15 (7.3%)
	nWHF	10–14	13–17	8–12	8–12	10–14
	WHF	1–5	1–5	1–5	1–5	1–5

The table shows the percentage of patients with at least one drug purchase during the year, including medications initiated before the incident HF diagnosis. For each follow-up year, only persons who had follow-up over the whole year were included. To be noted that ARNIs were not available during the first years of the study period and SGLT-2 inhibitor was only indicated for diabetes patients during the study. For categorical variables, results that concern one to five patients are presented as "1–5", and a range of five is also presented for the other category of the same variable. Categorical variables were reported by number and proportion (%).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; nWHF = patients without WHFE during the first year after the index date; SGLT-2, sodium-glucose cotransporter-2; WHF = patients with WHFE during the first year after the index date; WHFE = worsening heart failure event.

95% confidence interval [CI], 0.20–0.48; p<0.001) compared to non-adherence (<75%) (**Figure 2**). The sensitivity analysis, with an adherence measure of proportion of purchased vs. prescribed medications, showed that adherence ≥60% was associated with a 0.59-fold risk of WHFEs compared to adherence <60% (p=0.020) (**Supplementary Figure 2**).

Based on the register data, the differences in medication adherence could not be directly explained by demographic and clinical characteristics in adherent and non-adherent patient groups (data not shown). For example, the total number of comorbidities (multimorbidity index) or of medications used (polypharmacy index) did not differ in adherent and non-adherent patients. Based on the linkage of register and survey data, 82% (n=88) and 19% (n=20) of survey respondents were classified as being adherent and non-adherent, respectively. Of adherent patients, 82% (n=72) partially or completely agreed that they have had sufficient opportunity to discuss their HF medication with a healthcare professional, whereas

Table 4. Medication adherence

Strata	ACEIs/ARBs	BBs	MRAs
All			
No. of patients	499	514	232
Non-adherent (0–74%)	73 (14.6%)	75 (14.6%)	39 (16.8%)
Adherent (75–100%)	426 (85.4%)	439 (85.4%)	193 (83.2%)
WHF			
No. of patients	115	117	32
Non-adherent (0–74%)	35 (30.4%)	33 (28.2%)	12 (37.5%)
Adherent (75–100%)	80 (69.6%)	84 (71.8%)	20 (62.5%)
nWHF			
No. of patients	384	397	200
Non-adherent (0–74%)	38 (9.9%)	42 (10.6%)	27 (13.5%)
Adherent (75–100%)	346 (90.1%)	355 (89.4%)	173 (86.5%)

Adherence measures for patients with heart failure with reduced ejection fraction, overall and stratified by whether or not the patient had an episode of heart failure worsening during the first follow-up year (WHF and nWHF, respectively).
Adherence was evaluated using baseline data and for up to one year after the index date, end of follow-up, or first WHFE, whichever came first. For each medication group, adherence calculation started from the earliest purchase within the evaluation period. This adherence calculation period was divided into four 3-month time windows, and adherence was then defined as the fractions of the 3-month time windows in which there was a new medication purchase.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; nWHF = patients without WHFE during the first year after the index date; WHF = patients with WHFE during the first year after the index date; WHFE = worsening heart failure event.

