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RESEARCH ARTICLE

The role of multimorbidity in patients with heart failure across the left ventricular ejection fraction spectrum: Data from the Swedish Heart Failure Registry

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Aims The aim of this analysis was to provide data on the overall comorbidity burden, both cardiovascular (CV) and non-CV, in a large real-world heart failure (HF) population across the ejection fraction (EF).

Methods and results Patients with HF from the Swedish HF Registry between 2000 and 2021 were included. Of 91 463 patients (median age 76 years [interquartile range 67–82]), 98% had at least one among the 17 explored comorbidities (94% at least one CV and 85% at least one non-CV comorbidity). All comorbidities, except for coronary artery disease (CAD), were more frequent in HF with preserved EF (HFpEF). Patients with multiple comorbidities were older, more likely female, inpatients, with HFpEF, worse New York Heart Association class and higher N-terminal pro-B-type natriuretic peptide levels. In a multivariable Cox model, 12 comorbidities were independently associated with a higher risk of death from any cause. The highest risk was associated with dementia (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.45–1.65), chronic kidney disease (HR 1.37, 95% CI 1.34–1.41), chronic obstructive pulmonary disease (HR 1.32, 95% CI 1.28–1.35). Obesity was associated with a lower risk of all-cause death (HR 0.81, 95% CI 0.79–0.84). CAD and valvular heart disease were associated with a higher risk of all-cause and CV mortality, but not non-CV mortality, whereas cancer and musculo-skeletal disease increased the risk of non-CV mortality. A significant interaction with EF was observed for several comorbidities. Occurrence of CV and non-CV outcomes was related to the number of CV and non-CV comorbidities, respectively.

Conclusion The burden of both CV and non-CV comorbidities was high in HF regardless of EF, but overall higher in HFpEF. Multimorbidity was associated with a high risk of death with a different burden on CV or non-CV outcomes.

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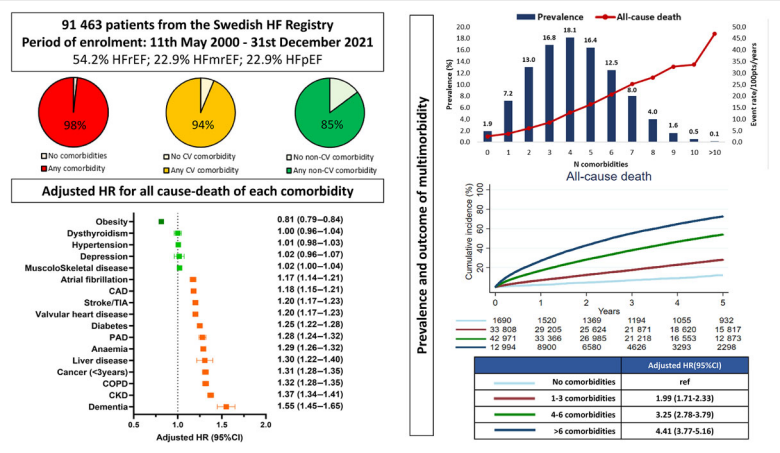
Graphical Abstract



Prevalence and outcome of cardiovascular and non-cardiovascular comorbidities and of multimorbidity among 91 463 patients from the Swedish Heart Failure Registry. CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PAD, peripheral artery disease; TIA, transient ischaemic attack.

Keywords Comorbidities • Cardiovascular • Non-cardiovascular • Heart failure • Mortality • Outcome

Introduction

Heart failure (HF) is a clinical syndrome characterized by severe morbidity and mortality.[1] A large proportion of patients with HF have coexisting cardiovascular (CV) and non-CV comorbid conditions. Comorbidities have been recognized as an important contributor to patients' frailty status, quality of life and prognosis,[2–8] and lead to the need of polypharmacy.[1,9]

Several studies explored the prevalence of CV and non-CV comorbidities and their association with outcomes and health status using data from major randomized clinical trials.[7,8,10] However, patients with comorbidities are often under-represented in clinical trials due to enrolment criteria, safety aspects, e.g. severe kidney disease, and to magnify the observed effects of the studied treatment, limiting the generalizability of multimorbidity assessment.[8]

Large registries can provide the adequate sample size and granular data to investigate the burden of CV and non-CV comorbidities as seen in daily clinical practice. A better knowledge of the comorbidity burden and its prognostic role is needed also to better define the management of HF patients as well as in identifying patients with frailty.

Thus, the primary objective of our study was to estimate the prevalence and the role on prognosis (e.g. all-cause, CV and non-CV death and hospitalizations) of multimorbidity, both CV and non-CV comorbidities, in a large nationwide real-world population of patients with HF across the ejection fraction (EF) spectrum.

Methods

Study protocol

The Swedish HF Registry (SwedeHF) has been previously described.[11] Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. A majority of Swedish hospitals (69 out of 76 hospitals) and to a minor extent also primary care centres enrol patients without financial compensation. Patients with clinically-judged HF were included until April 2017. Thereafter, the inclusion criterion was 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.[12,13] Coverage of SwedeHF in 2022 was 32% of the prevalent HF population in Sweden.[14] The registry includes HF patients regardless of EF, with EF collected in most patients as a categorical variable and therefore HF is classified as HF with reduced EF (HFrEF) whether EF <40%, HF with mildly reduced EF (HFmrEF) whether EF 40–49%, and HF with preserved EF (HFpEF) whether EF ≥50%. Approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult inpatient wards and outpatient clinics (www.swedehf.se) are recorded at the discharge from hospital (i.e. for inpatients) or at the outpatient visit date.

For this analysis, SwedeHF was linked with the Cause of Death Registry and the National Patient Registry. From the Cause of Death Registry we obtained the date of death and the underlying cause. The National Patient Registry provided additional baseline comorbidities and cause-specific hospitalizations as outcomes. Socioeconomic data were obtained from Statistics Sweden. Linkage between these registries

was allowed by the personal identification number, which all residents in Sweden have.

Establishment of the HF registry and this analysis including the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki. Individual patient consent was not required, but patients are informed of entry into SwedeHF and have the opportunity to opt out.

