ORIGINAL RESEARCH

Persistent High Burden of Heart Failure Across the Ejection Fraction Spectrum in a Nationwide Setting

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BACKGROUND: Heart failure (HF) has a dramatic impact on worldwide health care systems that is determined by the growing prevalence of and the high exposure to cardiovascular and noncardiovascular events. Prognosis remains poor. We sought to compare a large population with HF across the ejection fraction (EF) spectrum with a population without HF for patient characteristics, and HF, cardiovascular, and noncardiovascular outcomes.

METHODS AND RESULTS: Patients with HF registered in the Swedish HF registry in 2005 to 2018 were compared 1:3 with a sex-, age-, and county-matched population without HF. Outcomes were cardiovascular and noncardiovascular mortality and hospitalizations. Of 76 453 patients with HF, 53% had reduced EF, 23% mildly reduced EF, and 24% preserved EF. Compared with those without HF, patients with HF had more cardiovascular and noncardiovascular comorbidities and worse socioeconomic status. Incidence of cardiovascular and noncardiovascular events was higher in people with HF versus non-HF, with increased risk of all-cause (hazard ratio [HR], 2.53 [95% CI, 2.50–2.56]), cardiovascular (HR, 4.67 [95% CI, 4.59–4.76]), and noncardiovascular (HR, 1.49 [95% CI, 1.46–1.52]) mortality, 2- to 5-fold higher risk of first/repeated cardiovascular and noncardiovascular hospitalizations, and ~4 times longer in-hospital length of stay for any cause. Patients with HF with reduced EF had higher risk of HF hospitalizations, whereas those with HF with preserved EF had higher risk of all-cause and noncardiovascular hospitalization and mortality.

CONCLUSIONS: Patients with HF exert a high health care burden, with a much higher risk of cardiovascular, all-cause, and noncardiovascular events, and nearly 4 times as many days spent in hospital compared with those without HF. These epidemiological data may enable strategies for optimal resource allocation and HF trial design.

Key Words: comorbidity ■ ejection fraction ■ epidemiology ■ heart failure

Heart failure (HF) is a global pandemic that affects more than 64 million people worldwide and its prevalence is steadily growing.[1] Prognosis in HF remains poor, and the burden of HF-related hospitalizations is increasing.[2,3] Patients with HF are also exposed to cardiovascular and noncardiovascular events that are not directly explained by HF.[4] Consistently, in patients with HF, hospitalizations for HF and for cardiovascular causes account for <30% and 50%, respectively, of 30-day readmissions after diagnosis.[5,6] The increasing prevalence of HF with preserved ejection fraction (HFpEF) has in part modified the phenotypic distribution of patients admitted for HF, with larger representation of HFpEF.[7]

These aspects have a dramatic impact on worldwide health care systems, both in terms of human and financial resources. In Europe, the estimated

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CLINICAL PERSPECTIVE

What Is New?

- We described much higher burden of cardiovascular and noncardiovascular comorbidities in heart failure (HF) versus non-HF, which was linked with dramatically higher exposure to cardiovascular/noncardiovascular mortality and morbidity in the former versus the latter.
- We highlighted the different patient profiles and outcomes in HF across the ejection fraction spectrum.
- Patients with HF with reduced ejection fraction had more severe HF and higher risk of HF-related outcomes compared with those with mildly reduced ejection fraction and with preserved ejection fraction, whereas patients with HF with preserved ejection fraction had higher comorbidity burden and were more likely exposed to all-cause, cardiovascular and, in particular, noncardiovascular mortality/morbidity.

What Are the Clinical Implications?

- Information derived from this comprehensive epidemiological overview increases the awareness of the burden that HF exerts on the whole health care system and might promote initiatives for the optimization of resource allocation and for the identification of best targets of intervention.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor neprilysin inhibitor
IRR	incidence rate ratio
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
RASI	renin-angiotensin-system inhibitor
SwedeHF	Swedish Heart Failure Registry

costs for HF amount to ~€29 billion and are predominantly driven by frequent, prolonged, and recurrent hospitalizations.[8]

Therefore, in the present study we sought to comprehensively compare a large population with HF across the ejection fraction (EF) spectrum with a matched control population without HF with regard to demographic features, comorbidities and treatments, and HF-related and nonrelated outcomes, which might contribute to explain the significant burden of HF on health care resources.

METHODS

Data Sources

The data used in this study are available from the corresponding author, provided that data sharing is permitted by European Union General Data Protection Regulation and appropriate ethics committees. Patients with HF were identified through the SwedeHF (Swedish HF Registry). SwedeHF has been previously described.[9] Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are informed of registration and allowed to opt out. A majority of Swedish hospitals (~60 out of 75 hospitals) and to a minor extent also primary care centers enroll patients without financial compensation and collect approximately 80 variables, that is, data on demographics, comorbidities, clinical parameters, biomarkers, treatments, and organizational aspects, from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion was clinician-judged HF until April 2017 and after that defined as a diagnosis of HF according to the following *International Classification of Diseases, Tenth Revision (ICD-10)* codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, and I13.2. Reported coverage of SwedeHF in 2019 was 30.4% of the prevalent population with HF in Sweden.

Linkage to Statistics Sweden provided socioeconomic data and the control population without HF. The National Patient Registry, a national mandatory registration of administrative records from hospitalizations and nonprimary outpatient care maintained by The National Board of Health and Welfare, provided data on additional comorbidities and hospital accesses outcomes. The DDR (Dispensed Drug Registry, established in July 2005) provided data on medications prescribed and actually dispensed to the individual patients. More details on selection criteria and variable definitions are available at https://kiheartfailure.github.io/shfdb3/ (*ICD* codes for additional variables and Anatomical Therapeutic Chemical codes for medications are reported in Table S1). Linkage between the registries was allowed by the personal identification number, which all residents in Sweden have.

Establishment of the HF registry and this analysis with linking of the registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

Patients and Outcomes

For the current analysis, 76 453 patients with HF registered between December 1, 2005 (DDR activation +5 months in order to capture available treatments) and December 31, 2018 were considered. Patients with HF who died during the hospitalization that prompted to the SwedeHF registration or had reused/changed personal identification numbers were excluded. For patients with >1 registration, the first was selected. EF was recorded as a categorical variable in SwedeHF: EF ≥50% (defined as HFpEF), EF=40%–49% (defined as mildly reduced EF—HFmrEF), and EF <40% (defined as reduced EF—HFrEF).

A control cohort of 229 359 individuals without HF was derived from Statistics Sweden. Controls were selected in a ratio of 1:3 for each post in SwedeHF. Eligible controls were individuals without a diagnosis of HF and were matched by sex, year of birth, and county of residence at index.

The outcomes of interest were all-cause mortality, cardiovascular mortality, noncardiovascular mortality, first and repeated all-cause HF, cardiovascular and noncardiovascular hospitalizations, first and repeated all-cause outpatient visits and first emergency visits, and first coronary revascularization. Emergency visits were defined as unplanned admission to an emergency ward. Length of in-hospital stay (LOS) was defined as total in-hospital time (for the respective diagnosis in primary position) from index date to end of follow-up, calculated per follow-up year.