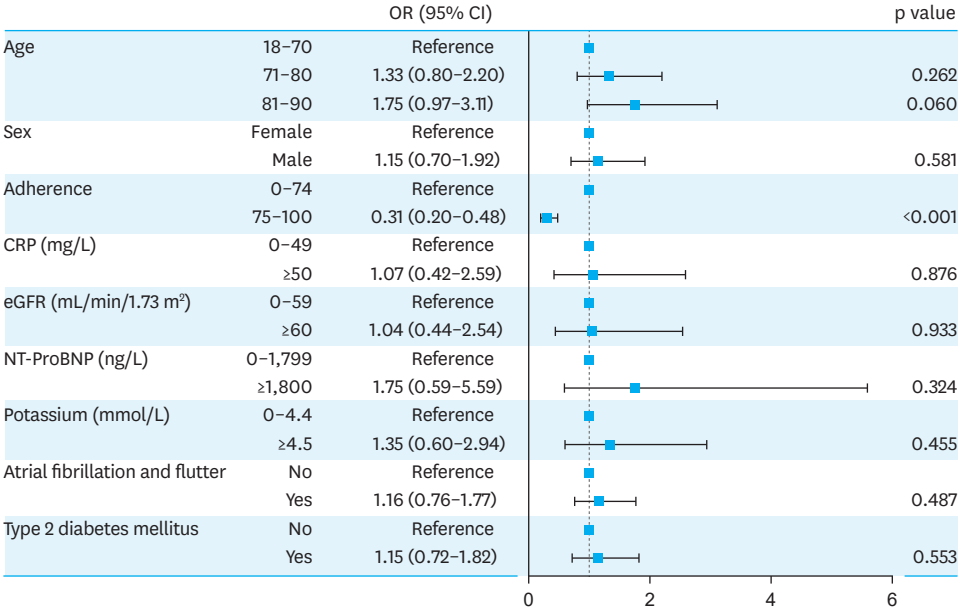

Figure 2. Predisposing factors for WHFE for 1 year follow-up.
The association (odds ratio) between the pre-selected predisposing factors and the binary outcome of whether or not a patient had the WHFE during the first year of follow-up, in patients with HFrEF, evaluated by a logistic regression model. Adherence was evaluated for each ATC group for a 1-year time period up to 1 year after the index date, end of follow-up, or first WHFE, whichever came first. Within this evaluation period, adherence was calculated as the number of 3-month windows with a refill purchase divided by the total number of time windows. A minimum adherence across ATC groups was used in the analysis.
ATC = Anatomic Therapeutic Chemical; CRP = C-reactive protein; eGFR = estimate glomerular filtrate rate; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; WHFE = worsening heart failure event.

the same proportion was 65% (n=13) in non-adherent patients (p=0.097). Moreover, 64% (n=56) of adherent patients compared to 30% (n=6) of non-adherent patients all the time or often utilized a method to remind themselves to take medication (p=0.005).

WHFEs and mortality

At 1 year after the index date, 75.9% (n=101) of the patients in the WHF subgroup and 89.9% (n=393) of the patients in the nWHF subgroup were alive. 6 years after the index date, the corresponding proportions were 52% (n=53) in the WHF and 72% (n=283) in the nWHF subgroups. Cardiovascular causes were either the primary or secondary cause of death in 82% of all HFrEF patients who died. In the multivariate model adjusted for sex and age group, WHFEs were associated with a significantly higher risk (hazard