Study population

Among patients enrolled in SwedeHF between 11 May 2000 and 31 December 2021,[15] those without missing data for EF and for the comorbidities of interest (listed below) were included in the current analysis. Patients in the SwedeHF registry can be registered more than once. If the same patient was registered more than once, we selected the first record after removal of the registrations with missing values for EF and comorbidities of interest, as the first record is considered more representative of the baseline patient's clinical status and treatment. End of follow-up was 31 December 2021.

Definitions

Index date was defined as the date of registration in SwedeHF, i.e. the date of the outpatient visit for outpatients and the date of discharge for inpatients.

Chronic comorbidities enlisted in 2021 HF guidelines as well as those explored in more recent studies were included and a total of 17 comorbidities was finally assessed. CV comorbidities included hypertension, coronary artery disease (CAD), atrial fibrillation, valvular heart disease (VHD), peripheral artery disease (PAD) and stroke/transient ischaemic attack (TIA). Non-CV comorbidities included obesity (i.e. body mass index [BMI] >30 kg/m^2), diabetes, chronic kidney disease (CKD defined as estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), anaemia (defined using the World Health Organization definitions of haemoglobin <13 g/L [8.1 mmol/L] in men and <12 g/L [7.5 mmol/L] in women), chronic obstructive pulmonary disease (COPD), liver disease, depression, dementia, history of cancer within the last 3 years, musculo-skeletal disorder and thyroid disorders (online supplementary *Table S1*).

Statistical methods

The prevalence of each comorbidity alone and of multimorbidity was assessed in the whole population and in patients with HFrEF versus HFmrEF versus HFpEF. Characteristics of patients with versus without each comorbidity and according to the number of comorbidities (i.e. no comorbidities vs. one to three comorbidities vs. four to six comorbidities vs. >6 comorbidities) were compared in the overall population and within each EF phenotype. Patient characteristics were reported as median (interquartile range [IQR]) and compared by Wilcoxon rank-sum test if continuous, and as counts (percentages) and compared by chi-square test if categorical variables.

The primary outcome of interest was time to all-cause mortality. Secondary outcomes were time to (1) CV mortality, (2) non-CV mortality, (3) first all-cause hospitalization, (4) first CV hospitalization, (5) first HF hospitalization, and (6) first non-CV hospitalization. Cumulative incidence of events was calculated with the Kaplan–Meier method. Univariable and multivariable Cox regression models (including as covariates all comorbidities and the variables marked with superscript 'a' in *Tables*) were fitted to calculate hazard ratios (HR) with 95% confidence interval (CI) for the associations between comorbidities and the outcomes. Outcomes were censored at death (if itself not the outcome), emigration from Sweden or at 5-year follow-up. The proportional hazard assumption was assessed by visual inspection of residuals and met.

Missing data for the variables included in multivariable models were handled by multiple imputation (MI) (10 iterations, 10 completed datasets generated) stratifying by EF phenotype. The proportion of missing data for each variable is reported in online supplementary *Table S2*.

A p-value <0.05, two-sided, was considered as statistically significant for all the analyses. No adjustment for multiple comparisons was made and therefore the results should be interpreted accordingly. Statistical analyses were performed by Stata 16.1 (StataCorp LLC, College Station, TX, USA).

Results

Baseline characteristics

Out of 203 428 records in SwedeHF during the study period (11 May 2000–31 December 2021), a total of 91 463 unique patients fulfilled the inclusion/exclusion criteria for this study and thus were included in the analyses. The patient flow-chart of the study is reported in online supplementary *Figure S1*. Of those, 49 589 (54%) patients had HFrEF, 20 921 (23%) HFmrEF and 20 953 (23%) HFpEF. Median age was 76 (67–82) years and 36% were female.

Individual comorbidities

Overall, at least one comorbidity was present in 98% of the patients, with at least one CV comorbidity in 94% and at least one non-CV comorbidity in 85% (online supplementary *Table S2* and *Graphical Abstract*). The most common comorbidities were hypertension (65%), atrial fibrillation (56%) and CAD (52%), followed by CKD (40%) and anaemia (34%) (*Figure 1A*, *Table 1*, categorized by EF). Depression, liver disease and dementia were the least represented (3.6%, 2.1% and 1.5%, respectively). All comorbidities, except for CAD, were more frequent in patients with HFpEF. Patient characteristics stratified according to the presence/absence of each comorbidity in the whole population and according to EF categories are presented in online supplementary *Tables S3–S19*.

Figure 1B shows the distribution of the number of comorbidities in the study population. The majority had 3 (17%), 4 (18%) or 5 (16%) coexisting comorbidities, whereas a minority had no (1.9%), or 10 or more comorbidities (<1%). Among patients with HFrEF the most had three or four comorbidities (18% for both); 19% of patients with HFmrEF had four comorbidities, whereas the most of HFpEF patients had five comorbidities (19%). No comorbidities were reported in 2.6%, 1.3% and 0.6% of patients with HFrEF, HFmrEF and HFpEF, respectively (online supplementary *Table S2*).

Figure 2 depicts how the different comorbidities aggregated. Patients with obesity often also had hypertension (74%), diabetes (39%), atrial fibrillation (57%) and CAD (49%). The prevalence of atrial fibrillation was higher among patients with a history of