Statistical Analysis

Categorical variables were presented as absolute frequencies (%), and differences across study groups were tested by chi-square test. Continuous variables were reported as median [interquartile range] and differences across groups were tested by Kruskal–Wallis test. The proportion of missing data for each variable is reported in Table S2. Percentage of use of HF treatments (renin-angiotensin-system inhibitors [RASI]/angiotensin receptor neprilysin inhibitors [ARNI], beta blockers, and mineralocorticoid receptor antagonists) over time was calculated, and the crude rate ratio for each EF phenotype was estimated using a generalized linear model with a binomial distribution and a log link.

Incidence rates per 1000 per year was calculated together with 95% Poisson CIs. Time to first events was presented by Kaplan–Meier curves for all-cause mortality and by cumulative incidence curves treating death as competing event for the other outcomes. Median survival free from the event of interest was calculated for each group. Mean cumulative function was used to depict repeated events. Univariate Cox proportional hazards regressions were fitted to model the time to first event. Repeated events were modeled by a negative binomial generalized linear model including the log of time as an offset. Data were censored at December 31, 2019 or death/emigration, and, for the controls, also at a later diagnosis of HF. The level of significance was set to 5%, 2 sided. All analyses were performed using R v.4.0.2 (R Core Team 2019). The R codes for data management and statistical analyses are found at https://github.com/KIHeartFailure/useofcare.

RESULTS

The overall HF population included 76 453 patients. Of these, 53% had HFrEF, 23% HFmrEF, and 24% HFpEF. The control population without HF included 229 359 patients. Median age was 76 (67–83) years, and 36.9% were female.

Baseline Characteristics of Populations with HF Versus Without HF

Compared with subjects without HF, patients with HF showed an overall higher cardiovascular comorbidity burden (ie, ischemic heart disease) was observed in 52.4% of patients with HF versus 14.6% without HF, diabetes in 25.2% versus 8.5%, atrial fibrillation in 51.8% versus 7.8%, hypertension in 56.1% versus 22.2%, history of stroke in 14.3% versus 9.1%, and peripheral artery disease in 8.8% versus 2.8%, respectively (Table 1 and Figure 1).

With the only exception of dementia (1.7% in HF versus 3.3% in non-HF), prevalence of noncardiovascular comorbidities was also higher in HF versus non-HF, that is, renal failure was reported in 12.4% in the HF versus 1.8% in the cohort without HF, chronic obstructive pulmonary disease in 13.1% versus 3.0%, anemia in 14.2% versus 4.1%, cancer in 14.2% versus 11.9%, and liver disease in 2.0% versus 0.6%, respectively. Patients with HF were also more likely to have lower education level and income.

All the examined therapies, including also non-HF drugs (ie, antiplatelet drugs, anticoagulants, oral glucose lowering drugs, and statins), were more likely prescribed to patients with HF.

Baseline Characteristics Across the Range of EF

Patients with HFpEF were more likely to be female (53.6%), whereas those with HFmrEF (61.7%) and HFrEF (71%) were more likely to be male. Patients with HFrEF were the youngest (median 73 years, interquartile range 64–81), whereas those with HFpEF were the oldest (median 80 years, interquartile range 72–85) (Table 2, Figure 2).

Across the EF spectrum, patients with HFpEF had longer history of HF, whereas patients with HFrEF had

Table 1.   Baseline Characteristics of the Population With HF Compared With the Population Without HF

	HF	Non-HF	*P*
No.	76 453	229 359	
Demographic/organizational characteristics			
Sex, male, n (%)	48 214 (63.1)	144 642 (63.1)	1.000
Age, y, median (IQR)	76.0 [67.0, 83.0]	76.0 [67, 83]	1.000
Outpatient, n (%)	39 872 (52.2)	…	
Follow-up referral HF nurse clinic, n (%)	40 813 (56.7)	…	
Follow-up referral specialty, n (%)			
Hospital	48 209 (66.1)	-	
Primary care	22 657 (31.1)	-	
Other	2018 (2.8)	-	
Year of registration, n (%)			1.000
2005–2010	27 514 (36.0)	82 542 (36.0)	
2011–2015	28 256 (37.0)	84 768 (37.0)	
2016–2018	20 683 (27.1)	62 049 (27.1)	
Clinical characteristics			
EF category, n (%)			
HF with reduced EF	40 893 (53.5)		
HF with mildly reduced EF	17 395 (22.8)		
HF with preserved EF	18 165 (23.8)		
HF duration >6 months, n (%)	36 178 (48.6)	-	
New York Heart Association class, n (%)			
I	6181 (11.8)	-	
II	25 423 (48.4)	-	
III	19 183 (36.6)	-	
IV	1693 (3.2)	-	
Systolic blood pressure, mm Hg, median (IQR)	125 [112, 140]	-	
Diastolic blood pressure, mm Hg, median (IQR)	72.0 [65, 80]	-	
HR, bpm, median (IQR)	72.0 [63, 83]	-	
HR >70 bpm, n (%)	39 108 (52.7)	-	
Left bundle-branch block, n (%)	11 550 (18.2)	-	
Laboratory measurements			
Hemoglobin, g/L, median (IQR)	133 [120, 145]	-	
eGFR (mL/min per 1.73 m^2)*, median (IQR)	62.2 [45.1, 80.2]	-	
eGFR <60 mL/min per 1.73 m^2, n (%)	35 145 (46.6)	-	
N-terminal pro-B-type natriuretic peptide, pg/mL, median (IQR)	2399 [1044, 5338]	-	
Hyperkalemia, n (%)	1099 (1.4)	345 (0.2)	<0.001
Hypokalemia, n (%)	1567 (2.0)	1117 (0.5)	<0.001
Medical history/comorbidities			
BMI, kg/m^2, median (IQR)	26.5 [23.4, 30.2]	-	
BMI ≥30, n (%)	12 092 (26.5)	-	
Former/current smoker, n (%)	32 764 (56.0)	-	
Diabetes, n (%)	19 258 (25.2)	19 429 (8.5)	<0.001
Renal failure, n (%)	9449 (12.4)	4124 (1.8)	<0.001
Atrial fibrillation, n (%)	39 593 (51.8)	17 950 (7.8)	<0.001
Ischemic heart disease, n (%)	40 056 (52.4)	33 591 (14.6)	<0.001
Anemia, n (%)	10 866 (14.2)	9456 (4.1)	<0.001
Hypertension, n (%)	42 910 (56.1)	50 935 (22.2)	<0.001

(Continued)