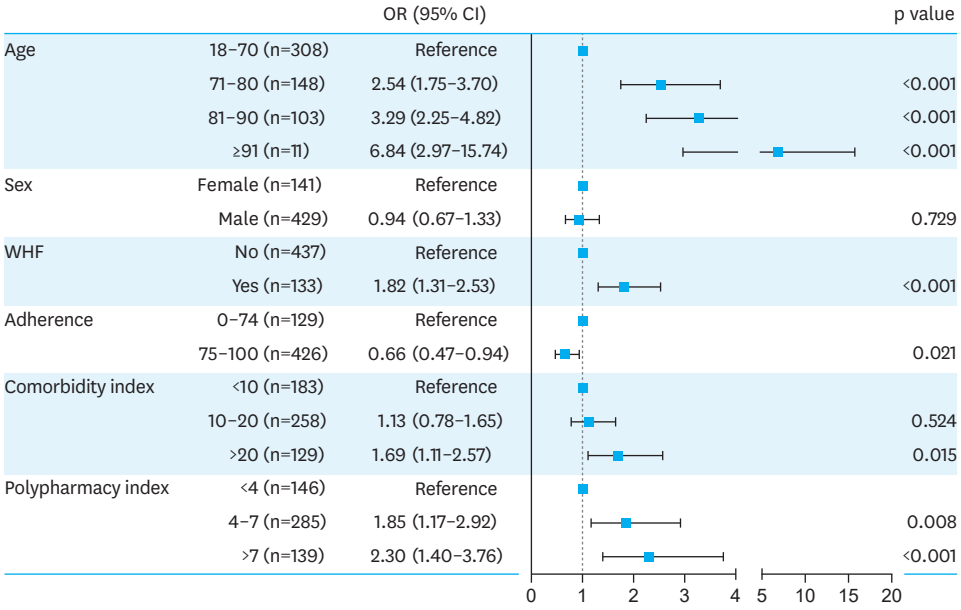

Figure 3. The association (hazard ratio) between all-cause mortality and explanatory factors evaluated by Cox regression model.
Adherence was evaluated for each ATC group for 1-year time period up to 1 year after the index date, end of follow-up, or first WHFE, whichever came first. Within this evaluation period, adherence was calculated as the number of 3-month windows with a refill purchase divided by the total number of time windows. A minimum adherence across ATC groups was used in the analysis. The multicomorbidity index is defined as a count of distinct ICD-10 codes with 3-digit accuracy, and polypharmacy index as a count of distinct ATC codes with 4-digit accuracy.
ATC = Anatomic Therapeutic Chemical; ICD-10 = International Classification of Diseases, 10th Revision; WHF = patients with WHFE during the first year after the index date; WHFE = worsening heart failure event.

ratio [HR], 1.82; 95% CI, 1.31–2.53; p<0.001) of all-cause mortality, whereas adherence was associated with a significantly lower risk (HR, 0.66; 95% CI, 0.47–0.94; p=0.021) (**Figure 3**).

WHFEs and QoL

Of the survey subpopulation, 31.9% (n=47) had a WHFE and 68.0% (n=100) did not have a WHFE during the last 3 follow-up years (2018–2020). Of the WHF patients in the survey subpopulation, 31.9% (n=15) were classified as NYHA I, 40.4% (n=19) NYHA II, and 27.7% (n=13) NYHA III–IV. For the nWHF patients, the corresponding proportions were 31.0% (n=31), 50.0% (n=50), and 19.0% (n=19).

Of the patients with both EQ-5D-5L and registry data available (n=102), 34.3% (n=35) had a WHFE during the last 3 follow-up years (2018–2020) whereas 65.7% (n=67) did not. The patients with WHFEs tended to have a lower VAS score (visual analogue scale) in EQ-5D-5L assessment than patients without WHFEs (**Figure 4**). In the model adjusted for age and sex, patients with a WHFE had an average 6.6±4.2 points lower VAS score than patients without WHFEs (p=0.120).

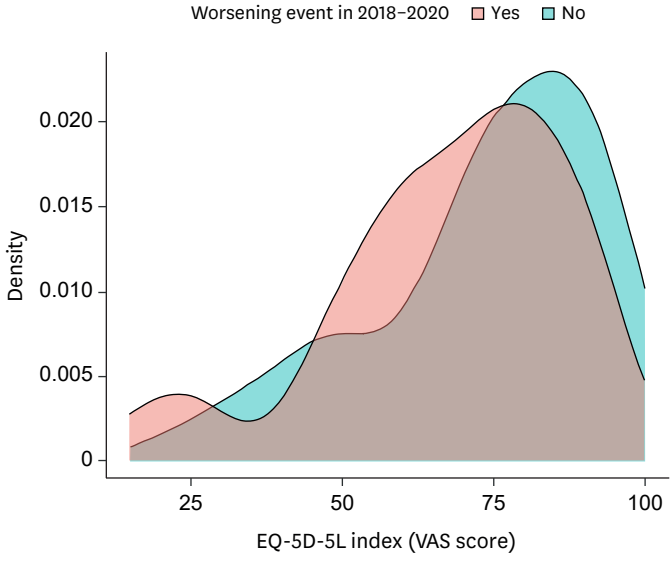

Figure 4. QoL in the survey population.
QoL was measured by VAS score in the EQ-5D-5L questionnaire, stratified by whether or not the patient had a worsening heart failure episode during 2018–2020 (n=35 and n=67, respectively).
QoL = quality of life; VAS = visual analog scale.