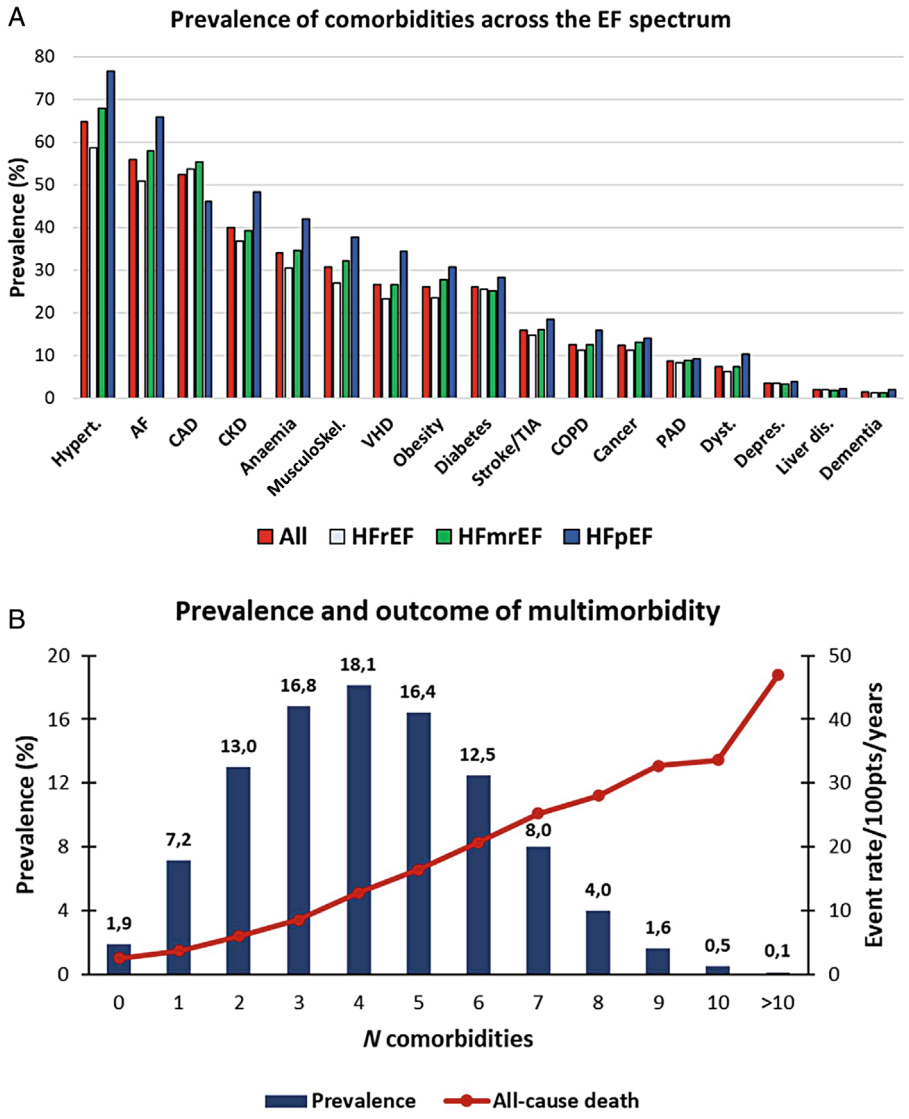


Figure 1 (*A*) Prevalence of comorbidities across the ejection fraction (EF) spectrum. (*B*) Prevalence of and outcome (event rate/100 patients-years) associated with multimorbidity. AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Depres., depression; Dyst., dysthyroidism; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Hypert., hypertension; Liver dis., liver disease; MusculoSkel., musculo-skeletal disease; PAD, peripheral artery disease; TIA, transient ischaemic attack; VHD, valvular heart disease.

stroke/TIA, dementia, coexisting VHD, dysthyroidism, and CKD. Hypertension, atrial fibrillation, CAD and anaemia were the most common comorbidities among patients with a history of cancer. Other specific patterns can be identified in *Figure 2*. Similar trends were observed across the EF spectrum (online supplementary *Tables S20–S22*).

Multimorbidity

Overall, 37% of our HF cohort had one to three comorbidities, 47% had four to six comorbidities and 14% had >6 comorbidities, and respective estimates were 43%, 36%, 25% (one to three comorbidities), 44%, 48%, 54% (four to six comorbidities) and 11%, 15%, 21% (>6 comorbidities) in HFrEF, HFmrEF and HFpEF, respectively (*Table 1*).

In the overall cohort, patients with the higher number of comorbidities were older, more likely female, inpatients, with HFpEF and longer duration of HF, worse New York Heart Association (NYHA) functional class, and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (*Table 2*). Similar results were found across the EF groups (online supplementary *Tables S23–S25*). Among patients with HFrEF, those with more comorbidities were less treated with HF drugs (*Figure 3*). Namely, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin

Table 1 Prevalence of multimorbidity, cardiovascular and non-cardiovascular comorbidities in the whole population and by ejection fraction

Variable	All	HFrEF	HFmrEF	HFpEF	*p*-value
n	91 463	49 589 (54.2%)	20 921 (22.9%)	20 953 (22.9%)	
Obesity	23 971 (26.2%)	11 719 (23.6%)	5822 (27.8%)	6430 (30.7%)	<0.001
Hypertension	59 383 (64.9%)	29 092 (58.7%)	14 212 (67.9%)	16 079 (76.7%)	<0.001
Diabetes	23 830 (26.1%)	12 628 (25.5%)	5281 (25.2%)	5921 (28.3%)	<0.001
CAD	47 933 (52.4%)	26 679 (53.8%)	11 591 (55.4%)	9663 (46.1%)	<0.001
Atrial fibrillation	51 261 (56.0%)	25 313 (51.0%)	12 127 (58.0%)	13 821 (66.0%)	<0.001
Valvular heart disease	24 373 (26.6%)	11 560 (23.3%)	5580 (26.7%)	7233 (34.5%)	<0.001
CKD	36 579 (40.0%)	18 239 (36.8%)	8223 (39.3%)	10 117 (48.3%)	<0.001
Anaemia	31 188 (34.1%)	15 118 (30.5%)	7257 (34.7%)	8813 (42.1%)	<0.001
COPD	11 597 (12.7%)	5624 (11.3%)	2647 (12.7%)	3326 (15.9%)	<0.001
Liver disease	1916 (2.1%)	1060 (2.1%)	379 (1.8%)	477 (2.3%)	0.002
PAD	7916 (8.7%)	4107 (8.3%)	1854 (8.9%)	1955 (9.3%)	<0.001
Stroke/TIA	14 660 (16.0%)	7402 (14.9%)	3360 (16.1%)	3898 (18.6%)	<0.001
Depression	3262 (3.6%)	1738 (3.5%)	702 (3.4%)	822 (3.9%)	0.004
Dementia	1400 (1.5%)	674 (1.4%)	292 (1.4%)	434 (2.1%)	<0.001
Cancer (<3 years)	11 364 (12.4%)	5663 (11.4%)	2742 (13.1%)	2959 (14.1%)	<0.001
Musculoskeletal disease	28 120 (30.7%)	13 438 (27.1%)	6752 (32.3%)	7930 (37.8%)	<0.001
Dysthyroidism	6861 (7.5%)	3128 (6.3%)	1578 (7.5%)	2155 (10.3%)	<0.001
Charlson comorbidity Index					<0.001
0–1	26 863 (29.4%)	15 115 (30.5%)	6072 (29.0%)	5676 (27.1%)	
2–3	35 155 (38.4%)	19 428 (39.2%)	8012 (38.3%)	7715 (36.8%)	
4–7	24 204 (26.5%)	12 510 (25.2%)	5586 (26.7%)	6108 (29.2%)	
≥8	5241 (5.7%)	2536 (5.1%)	1251 (6.0%)	1454 (6.9%)	
No. of comorbidities (groups)					<0.001
No comorbidities	1690 (1.8%)	1283 (2.6%)	282 (1.3%)	125 (0.6%)	
1–3 comorbidities	33 808 (37.0%)	21 138 (42.6%)	7419 (35.5%)	5251 (25.1%)	
4–6 comorbidities	42 971 (47.0%)	21 659 (43.7%)	10 053 (48.1%)	11 259 (53.7%)	
>6 comorbidities	12 994 (14.2%)	5509 (11.1%)	3167 (15.1%)	4318 (20.6%)	
No. of non-CV comorbidities (groups)					<0.001
No comorbidities	13 574 (14.8%)	8662 (17.5%)	3010 (14.4%)	1902 (9.1%)	
1–3 comorbidities	64 769 (70.8%)	35 364 (71.3%)	14 829 (70.9%)	14 576 (69.6%)	
4–6 comorbidities	12 958 (14.2%)	5511 (11.1%)	3049 (14.6%)	4398 (21.0%)	
>6 comorbidities	162 (0.2%)	52 (0.1%)	33 (0.2%)	77 (0.4%)	
No. of CV comorbidities (groups)					<0.001
No comorbidities	5735 (6.3%)	4114 (8.3%)	1003 (4.8%)	618 (2.9%)	
1–3 comorbidities	72 149 (78.9%)	39 170 (79.0%)	16 554 (79.1%)	16 425 (78.4%)	
4–6 comorbidities	13 579 (14.8%)	6305 (12.7%)	3364 (16.1%)	3910 (18.7%)	