Table 1.   **Continued**

|	HF	Non-HF	P
Peripheral artery disease, n (%)	6715 (8.8)	6378 (2.8)	<0.001
Percutaneous coronary intervention, n (%)	10076 (13.2)	4563 (2.0)	<0.001
Coronary artery bypass graft, n (%)	17014 (22.3)	8442 (3.7)	<0.001
Stroke, n (%)	10959 (14.3)	20871 (9.1)	<0.001
Valvular disease, n (%)	15373 (20.1)	5297 (2.3)	<0.001
Malignant cancer, n (%)	10853 (14.2)	27332 (11.9)	<0.001
Chronic obstructive pulmonary disease, n (%)	10002 (13.1)	6821 (3.0)	<0.001
Liver disease, n (%)	1552 (2.0)	1482 (0.6)	<0.001
Dementia, n (%)	1310 (1.7)	7520 (3.3)	<0.001
Severe bleeding, n (%)	13486 (17.6)	16594 (7.2)	<0.001
Musculoskeletal/connective tissue diseases, n (%)	23616 (30.9)	46145 (20.1)	<0.001
Alcohol abuse, n (%)	2430 (3.2)	3117 (1.4)	<0.001
Charlson comorbidity index	2.0 [1.0, 4.0]	0.0 [0.0, 2.0]	<0.001
Treatments			
Devices (implantable cardioverter-defibrillator/cardiac resynchronization therapy)	3530 (4.6)	78 (0.0)	<0.001
Renin-angiotensin system/angiotensin receptor neprilysin inhibitors, n (%)	66654 (87.2)	68008 (29.7)	<0.001
Diuretics, n (%)	59022 (77.2)	54737 (23.9)	<0.001
Beta blockers, n (%)	67377 (88.1)	61882 (27.0)	<0.001
Calcium channel blockers, n (%)	16804 (22.0)	44029 (19.2)	<0.001
Mineralocorticoid receptor antagonists, n (%)	27721 (36.3)	4255 (1.9)	<0.001
Antiplatelet therapy, n (%)	37776 (49.4)	60663 (26.4)	<0.001
Anticoagulant therapy, n (%)	34936 (45.7)	17775 (7.7)	<0.001
Insulin, n (%)	9309 (12.2)	9714 (4.2)	<0.001
Oral glucose lowering therapy, n (%)	10733 (14.0)	17906 (7.8)	<0.001
Lipid lowering therapy, n (%)	38270 (50.1)	54300 (23.7)	<0.001
Digoxin, n (%)	12389 (16.2)	3438 (1.5)	<0.001
Nitrates, n (%)	22696 (29.7)	13108 (5.7)	<0.001
Antiarrhythmic therapy, n (%)	2694 (3.5)	807 (0.4)	<0.001
Socioeconomic characteristics			
Family type living alone, n (%)	36985 (48.5)	100138 (43.7)	<0.001
Children, n (%)	63815 (83.5)	194416 (84.8)	<0.001
Education, n (%)			<0.001
Compulsory school	33681 (45.0)	91255 (40.5)	
Secondary school	29013 (38.8)	84227 (37.4)	
University	12107 (16.2)	49671 (22.1)	
Income above median, n (%)	34588 (45.3)	118275 (51.6)	<0.001

Categorical variables are presented with number and percentage, continuous variables with median and interquartile range. BMI indicates body mass index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; and IQR, interquartile range.

*GFR estimation derived from Chronic Kidney Disease Epidemiology Collaboration formula.

more severe HF (ie, higher New York Heart Association functional class and NT-proBNP [N-terminal pro–B-type natriuretic peptide]). Compared with those with HFrEF and HFmrEF, patients with HFpEF were more likely to live alone rather than cohabitate, to have lower education level and income, and to be inpatients at the time of registration in SwedeHF and less likely to be followed in specialized care and to be referred to HF nurse-led clinics.

With the exception of ischemic heart disease, the spectrum of comorbidities, including diabetes, impaired renal function, anemia, atrial fibrillation, history of stroke, and noncardiovascular comorbidities such as chronic obstructive pulmonary disease, cancer, and dementia, was more prevalent in HFpEF and consequently the Charlson comorbidity index[10] was highest in this HF subtype. HFmrEF was more similar to HFrEF in terms of comorbidity burden (eg, renal function,
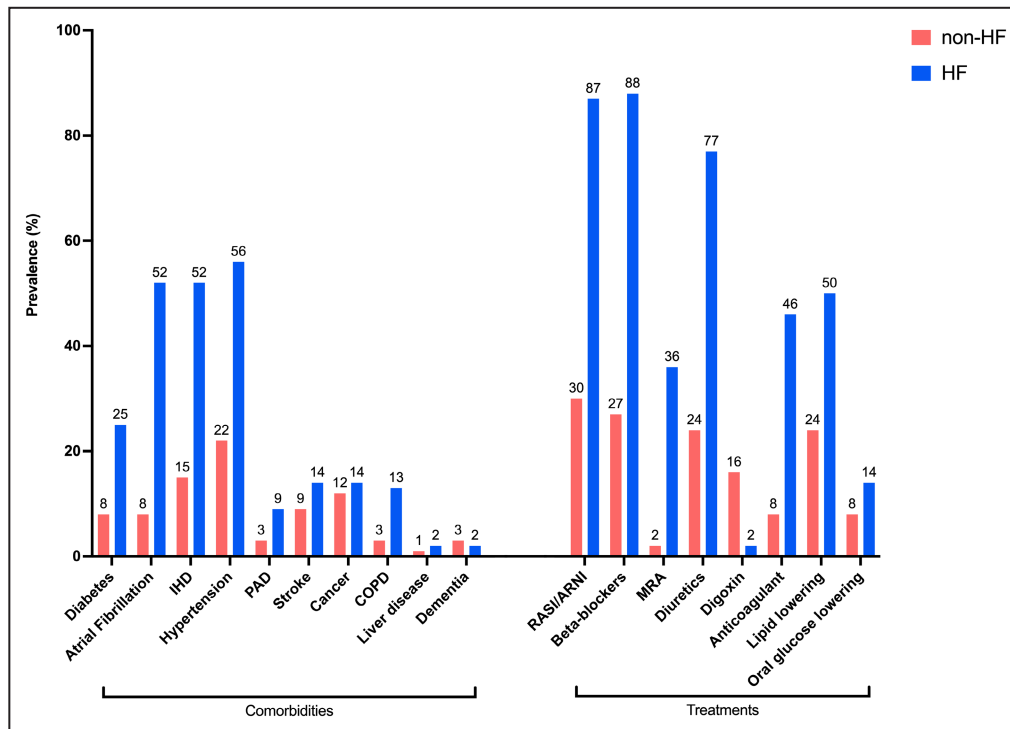
Figure 1. Differences in comorbidities and treatments between patients with HF and control individuals without HF.

COPD indicates chronic obstructive pulmonary disease; HF, heart failure; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonists; PAD, peripheral artery disease; and RASI/ARNI, renin-angiotensin system inhibitor/angiotensin receptor neprilysin inhibitor.

diabetes, anemia), and in particular for the prevalence of ischemic heart disease, but more similar to HFpEF for NT-proBNP levels and New York Heart Association class.

Regarding treatments, patients with HFrEF were more likely to receive RASI/ARNI inhibitors, beta blockers, mineralocorticoid receptor antagonists, antiplatelet therapy, and statins. Use of RASI/ARNI and diuretics in HFmrEF was more similar to HFrEF. The use of oral glucose lowering drugs was similar across the EF spectrum. The use of device therapy (eg, implantable cardioverter-defibrillator or cardiac resynchronization therapy) was more likely in HFrEF. As shown in Figure 3, a slight increase in the use of RASI/ARNI over time was observed across the entire EF spectrum. For beta blockers, treatment use remained stable in patients with HFrEF and HFpEF and slightly increased in patients with HFmrEF. Finally, the use of mineralocorticoid receptor antagonists decreased up to 2012 and then increased thereafter, with a larger increase in HFrEF compared with HFmrEF and HFpEF.