DISCUSSION

This study with a unique combination of register-based and survey data characterized WHFEs and associated factors, as well as the real-world implementation of GDMT in patients with HFrEF in Finland. The results indicated that approximately one in five patients developed a WHFE during the first year after the incident HF diagnosis. WHFEs were associated with a higher risk of mortality, and patients with WHFEs had a tendency for lower QoL compared to patients without WHFEs. Overall, the implementation of GDMT and adherence to HF medications was good. Adherence to HF medications was associated with a significantly lower risk of WHFEs and a lower risk of mortality independently of WHFEs.

Episodes of WHF are hallmarks in the course of HF, indicating a new phase in the natural history of the disease, and thus, they have long been recognized as central outcomes in both clinical trials and real-world clinical practice.[1,22] Based on this study, the percentage of HFrEF patients with a WHFE during the first year after the incident diagnosis was lower (23%) than the percentage of HFrEF patients shown to be hospitalized (30%) due to any cardiovascular reason in Finland within 1-year time frame.[16] In comparison, a large multicenter study in the United States reported that 17% of HFrEF patients developed a WHFE within two years following the incident diagnosis.[23]

The difference in reported WHFE and hospitalization rates may arise from improved clinical practices in HF and heterologous definitions used to define WHFE in various studies. The concept of WHFE has evolved remarkably during recent years: instead of comprising only events requiring hospital care, a WHFE is now seen more broadly as a worsening of HF symptoms requiring intensification of treatment with intravenous therapy or escalation of oral diuretic therapy.[1,22] Here, a WHFE was defined as an event including HF as the primary or secondary diagnosis and either a hospitalization after an emergency room visit or treatment with intravenous furosemide or levosimendan in a cardiology clinic.

In line with previous findings, our results indicated that WHFEs were associated with a 1.8-fold higher risk of mortality in HFrEF patients. In a previous Danish study, intensification of diuretic therapy and HF hospitalization led to 1.5- and 1.9-fold higher 1-year mortality, respectively, compared to patients without WHFEs.[24] An even higher risk (approximately 5-fold) of mortality associated with WHFEs has also been observed.[2] The mortality rate observed in this study was slightly lower compared to a previous Finnish study indicating a 5-year all-cause mortality of 55% in HFrEF patients.[18] Our data showed that at 6 years after the incident diagnosis, 48% and 28% of patients in the WHF and nWHF subgroups, respectively, have died. The lower rates of mortality may reflect earlier diagnostics or improved treatment implementation during recent years. Overall, trends in the survival of HF patients have shown only modest improvement during the 21st century.[25]

Along with higher risk of death, the survey data suggested that patients with WHFEs tended to have a lower QoL than patients without WHFEs. The VAS score in EQ-5D-5L was on average 6.6 points lower for patients with WHFEs than without. However, the difference was not statistically significant, likely due to a relatively small number of patients in the WHF subgroup. In general, a minimal clinically important difference (MCID) of health-related QoL has been reported to vary from 6.5 to 8.2 in different diseases using the EQ-5D-5L VAS, however, MCID has not been defined specifically to HF.[26,27]

Several studies have shown that implementation of GDMT is suboptimal in clinical practice.[23,28] Our results indicated that during the first year after the diagnosis, over 85% of all HFrEF patients used ACEIs/ARBs and BBs, and 44% used MRAs. The percentages are higher compared to many other countries: a large study based on administrative claims data in the US showed that 78% of patients with HFrEF had a HF-related prescriptions in the year after diagnosis.[28] In the PINNACLE study, 70% of patients used BBs, 47% ACEI/ARBS, and 22% MRAs 3 months before the onset of WHFE, but the percentage of users decreased notably at 6 months after the WHFE.[23]