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PAD, peripheral artery disease; TIA, transient ischaemic attack.

receptor blocker (ARB)/angiotensin receptor–neprilysin inhibitor (ARNI) were prescribed in 98%, 96%, 90% and 83% of patients with no, 1–3, 4–6 and >6 comorbidities, respectively. Patients with multiple comorbidities more frequently received other drugs (i.e. diuretics, nitrates, statins, and anticoagulant therapy) and HF devices (e.g. cardiac resynchronization therapy [CRT] and implantable cardiac defibrillator [ICD]) (*Figure 3*) (online supplementary *Table S23*). However, in a multivariable logistic regression analysis, after adjustment for baseline patients' characteristics, a higher number of comorbidities was associated with a lower probability to receive a device.

Outcome

Individual comorbidities

Overall, 40% patients died during a median follow-up of 1.9 (0.8–3.2) years. All comorbidities, except for obesity, were associated with a higher crude risk of all-cause mortality (online supplementary *Figure S2–S18*). As shown in *Figure 4* (upper panel), 12 of the 17 examined comorbidities were independently associated with a higher risk of death from any cause.

The highest risk was associated with dementia (adjusted HR 1.55, 95% CI 1.45–1.65), CKD (adjusted HR 1.37, 95% CI 1.34–1.41), COPD (adjusted HR 1.32, 95% CI 1.28–1.35),