Table S3 reports the comparison between each EF category and respective control subjects without HF. The higher comorbidity burden and the larger use of HF and non-HF drugs in the population with HF versus non-HF were consistent across the range of EF.

Study Outcomes in the Population With HF Versus Non-HF

The median follow-up time was 4.0 (2.0–7.3) years. Compared with non-HF, HF was characterized by higher incidence of first (hazard ratio [HR], 2.86 [95% CI, 2.83–2.89]) and repeated (incidence rate ratio [IRR], 3.93 [95% CI, 3.89–3.98]) all-cause hospitalizations, first (HR, 5.47 [95% CI, 5.39–5.54]) and repeated (IRR, 10.4 [95% CI, 10.3–10.6]) cardiovascular hospitalizations, first (HR, 2.03 [95% CI, 2.01–20.5]) and repeated (IRR, 2.44 [95% CI, 2.41–2.47]) noncardiovascular hospitalizations, first (HR, 2.95 [95% CI, 2.92–2.97]) and repeated (IRR, 2.26 [95% CI, 2.24–2.28]) all-cause outpatient visits, and repeated emergency visits (IRR, 2.38 [95% CI, 2.34–2.43]). Patients with HF also more likely required coronary revascularization procedures after diagnosis (IRR, 2.64 [95% CI, 2.54–2.74]) (Figure 4, Tables S4 and S5).

The average in-hospital LOS for any cause per follow-up year was 7.1 days in subjects with HF versus 2.1 days in subjects without HF. Patients with HF had 2.9 days of average in-hospital LOS for cardiovascular causes per follow-up year versus 0.4 in subjects without HF. The majority of in-hospital stay was owing to noncardiovascular causes in both patients with HF

Table 2. Baseline Characteristics of the HF Population Across the EF Categories

Variable	HF with reduced EF	HF with mildly reduced EF	HF with preserved EF	P
No.	40 893	17 395	18 165	
Demographic/organizational characteristics				
Sex male, n (%)	29 047 (71.0)	10 733 (61.7)	8434 (46.4)	<0.001
Age, y, median (IQR)	73 [64, 81]	76 [68, 83]	80 [72, 85]	<0.001
Outpatient, n (%)	22 347 (54.6)	9899 (56.9)	7626 (42.0)	<0.001
Follow-up referral HF nurse clinic, n (%)	24 691 (63.7)	9143 (55.6)	6979 (41.6)	<0.001
Follow-up referral speciality, n (%)				<0.001
Hospital	29 757 (75.9)	10 324 (62.1)	8128 (47.6)	
Primary care	8437 (21.5)	5852 (35.2)	8368 (49.1)	
Other	1012 (2.6)	444 (2.7)	562 (3.3)	
Year of registration, n (%)				<0.001
2005–2010	15 174 (37.1)	5971 (34.3)	6369 (35.1)	
2011–2015	15 075 (36.9)	6355 (36.5)	6826 (37.6)	
2016–2018	10 644 (26.0)	5069 (29.1)	4970 (27.4)	
Clinical characteristics				
HF duration >6 months, n (%)	18 326 (45.8)	8458 (50.0)	9394 (53.8)	<0.001
New York Heart Association class, n (%)				<0.001
I	2753 (9.2)	1872 (15.6)	1556 (14.8)	
II	14 160 (47.2)	6436 (53.6)	4827 (46.0)	
III	11 962 (39.9)	3451 (28.7)	3770 (35.9)	
IV	1100 (3.7)	257 (2.1)	336 (3.2)	
Systolic blood pressure, mmHg, median (IQR)	120 [110, 140]	130 [117, 140]	130 [120, 145]	<0.001
Diastolic blood pressure, mmHg, median (IQR)	71 [65, 80]	74 [65, 80]	70 [65, 80]	<0.001
HR, bpm, median (IQR)	72 [64, 84]	71 [62, 81]	72 [63, 82]	<0.001
HR >70 bpm, n (%)	21 539 (54.1)	8438 (50.1)	9131 (52.2)	<0.001
Left bundle-branch block, n (%)	8352 (24.5)	2026 (14.1)	1172 (7.8)	<0.001
Laboratory measurements				
Hemoglobin, g/L, median (IQR)	135 [122, 147]	132 [120, 144]	127 [115, 139]	<0.001
eGFR (mL/min per 1.73 m^2)*, median (IQR)	64 [47, 82]	63 [46, 80]	57 [41, 75]	<0.001
eGFR <60 mL/min per 1.73 m^2, n (%)	17 522 (43.3)	7833 (45.7)	9790 (55.0)	<0.001
N-terminal pro-B-type natriuretic peptide, pg/mL, median (IQR)	2904 [1270, 6440]	1932 [799, 4247]	2020 [913, 4163]	<0.001
Hyperkalemia, n (%)	541 (1.3)	226 (1.3)	332 (1.8)	<0.001
Hypokalemia, n (%)	708 (1.7)	361 (2.1)	498 (2.7)	<0.001
Medical history/comorbidities				
BMI, kg/m^2, median (IQR)	26 [23, 30]	27 [24, 30]	27 [24, 31.]	<0.001
BMI ≥30, n (%)	5875 (23.8)	2958 (28.2)	3259 (31.2)	<0.001
Former/current smoker, n (%)	19 172 (59.4)	7243 (54.7)	6349 (49.1)	<0.001
Diabetes, n (%)	10 125 (24.8)	4212 (24.2)	4921 (27.1)	<0.001
Renal failure, n (%)	4757 (11.6)	2078 (11.9)	2614 (14.4)	<0.001
Atrial fibrillation, n (%)	19 290 (47.2)	9304 (53.5)	10 999 (60.6)	<0.001
Ischemic heart disease, n (%)	22 076 (54.0)	9569 (55.0)	8411 (46.3)	<0.001
Anemia, n (%)	4790 (11.7)	2508 (14.4)	3568 (19.6)	<0.001
Hypertension, n (%)	20 401 (49.9)	10 196 (58.6)	12 313 (67.8)	<0.001
Peripheral artery disease, n (%)	3450 (8.4)	1574 (9.0)	1691 (9.3)	0.001
Percutaneous coronary intervention, n (%)	5970 (14.6)	2671 (15.4)	1435 (7.9)	<0.001
Coronary artery bypass graft, n (%)	9723 (23.8)	4198 (24.1)	3093 (17.0)	<0.001
Stroke, n (%)	5491 (13.4)	2486 (14.3)	2982 (16.4)	<0.001

(Continued)