A similar decreasing trend in GDMT use was observed during the follow-up years in our study population, especially in the WHF subgroup. From the 1st to the 2nd follow-up year, the proportion of ACEI/ARB and BB users decreased from 90% to 68% and from 95% to 82%, respectively, in the WHF subgroup. These findings are in line with previous studies showing that discontinuation of these medications is common in real-world clinical practice.[13,29] It should be noted that in this study, only prescription medications purchased at community pharmacies were included in the analysis. Thus, the observed decrease in the prescription medication use can be partly explained by the hospitalization of patients with the poorest health condition, as medications used in the hospital ward were not recorded in the drug registry used in the study. Instead, discharge medications are typically prescription drugs purchased at community pharmacies, and individuals living in long-term care facilities, e.g., nursing homes, buy their medications with a prescription at the pharmacies. Thus, only medications dispensed during typically short, temporary hospital stays are excluded from the analyses.

Overall, medication adherence in this study population was higher than in many of the previous reports.[12,13,30] In a previous study evaluating medication adherence in HF patients by detecting medicine or its metabolites in urine samples, non-adherence to at least one class of prescribed medication was observed in 45.9% of the patients.[13] As previously reported, non-adherence to all studied medication groups was more common in patients with WHFEs than without.[30] Importantly, adherence to HF medications was associated with a significantly lower (0.31-fold) risk of WHFEs, and when adjusted for WHFEs, a 0.66-fold lower risk for all-cause mortality. Clinical characteristics, e.g., the comorbidity burden and laboratory records or the number of medications used, did not seem to differ in adherent and non-adherent patients. This suggests that considering new medications for patients with multiple existing medications should not be hindered by the fear of lower adherence due to an increasing number of prescriptions. However, survey results highlighted the importance of healthcare personnel and patient discussions, as well as of medication reminder methods to improve adherence in HF patients. Patient-centered interventions are shown to improve medication adherence, such as education or self-monitoring, and reduce hospital admissions and mortality.[31]

It should be noted that approaches used to assess adherence vary between studies, from objective measures such as the ones used in this study to subjective measures explaining patient's medication-taking behavior.[21] Currently none of the available measures can be considered as a gold standard and the selection of the method should be based on study setting and goals. In this study, the main method, methodologically corresponding to the medication possession ratio, was chosen based on the 3-month period for the dispensation practice of reimbursement drugs in Finland, meaning that the patient should refill the prescription every 3 months.[21] An alternative method with similar logic to pill count method, defined as the number of purchased prescriptions divided by the total number of prescriptions, was used as a sensitivity analysis. Both methods were adaptations of existing adherence measurement approaches, as only the dispensed prescriptions, but not the exact prescribed daily dosage or the number of dispensed pills, were available in the during register used. Notably, as both methods were based on the purchases of prescribed medications, the information on medication actually taken by the patient was missing in the analysis.

The main strength of this study is the comprehensive set of data combining clinical characteristics of patients, healthcare resource and medication use, and survey data, allowing a detailed characterization of disease outcomes and treatment implementation in the real-world clinical practice. For example, assessing medication adherence by comparing prescribed and purchased medications is more reliable than surveys, which are subject to self-reporting bias and tend to overestimate adherence measures.[10] The fact that the Finnish healthcare system allows equal access to healthcare to all citizens minimizes the bias in the study population selection.