Table 2 Baseline characteristics stratified by the number of comorbidities

Variable	No comorbidities	1 to 3 comorbidities	4 to 6 comorbidities	>6 comorbidities	*p*-value
n	1690 (1.8%)	33 808 (37.0%)	42 971 (47.0%)	12 994 (14.2%)	
Demographics and organizational/socioeconomics					
Sex[a]					<0.001
Female	550 (32.5%)	11 190 (33.1%)	16 499 (38.4%)	5095 (39.2%)	
Male	1140 (67.5%)	22 618 (66.9%)	26 472 (61.6%)	7899 (60.8%)	
Age, years, median (IQR)[a]	60 (49–69)	71 (61–79)	78 (70–84)	79 (73–84)	<0.001
Smoking[a]	282 (19.3%)	4070 (14.5%)	3361 (10.2%)	841 (8.8%)	<0.001
Alcohol user	93 (7.2%)	1348 (5.9%)	1014 (4.0%)	232 (3.3%)	<0.001
Location of care[a]					<0.001
Outpatient	1210 (71.6%)	21 678 (64.1%)	21 970 (51.1%)	5242 (40.3%)	
Inpatient	480 (28.4%)	12 130 (35.9%)	21 001 (48.9%)	7752 (59.7%)	
Follow-up location[a]					<0.001
Primary care	158 (9.6%)	7951 (24.3%)	14 889 (36.3%)	5128 (41.7%)	
Hospital	1495 (90.4%)	24 833 (75.7%)	26 099 (63.7%)	7171 (58.3%)	
Family type[a]					<0.001
Cohabitating	1021 (60.6%)	18 513 (54.9%)	21 561 (50.2%)	6417 (49.4%)	
Living alone	663 (39.4%)	15 211 (45.1%)	21 372 (49.8%)	6577 (50.6%)	
Education[a]					<0.001
Compulsory school	464 (27.9%)	12 484 (37.6%)	19 733 (46.9%)	6424 (50.5%)	
Secondary school	742 (44.7%)	14 110 (42.5%)	15 812 (37.6%)	4643 (36.5%)	
University	455 (27.4%)	6610 (19.9%)	6498 (15.5%)	1648 (13.0%)	
Index year[a] (≥2014)	888 (52.5%)	16 809 (49.7%)	21 542 (50.1%)	6790 (52.3%)	<0.001
Income categories[a] (≥median)	1152 (68.4%)	18 935 (56.1%)	19 877 (46.3%)	5760 (44.3%)	<0.001
Clinical variables					
Duration of HF[a]					<0.001
<6 months	1293 (78.0%)	22 034 (66.5%)	19 898 (47.5%)	4397 (34.8%)	
≥6 months	365 (22.0%)	11 097 (33.5%)	21 955 (52.5%)	8243 (65.2%)	
Previous HF hospitalization (<12 months)[a]	1007 (59.6%)	18 400 (54.4%)	28 264 (65.8%)	10 000 (77.0%)	<0.001
NYHA functional class[a]					<0.001
I–II	1132 (79.2%)	19 233 (71.9%)	16 426 (54.7%)	3288 (40.5%)	
III–IV	297 (20.8%)	7500 (28.1%)	13 629 (45.3%)	4837 (59.5%)	
BMI, kg/m^2, median (IQR)	25 (22–27)	26 (23–29)	27 (23–31)	29 (24–33)	<0.001
SBP, mmHg, median (IQR)	120 (109–130)	125 (110–140)	127 (113–140)	126 (113–140)	<0.001
DBP, mmHg, median (IQR)	70 (65–80)	75 (67–80)	70 (65–80)	70 (61–80)	<0.001
MAP, mmHg, median (IQR)[a]	88 (80–97)	92 (83–100)	90 (82–100)	90 (81–98)	<0.001
Heart rate, bpm, median (IQR)[a]	69 (60–80)	71 (62–82)	72 (64–83)	72 (64–83)	<0.001
EF categories[a]					<0.001
HFrEF	1283 (75.9%)	21 138 (62.5%)	21 659 (50.4%)	5509 (42.4%)	
HFmrEF	282 (16.7%)	7419 (21.9%)	10 053 (23.4%)	3167 (24.4%)	
HFpEF	125 (7.4%)	5251 (15.5%)	11 259 (26.2%)	4318 (33.2%)	
Charlson comorbidity index					<0.001
0–1	1421 (84.1%)	17 011 (50.3%)	8001 (18.6%)	430 (3.3%)	
2–3	202 (12.0%)	13 185 (39.0%)	18 875 (43.9%)	2893 (22.3%)	
4–7	58 (3.4%)	3027 (9.0%)	13 792 (32.1%)	7327 (56.4%)	
≥8	9 (0.5%)	585 (1.7%)	2303 (5.4%)	2344 (18.0%)	
Laboratory					
eGFR, ml/min, median (IQR)	90 (78–100)	79 (65–92)	60 (45–79)	47 (35–59)	<0.001
Potassium categories[a]					<0.001
Normakalaemia	1362 (96.1%)	26 111 (94.9%)	31 653 (91.8%)	9567 (90.0%)	
Hypokalaemia	33 (2.3%)	882 (3.2%)	1771 (5.1%)	589 (5.5%)	
Hyperkalaemia	22 (1.6%)	515 (1.9%)	1041 (3.0%)	478 (4.5%)	
Haemoglobin, g/L, median (IQR)	144 (136–152)	140 (131–150)	129 (118–141)	119 (109–129)	<0.001
NT-proBNP, ng/L, median (IQR)[a]	1360 (436–3580)	1741 (700–3850)	2590 (1198–5690)	3340 (1588–7384)	<0.001

Table 2 (Continued)

Variable	No comorbidities	1 to 3 comorbidities	4 to 6 comorbidities	>6 comorbidities	*p*-value
Treatments					
ACEi/ARB/ARNI[a]	1589 (95.1%)	30 474 (91.1%)	35 547 (83.6%)	9660 (75.3%)	<0.001
Beta-blockers[a]	1446 (85.8%)	30 019 (89.0%)	37 792 (88.2%)	11 371 (87.9%)	<0.001
MRA[a]	557 (33.0%)	11 331 (33.7%)	15 625 (36.6%)	4562 (35.3%)	<0.001
Diuretics[a]	876 (52.0%)	21 512 (63.8%)	35 186 (82.1%)	11 804 (91.2%)	<0.001
Digoxin[a]	40 (2.4%)	4334 (12.9%)	6159 (14.4%)	1637 (12.7%)	<0.001
Antiplatelet therapy[a]	411 (24.4%)	13 800 (41.0%)	18 481 (43.2%)	5337 (41.3%)	<0.001
Anticoagulant therapy[a]	243 (14.4%)	13 114 (38.9%)	21 709 (50.7%)	7297 (56.4%)	<0.001
Statins[a]	334 (19.8%)	13 624 (40.4%)	22 543 (52.6%)	7834 (60.5%)	<0.001
Nitrates[a]	14 (0.8%)	1992 (5.9%)	6468 (15.1%)	3111 (24.1%)	<0.001
HF devices[a]	118 (7.0%)	1718 (5.2%)	2417 (5.7%)	685 (5.3%)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
[a]Variables that were included in multiple imputation together with the primary outcome and in the multivariable Cox regression models.

cancer (adjusted HR 1.31, 95% CI 1.28–1.35), liver disease (adjusted HR 1.30, 95% CI 1.22–1.40), anaemia (adjusted HR 1.29, 95% CI 1.26–1.32), and, among CV comorbidities, PAD (adjusted HR 1.28, 95% CI 1.24–1.32) and VHD (adjusted HR 1.20, 95% CI 1.17–1.23). Diabetes, atrial fibrillation, CAD, and previous stroke/TIA were also independently associated with a higher risk of mortality, whereas hypertension, depression, musculo-skeletal disease and dysthyroidism were not. Obesity was independently associated with a significantly lower risk of all-cause death (adjusted HR 0.81, 95% CI 0.79–0.84) (*Figure 4* upper panel, online supplementary *Table S26*).

Cardiovascular and non-cardiovascular mortality and hospitalizations

At multivariable analysis, diabetes, atrial fibrillation, CKD, anaemia, COPD, liver disease, PAD, stroke/TIA and dementia were independently associated with a higher risk of both CV and non-CV mortality. CAD and VHD were associated with a higher risk of CV mortality but not non-CV mortality. Cancer and musculo-skeletal disease increased the risk of non-CV mortality only. Obesity was associated with a lower risk of both CV and non CV-mortality. No significant association with either CV or non-CV mortality was found for hypertension, depression, and dysthyroidism (*Figure 4* upper panel; online supplementary *Tables S27* and *S28*).

Most comorbidities were also independently associated with a higher risk of all-cause, CV and non-CV hospitalizations (online supplementary *Tables S29–S32*). All comorbidities, except for dementia, led to a higher adjusted risk of HF hospitalizations. Obesity was associated with a higher risk of HF hospitalizations only.