Table 2. **Continued**

Variable	HF with reduced EF	HF with mildly reduced EF	HF with preserved EF	*P*
Valvular disease, n (%)	6806 (16.6)	3660 (21.0)	4907 (27.0)	<0.001
Malignant cancer, n (%)	5332 (13.0)	2557 (14.7)	2964 (16.3)	<0.001
Chronic obstructive pulmonary disease, n (%)	4788 (11.7)	2253 (13.0)	2961 (16.3)	<0.001
Liver disease, n (%)	849 (2.1)	309 (1.8)	394 (2.2)	0.020
Dementia, n (%)	623 (1.5)	263 (1.5)	424 (2.3)	<0.001
Severe bleeding, n (%)	6120 (15.0)	3208 (18.4)	4158 (22.9)	<0.001
Musculoskeletal/connective tissue diseases, n (%)	11 162 (27.3)	5574 (32.0)	6880 (37.9)	<0.001
Alcohol abuse, n (%)	1502 (3.7)	464 (2.7)	464 (2.6)	<0.001
Charlson comorbidity index	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	3.0 [1.0, 4.0]	<0.001
Treatments				
Devices (implantable cardioverter-defibrillator/cardiac resynchronization therapy)	2917 (7.1)	422 (2.4)	191 (1.1)	<0.001
Renin-angiotensin system/angiotensin receptor neprilysin inhibitors, n (%)	37 606 (92.0)	15 117 (86.9)	13 931 (76.7)	<0.001
Diuretics, n (%)	31 563 (77.2)	12 345 (71.0)	15 114 (83.2)	<0.001
Beta blockers, n (%)	37 291 (91.2)	15 137 (87.0)	14 949 (82.3)	<0.001
Calcium channel blockers, n (%)	6706 (16.4)	4137 (23.8)	5961 (32.8)	<0.001
Mineralocorticoid receptor antagonists, n (%)	16 693 (40.8)	5053 (29.0)	5975 (32.9)	<0.001
Antiplatelet therapy, n (%)	21 157 (51.7)	8718 (50.1)	7901 (43.5)	<0.001
Anticoagulant therapy, n (%)	18 291 (44.7)	7908 (45.5)	8737 (48.1)	<0.001
Insulin, n (%)	4803 (11.7)	2036 (11.7)	2470 (13.6)	<0.001
Oral glucose lowering therapy, n (%)	5795 (14.2)	2358 (13.6)	2580 (14.2)	0.113
Lipid lowering therapy, n (%)	21 198 (51.8)	9086 (52.2)	7986 (44.0)	<0.001
Digoxin, n (%)	6691 (16.4)	2572 (14.8)	3126 (17.2)	<0.001
Nitrates, n (%)	12 352 (30.2)	5394 (31.0)	4950 (27.3)	<0.001
Antiarrhythmic therapy, n (%)	1807 (4.4)	480 (2.8)	407 (2.2)	<0.001
Socio-economic characteristics				
Family type living alone, n (%)	18 854 (46.2)	8167 (47.0)	9964 (54.9)	<0.001
Children, n (%)	33 655 (82.3)	14 736 (84.7)	15 424 (84.9)	<0.001
Education, n (%)				<0.001
Compulsory school	17 414 (43.4)	7524 (44.2)	8743 (49.5)	
Secondary school	16 115 (40.2)	6617 (38.8)	6281 (35.6)	
University	6572 (16.4)	2892 (17.0)	2643 (15.0)	
Income above median, n (%)	19 857 (48.7)	7996 (46.0)	6735 (37.1)	<0.001

Categorical variables are presented with number and percentage, continuous variables with median and interquartile range. BMI indicates body mass index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; and IQR, interquartile range.

*GFR estimation derived from Chronic Kidney Disease Epidemiology Collaboration formula.

(4.2 days per follow-up year) and patients without HF (1.7 days per follow-up year).

The risk of all-cause (HR, 2.53 [95% CI, 2.50–2.56]), cardiovascular (HR, 4.67 [95% CI, 4.59–4.76]), and noncardiovascular (HR, 1.49 [95% CI, 1.46–1.52]) death was higher in the population with HF compared with non-HF.

Study Outcomes Across the Range of EF

As summarized in Figure 5 and Table S6, within the population with HF the risk of outcomes varied according to the EF subtype. Patients with HFrEF reported the highest, patients with HFpEF intermediate, and patients with HFmrEF the lowest risk of first and repeated HF hospitalizations, with a median survival free from first HF hospitalization of 10.3 years in the cohort with HFrEF (Figure S1). For first all-cause hospitalizations and first and repeated noncardiovascular hospitalization, patients with HFpEF were at higher risk, those with HFrEF at lowest risk, and those with HFmrEF had intermediate risk but more similar to HFrEF (Figures S2 and S3). Median survival free from all-cause and noncardiovascular hospitalization was consistently shorter in HFpEF
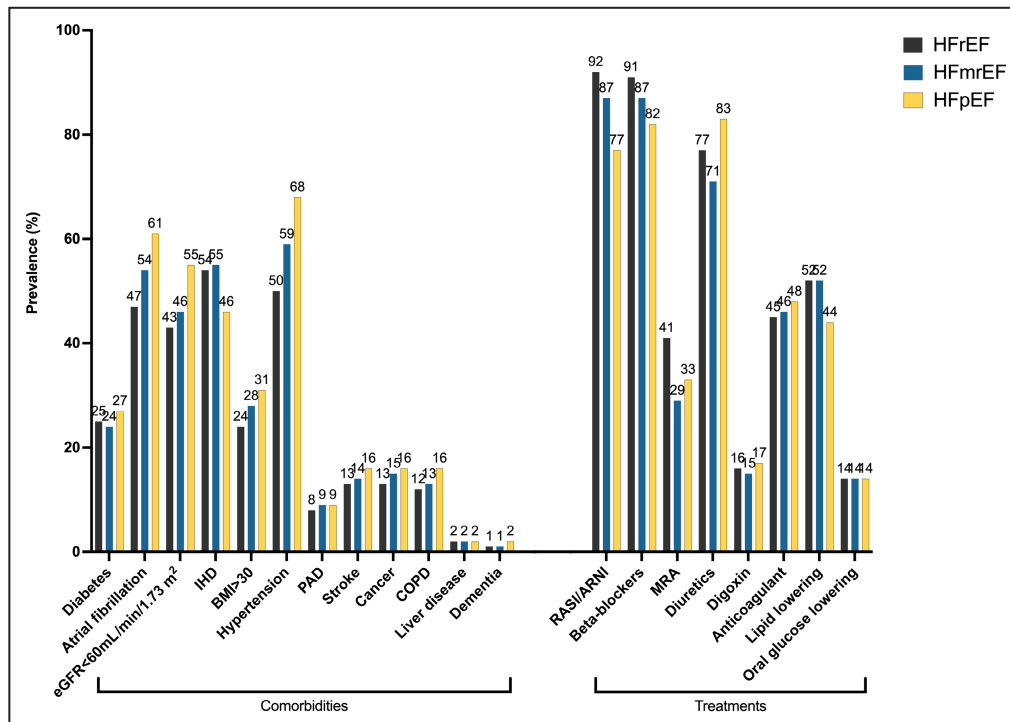
Figure 2. **Distribution of the main cardiovascular and noncardiovascular comorbidities and of HF and non-HF treatments across the EF spectrum.**

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, mildly reduced ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonists; PAD, peripheral artery disease; and RASI/ARNI, renin-angiotensin system inhibitors/angiotensin receptor neprilysin inhibitors.