Compared to previous registry studies in Finland, a new, advanced text mining method was used for obtaining LVEF values from register data, improving the reliability of identification of patients with HFrEF.[16-18] However, with this stricter method, which was designed to identify real HFrEF patients more accurately, the LVEF value was reliably found in only 18% of patients. This does not directly indicate the percentage of patients for which the ECHO had not been performed, instead it reflects the percentage of patients which the text mining algorithm could reliably identify. The challenges in retrieving the data reliably from the registers can originate from variable data recording practices in the clinics, which may be improved in the future by standardizing and structuring the way of patient data recording.

Other limitations of the study include a temporal gap between the survey conduction and registry data, as the survey was sent out 12–18 months after the end of registry data collection. Additionally, a definition of WHFE cannot fully rule out the possibility that for some patients, HF is not the main reason for hospitalization. Considering the nature of the study (retrospective data collection from routine healthcare practice), the operational definition used for a WHFE contains some inaccuracy compared to clinical trials. Here, the definitions used were designed based on both existing literature and expertise of local physicians, who have an in-depth understanding of HF patients' care pathway in Finnish clinical practice. The same limitations apply to other operational definitions, as well as to time periods selected for assessment of laboratory values, which were chosen together with physicians taking into account the limitations of data availability. As these definitions are partly based on specific features of the Finnish healthcare system, they may not be directly comparable to other countries and studies. In addition, clinical practices in Finland differ in certain aspects from some other European countries: patients with WHFEs are treated primarily in the ward and not as an emergency room visit. Data-driven cutoff-points were used, e.g., in the categorization of the adherence measures; thus, the significance of the finding should be interpreted together with the size of the effect. To avoid bias, a sensitivity analysis with a different adherence definition method was also included.

The study showed that in general, GDMT was well implemented in this Finnish patient cohort, as a vast majority of patients were using relevant HF medications. Adherence to GDMT was

associated with lower risk of WHFEs and mortality. Adherence was not affected by clinical characteristics, comorbidities, or polypharmacy, suggesting that adding relevant medications should not be hindered by the concern of non-adherence to an increasing number of medications. The patient survey results suggested that adequate opportunities to discuss the treatment with healthcare professionals and methods to remind patients to take medication may contribute to improved adherence.

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Conflict of Interest
Kirjavainen A, Huupponen J, and Säävuori N are employed by Bayer Oy.

Author Contributions
Conceptualization: Vesikansa A, Mehtälä J, Kirjavainen A, Huupponen J, Säävuori N, Pitkänen K, Ukkonen H; Data curation: Mehtälä J, Smith S; Formal analysis: Mehtälä J; Funding acquisition: Kirjavainen A, Huupponen J, Säävuori N; Investigation: Vesikansa A, Mehtälä J, Smith S, Kirjavainen A, Huupponen J, Säävuori N, Pitkänen K, Ukkonen H; Methodology: Vesikansa A, Mehtälä J, Smith S, Kirjavainen A, Huupponen J, Säävuori N, Pitkänen K, Ukkonen H; Project administration: Vesikansa A, Mehtälä J, Smith S, Kirjavainen A, Huupponen J, Säävuori N; Resources: Vesikansa A, Mehtälä J, Smith S, Kirjavainen A, Huupponen J, Säävuori N; Software: Vesikansa A, Mehtälä J; Supervision: Vesikansa A; Validation: Mehtälä J, Pitkänen K, Ukkonen H; Visualization: Vesikansa A, Mehtälä J; Writing - original draft: Vesikansa A; Writing - review & editing: Vesikansa A, Mehtälä J, Smith S, Kirjavainen A, Huupponen J, Säävuori N, Pitkänen K, Ukkonen H.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Description of laboratory measurements in subgroups of patients with and without WHFE

Supplementary Table 2
Description of comorbidities for patients with or without WHFE during the first year after the index date

Supplementary Figure 1
Patient follow-up and periods for collection of different variables.

Supplementary Figure 2
Sensitivity analysis: a logistic regression analysis with worsening heart failure event during the first year of follow-up as an outcome, with alternative adherence definition (adherence defined as the number of purchased prescriptions divided by the total number of prescriptions).

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