Role of ejection fraction

A significant interaction with EF was observed for several comorbidities (*Figure 4* lower panel). CAD was associated with a significant higher risk of all-cause mortality in patients with HFrEF and HFmrEF but not in those with HFpEF (adjusted HR 1.35, 95% CI 1.31–1.40; adjusted HR 1.09, 95% CI 1.04–1.14; adjusted HR 1.02, 95% CI 0.98–1.06, respectively, *p*-interaction <0.001). Furthermore, hypertension was not independently associated with all-cause mortality in patients with HFrEF and HFmrEF, whereas it was associated with a lower risk in patients with HFpEF (adjusted HR 0.93, 95% CI 0.88–0.97, *p*-interaction 0.0004) (*Figure 4* lower panel; online supplementary *Table S26*). VHD, COPD, liver disease and dementia displayed a similar increased risk of mortality regardless of EF subgroups. Atrial fibrillation, stroke/TIA, diabetes, PAD, anaemia and cancer were associated with a higher risk of all-cause death in patients with HFrEF and HFmrEF compared to HFpEF, whereas CKD displayed the highest risk in HFrEF patients. Obesity was associated with a lower risk of all-cause, CV and non CV-mortality irrespective of EF and with a lower risk of all-cause hospitalizations in patients with HFrEF and HFmrEF but not HFpEF. The association of obesity with a higher risk of HF hospitalizations was confirmed across all EF subgroups (online supplementary *Tables S27–S32*).

Further data as regards the risk of CV and non-CV mortality, CV, non-CV and HF-related hospitalizations as well as the interaction with EF subgroups are presented in online supplementary *Tables S27–S32*.

Multimorbidity

Patients without any pre-specified comorbidity had the lowest event rate for all-cause death (event rate/100 patients-years 2.54 [2.18–2.97]). Death rate proportionally increased with the number of comorbidities up to about 47 events/100 patients-years in patients with more than 10 comorbidities (*Figure 1B*). The unadjusted HRs for all-cause mortality were 2.59 (2.22–3.03), 6.20 (5.31–7.22), 10.40 (8.91–12.14) for patients with 1 to 3, 4

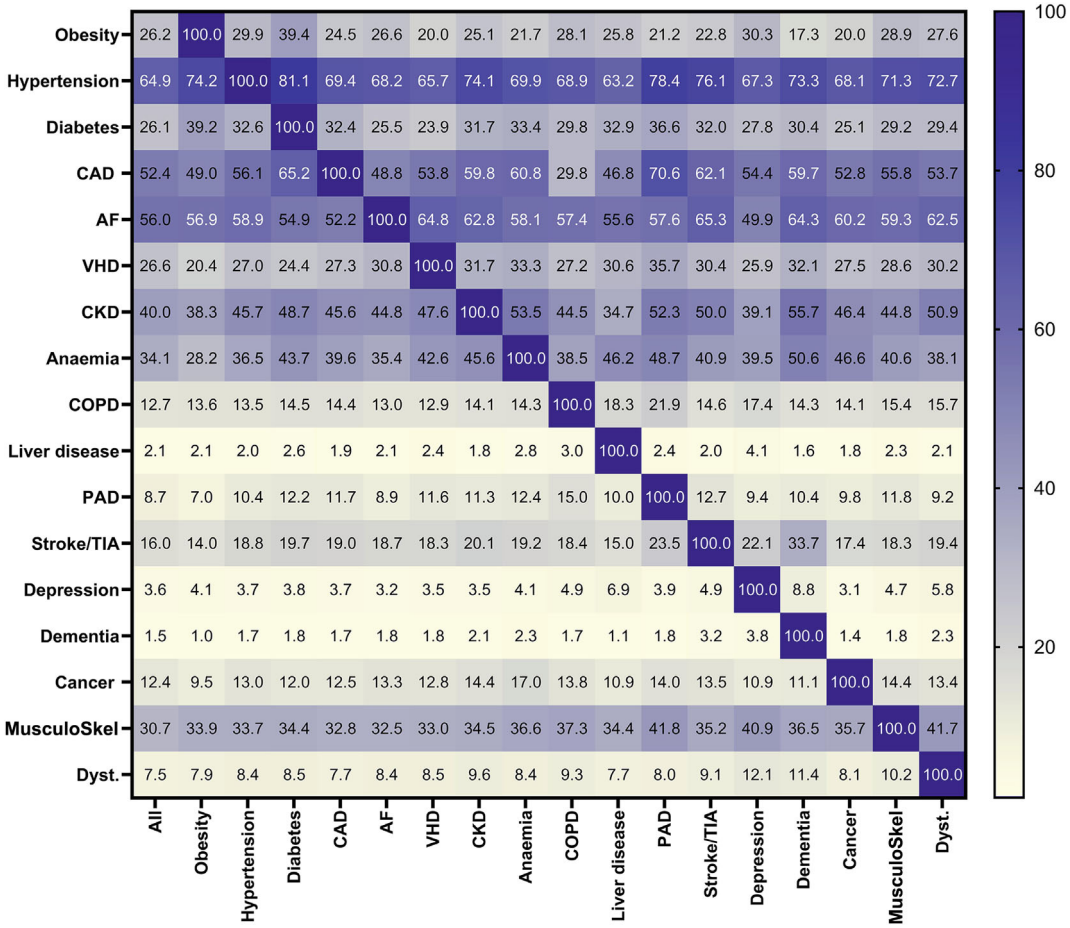


Figure 2 Heatmap for the cross-tabulation among comorbidities. The figure reports the prevalence of each comorbidity (rows) among the overall population and among each other comorbidity (columns). AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Dyst., dysthyroidism; MusculoSkel., musculo-skeletal disease; PAD, peripheral artery disease; VHD, valvular heart disease.

to 6 and >6 comorbidities compared to those without comorbidities, respectively (*Figure 5*, online supplementary *Table S33*). The association with all-cause death was confirmed after adjustments (adjusted HRs 1.99 [1.71–2.33], 3.25 [2.78–3.79] and 4.41 [3.77–5.16], respectively) (*Figure 6*, online supplementary *Table S33*). The association was confirmed across all EF categories. However, patients with HFrEF and multimorbidity presented a higher risk of all-cause death compared to those with HFmrEF and HFpEF (p-interaction <0.001). Both the adjusted risk of CV and non-CV mortality was higher among patients with multimorbidity. Furthermore, the higher was the number of comorbidities, the higher was the adjusted risk of CV, non-CV and HF-related hospitalizations (*Figure 6*, online supplementary *Table S33*). A significant interaction with EF was observed for all secondary endpoints. The number of CV and non-CV comorbidities were directly related to the risk of CV and non-CV outcomes, respectively (*Table 3*).