(0.7 and 1.6 years, respectively) compared with HFrEF (0.8 and 2.9 years, respectively) and HFmrEF (0.9 and 2.2 years, respectively). The risk of repeated all-cause hospitalization was highest in HFpEF and similar in HFmrEF and HFrEF (Figure S2). The risk of first cardiovascular hospitalization was slightly higher in HFpEF and lower in HFmrEF compared with HFrEF, with a similar median survival free from cardiovascular hospitalization between HFrEF (2.4 years) and HFpEF (2.5 years) and slightly longer in HFmrEF (3.2 years), whereas the risk of repeated cardiovascular hospitalizations was similar in HFrEF versus HFpEF and lowest in HFmrEF (Figure S4). The risk of first all-cause outpatient visit was highest in HFrEF versus HFpEF and HFmrEF, whereas patients with HFpEF had higher risk of repeated all-cause and emergency visits compared with HFrEF, with HFmrEF being similar to HFrEF for the risk of repeated all-cause and emergency visits (Figure S5). Incidence rates of revascularization procedures were higher in HFrEF and HFmrEF compared with HFpEF (Table S6).

The risk of cardiovascular death was higher in HFpEF and lower in HFmrEF compared with HFrEF, whereas the risk of all-cause and noncardiovascular death was the highest in HFpEF and higher in HFmrEF

versus HFrEF (Figure S6). Median survival was shorter in HFpEF (4.2 years), compared with HFmrEF (5.8 years) and HFrEF (6.1 years). Patients with HFpEF had the longest average in-hospital LOS for any cause, cardiovascular causes, and noncardiovascular causes (Table S5).

The comparison in risk of outcomes between each EF subtype and its matched non-HF population was reported in Table S7 and Figures S1–S6. The higher risk in outcomes in HF versus non-HF was consistent regardless of EF. Patients with HF presented shorter median overall survival (5.5 versus >10 years) and shorter survival free from all-cause (0.8 versus 4.4 years), cardiovascular (2.6 versus >10 years) and noncardiovascular hospitalization (2.3 versus 5.7 years) compared with subjects without HF in the overall population and also across the entire EF spectrum. Patients with an ischemic cause of HF had higher incidence of the study outcomes compared with patients who were nonischemic (Table S8).

DISCUSSION

HF is progressively becoming the most demanding disease for the worldwide health care systems. In this
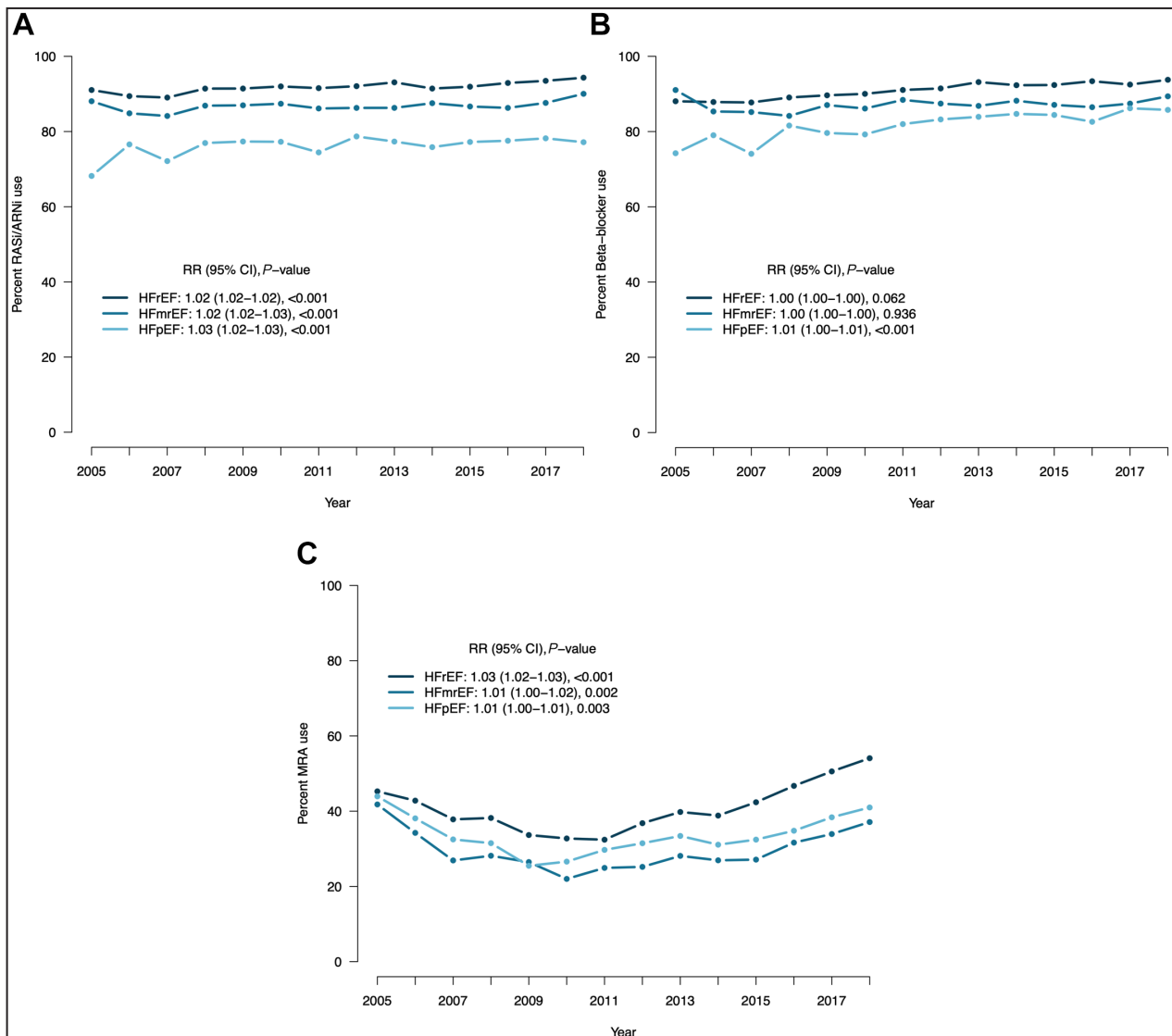
**Figure 3. Temporal trends in the use of HF medications across the EF spectrum.**
EF indicates ejection fraction; HFmrEF, mildly reduced ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure; RASI/ARNI, renin-angiotensin system inhibitors/angiotensin receptor neprilysin inhibitors; and RR, relative risk.

study by comparing a large contemporary nationwide cohort of ≈76 000 patients with HF versus a control population of >200 000 individuals without HF, we showed that (1) the prevalence of comorbidities that burden HF is extremely high compared with non-HF and involves both cardiovascular and noncardiovascular comorbidities; (2) the risk of cardiovascular and noncardiovascular mortality, and hospitalizations are much higher in HF versus non-HF; (3) HfpEF, HfmrEF, and HFrEF show different profiles, with ischemic heart disease more prevalent in HFrEF and HFmrEF compared with HFpEF, patients with HFrEF with the most severe HF, and HFpEF characterized by older age and higher comorbidity burden; and (4) there are differences in the risk of HF-related and unrelated events across the EF range, with patients with HFrEF more exposed to HF hospitalizations and patients with HFpEF at higher risk of all-cause, cardiovascular and, in particular, noncardiovascular hospitalizations and mortality.

Differences in Patient Characteristics and Outcomes in HF Versus Non-HF and Their Impact on the Health Care System

Previous studies suggested that ~80% of patients with HF have ≥3 coexisting comorbidities, and there is an increasing trend over time in the overall amount of cardiovascular and noncardiovascular comorbidities.[1,11] By comparing patients with versus without HF, we showed that the comorbidity burden is much higher in
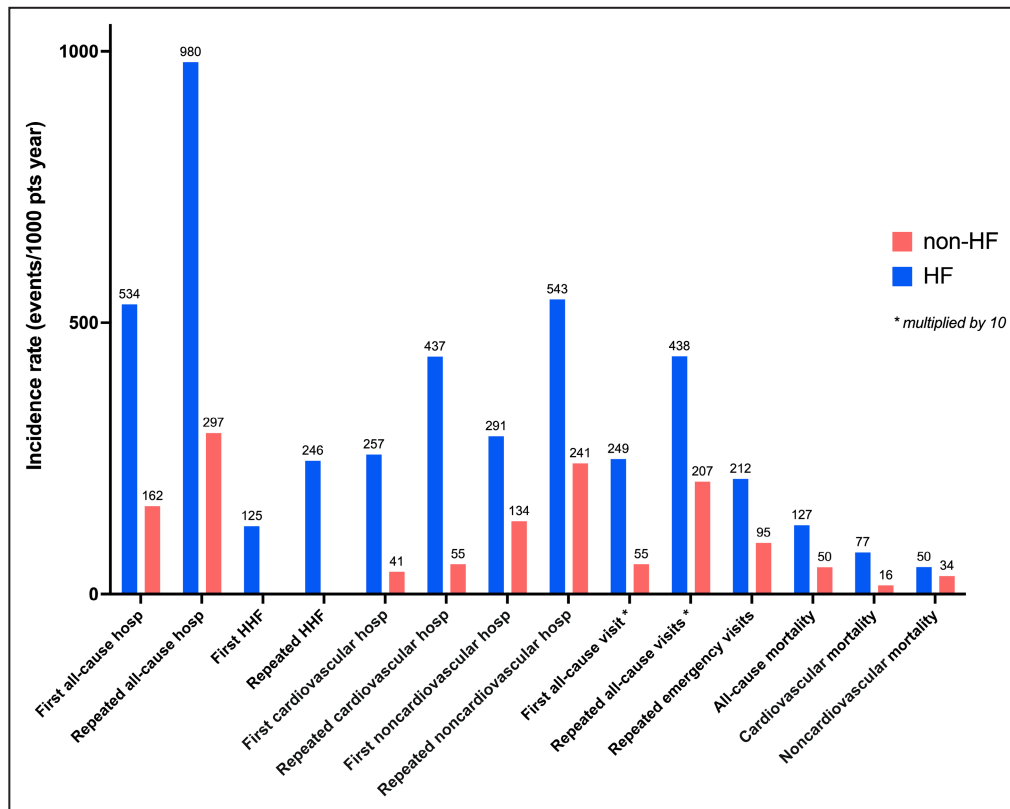
Figure 4.   **Differences in outcomes between patients with HF and control individuals without HF.**
HF indicates heart failure; and HHF, hospitalization for heart failure. * ×10.

the presence of HF. For instance, patients with HF had a 3-fold higher prevalence of ischemic heart disease and diabetes, 5- to 6-fold higher prevalence of atrial fibrillation and obesity, and 6- to 7-fold higher prevalence of renal failure. The increasing number of comorbidities is likely to be influenced by several factors, such as population aging, enhanced screening and diagnostics, physician awareness, and changes in risk factors over time.[1] Cardiac comorbidities have a well-known unfavorable effect on the outcome in HF,[12] but the growing prevalence of noncardiac comorbidities has been shown to similarly influence prognosis.[13] Multimorbidity increases the complexity of the management of patients with HF and has obvious consequences in terms of health care system management and costs. Each comorbidity leads to a considerable increase in need of resources. The presence of HF doubles the annual costs of care in patients with diabetes,[14] and impaired renal failure is one of the major determinant of increasing costs in patients with HF.[15] In Spain, the average expenditure per patient with HF was €1147/year in patients with 1 comorbidity and €16 806/year in patients with >9 comorbidities.[16] Similar findings have been reported in Sweden.[17] Consistently with the higher comorbidity burden in HF versus non-HF, in our analysis we showed that patients with HF were also more likely

treated with non-HF drugs, which further contributes to increasing costs.

The complexity of the population with HF has massive consequences in terms of prognosis. We observed dramatically higher mortality and risk of hospitalizations in patients with versus without HF, which was not only limited to HF- and cardiovascular-related events but also to noncardiovascular outcomes. The risk was ~3-fold higher for first and repeated all-cause hospitalizations and 2-fold higher for all-cause mortality in HF versus non-HF. The overall median survival was >6 years shorter in patients with HF versus individuals without HF and the survival free from all-cause hospitalization 3 to 4 years shorter according to HF phenotype. However, we could also identify a higher risk of first and repeated noncardiovascular hospitalizations and, to a lesser extent, of noncardiovascular death in HF versus non-HF, which might mirror the higher burden of noncardiovascular comorbidities in HF. Average in-hospital LOS for cardiovascular and noncardiovascular reasons was also >3-fold higher in HF versus non-HF.

The growing number of hospitalizations characterizing the HF course determines an exponential increase in the health care expenditures, with the increasing number of HF hospitalizations over time being also a
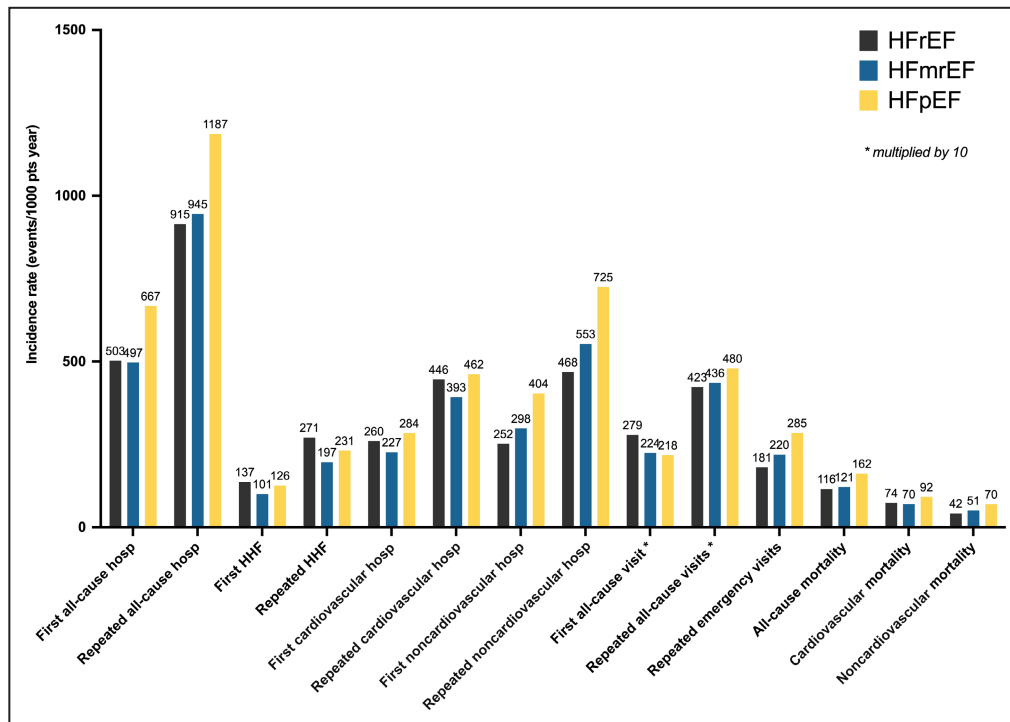
Figure 5.   Incidence of the study outcomes in the population with HF across the EF categories.
EF indicates ejection fraction; HF, heart failure; HFmrEF, mildly reduced ejection fraction heart failure; HFpEF, preserved ejection fraction heart failure; HFrEF, reduced ejection fraction heart failure; and HHF, hospitalization for heart failure. * ×10.