Discussion

The current analysis from the SwedeHF registry represents the largest and most comprehensive study regarding the prevalence and prognosis related to a large number of CV and non-CV comorbidities, in a real-world population with HF across the EF spectrum.

The key findings of this study are the following: (1) almost all patients had at least one comorbidity with 37%, 47% and 14% of patients having 1 to 3, 4 to 6 and >6 comorbidities, respectively; (2) all comorbidities, except for CAD, were more prevalent in patients with HFpEF; (3) obesity was the only comorbidity associated with a lower risk of mortality, regardless of EF, but it led to a higher risk of HF hospitalizations; (4) CAD and VHD were associated with a higher risk of CV mortality but not non-CV mortality, whereas cancer and musculo-skeletal disease increased the risk of non-CV mortality only; also, a significant interaction with EF was observed for several comorbidities; (5) patients with multimorbidity were

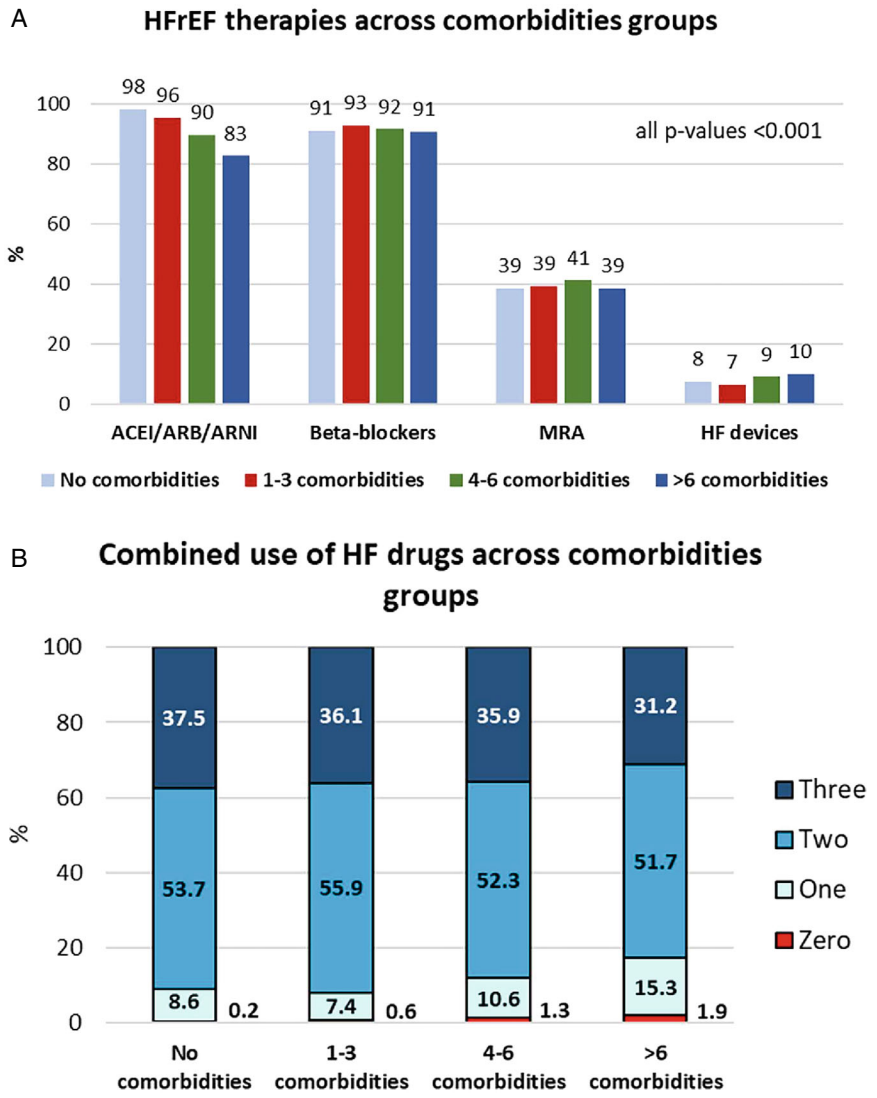


Figure 3 (*A*) Prescription of angiotensin converting enzyme inhibitor/angiotensin receptor blocker/ angiotensin receptor–neprilysin inhibitor (ACEi/ARB/ARNI), beta-blockers, mineralocorticoid receptor antagonist (MRA) and heart failure (HF) devices in patients with HF with reduced ejection fraction (HFrEF), stratified according to the number of comorbidities. (*B*) Combined use of HF medical therapies across comorbidities groups. HF devices include cardiac resynchronization therapy and implantable cardiac defibrillator).

older, with more severe HF and a higher adjusted risk of events (*Graphical Abstract*); (6) patients with HFrEF and multimorbidity were less likely prescribed with HF drugs, namely ACEi/ARB/ARNI but more frequently received other drugs, including diuretics; and (7) occurrence of CV and non-CV outcomes was related to the number of CV and non-CV comorbidities, respectively.