predictor of mortality.[18] In Sweden, the total amount of all-cause secondary care costs in the first year after HF diagnosis was €12 890/patient/year.[17] The cardiovascular inpatient care accounted for the largest part of the total secondary care costs (€11 578/patient/year) and exhibited a strong decline after the first year from diagnosis.[17] However, this declining trend in costs is limited to the individual longitudinal trajectory. At a population level, costs are still rising over time because of growing prevalence of HF, higher burden of comorbidities, longer survival linked with advances in medical care, and the consequent increasing number of repeated HF and non-HF hospitalizations.[17,19] The overall costs attributed to HF have been estimated to account for 1% to 2% of the total health care expenditure, reaching 7% in Spain.[16,20] Importantly, in accordance with the increasing weight of noncardiovascular events, HF-specific costs accounted for 69% of the total costs in the first year but only 49% and 46% in the second and third year after the diagnosis.[17]

Differences in Patient Characteristics and Outcomes Across the EF Subtypes

We confirmed that the 3 EF subtypes largely vary in demographic, clinical, and socioeconomic characteristics, with consequent differences in prognosis. These aspects are worth critical assessment as they might determine a different impact of these phenotypes on costs and allocation of resources. As previously reported, patients with HFpEF were older and had higher prevalence of cardiovascular and noncardiovascular comorbidities compared with patients with HFrEF and HFmrEF.[21] They were also less likely referred to specialized care and to HF nurse-led clinics. The use of skilled nursing facilities and a multidisciplinary follow-up in specialty care could aid to reduce the global costs linked with HFpEF by reducing the need of a hospital admission for HF.[22]

We also observed different distribution of HF-related and unrelated events across the EF spectrum. The risk of HF hospitalizations was higher in HFrEF, whereas HFpEF was characterized by more all-cause and noncardiovascular hospitalizations and higher unadjusted risk of all-cause, cardiovascular, and noncardiovascular death, which might reflect the lack of evidence-based therapies and the overall higher comorbidity burden in HFpEF. The larger increase in costs linked with HFpEF versus HFmrEF and HFrEF might be explained by the higher LOS, risk of all-cause hospitalization, disease complexity, and comorbidity burden in HFpEF, as we showed in our analysis.[17,23,24] In a previous analysis focusing on HFpEF, noncardiovascular hospitalizations

accounted for ~40% of the overall hospitalization-related costs (ie, € 3618/patient/year).[25] Annual costs for emergency noncardiovascular admissions have been reported to be higher in HFpEF versus HFrEF,[26] and in United States the total medication cost per patient was higher for HFpEF ($495/month/patient) versus HFrEF ($429/month/patient), although the costs related to HF medications were higher in HFrEF ($90/month/patient) versus HFpEF ($87/month/patient).[27] Costs specifically linked with HF hospitalizations have been reported to be highest in HFrEF, which is likely explained by the larger use of invasive treatments and devices in HFrEF compared with HFpEF/HFmrEF.[16,28] The use of HF medications showed only minimal variation over time for RASI/ARNI and beta blockers, whereas after an initial decrease the use of mineralocorticoid receptor antagonists progressively increased from 2012 to the end of follow-up, particularly in HFrEF, probably related to the extension of the indications reported in the 2012 European Society of Cardiology Guidelines.

In the process of resource allocation, our observations might aid the identification of the better targets of intervention that could not necessarily be the same across the EF spectrum. For instance, actions aiming to improve the management of noncardiovascular comorbidities are more likely to play a role in the reduction of costs in HFpEF versus HFrEF, whereas optimizing the use of guideline-recommended therapies might be the key in HFrEF/HFmrEF.[3] Use of drugs significantly decreasing the risk of HF hospitalizations/urgent visits may, thus, prove convenient in terms of economical net benefit. Post hoc analyses from trials on HFrEF supported their cost-effectiveness both in the European and US health care systems.[29,30] In HFpEF/HFmrEF the sodium-glucose cotransporter-2 inhibitor empagliflozin has recently been shown to reduce the risk of HF hospitalization/cardiovascular death,[31] and use of dapagliflozin in the same setting is currently tested in the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial (NCT03619213). The eligibility to treatments with novel drugs in the real-world scenario has been recently defined in the SwedeHF registry and demonstrated discrete variability based on the adopted criteria (randomized clinical trial criteria versus pragmatic clinical or label criteria). For instance, patients eligible for sacubitril/valsartan were 63% and 52% in the pragmatic scenario with, respectively, EF <50% and ≥40%, but decreased to 32% and 22%, respectively, according to randomized clinical trial criteria.[32] Eligibility to sodium-glucose cotransporter-2 inhibitors using trial, pragmatic, and label scenarios ranged between 31% and 81% in HFrEF and between 30% and 75% in HFmrEF/HFpEF.[33]

Limitations

SwedeHF coverage is not complete, and thus selection bias may be a limitation. EF is recorded in SwedeHF as a categorical variable, with HFmrEF defined as EF=40% to 49%, and therefore we could not adopt the HFmrEF definition recently proposed by the European Society of Cardiology guidelines (ie, 41–49%).[3] Comorbidities were derived from the National Patient Registry, and thus we cannot exclude that all the diagnoses were correctly captured. We were not able to provide a precise quantification of the economic impact of HF as no direct cost estimation was available.

CONCLUSIONS

In this large nationwide study, HF was characterized by a demanding profile that did not involve only cardiovascular aspects, that is, comorbidities and treatments. Patients with HF versus non-HF had not only a 5- to 10-fold higher risk of cardiovascular events but also a 2- to 4-fold higher occurrence of all-cause events, a 1.5- to 2.5- fold higher incidence of noncardiovascular events, together with a nearly 4 times longer length of in-hospital stay. The high burden of hospitalizations, the large amount of coexisting comorbidities. and the large requirement of multiple therapies explain the exponential increase in costs linked with HF, with a dramatically growing burden on the health care system. Different strategies might be required to reduce costs in HFpEF versus HFrEF.

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Supplemental Material

Tables S1–S8
Figures S1–S6

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