Prevalence of comorbidities and multimorbidity

Our results are consistent with a recent pooled analysis of the PARADIGM-HF and the ATMOSPHERE trials including 15 066 patients and showing that >93% of HFrEF patients had at least one comorbidity and 79% had at least two comorbidities.[7] In our study we found that about 98% of HF patients had at least one comorbidity (94% had at least one CV comorbidity and 85% had at least one non-CV comorbidity). The inclusion of a real-world population in our study may explain the observed difference in estimates. A similar prevalence of multimorbidity was found in different HF populations from Europe and Asia.[16,17] A novel aspect of our study was also that we included HF patients across the EF spectrum and provided detailed analyses for each EF category, i.e. not only HFrEF. HFpEF has an even higher burden of comorbidities,[4] with a key role of comorbidities in the aetiopathogenesis of HFpEF,

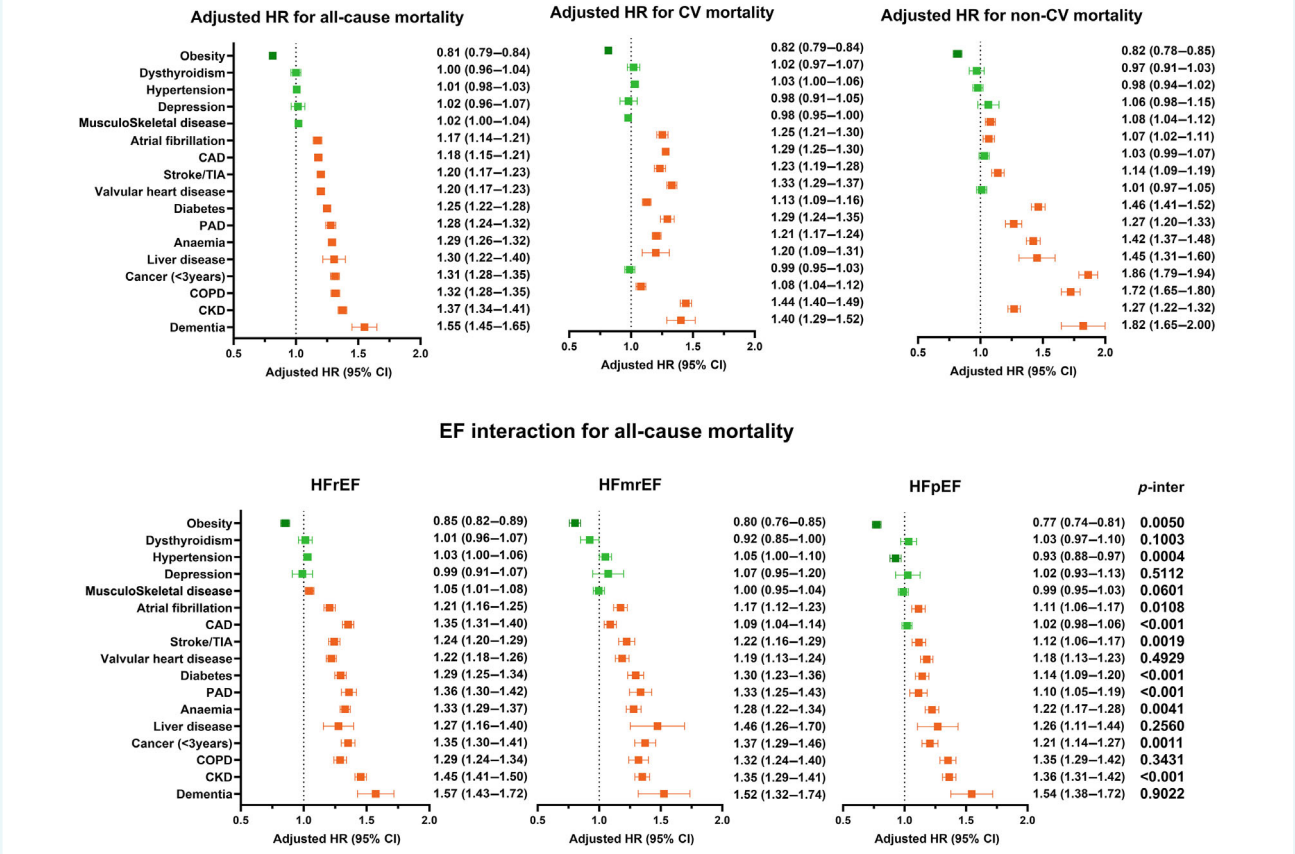


Figure 4 Adjusted hazard ratio (HR) for all-cause mortality, cardiovascular (CV) and non-CV mortality for each comorbidity in the overall cohort (upper panel) and adjusted HR for all-cause mortality for each comorbidity across the ejection fraction (EF) spectrum (lower panel). CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PAD, peripheral artery disease; TIA, transient ischaemic attack.

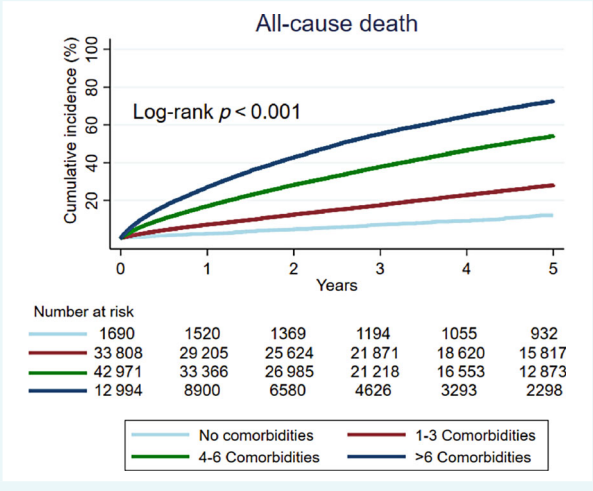


Figure 5 Kaplan–Meier curves for all-cause mortality according to the number of comorbidities (none vs. 1 to 3 vs. 4 to 6 vs. >6 comorbidities).

namely hypertension, obesity, diabetes, CKD and atrial fibrillation that often coexist.[18,19]

In the present study we provided extensive data regarding the prevalence of several comorbidities across the EF spectrum. The most common comorbidities were hypertension (65%), atrial fibrillation (56%) and CAD (52%), followed by CKD (40%) and anaemia (34%). Results are consistent with those in the PARADIGM-HF and ATMOSPHERE trials.[7] On the other hand, we found a significantly higher prevalence of atrial fibrillation (ranging from 51% to 66% in patients with HFrEF and HFpEF, respectively) compared to the previously motioned analyses from trials (24–36%). This could be related to the inclusion of both paroxysmal and permanent atrial fibrillation in our study.[4,7] Compared to previous studies, we found an overall lower prevalence of depression, which might reflect our definition of the disease through ICD-10 in the Swedish National Patient Registry, and therefore reflect the more severe cases of the disease.[20,21] Except for CAD that is a well-known cause of left ventricular systolic dysfunction[1] and therefore more prevalent in HFrEF and HFmrEF versus HFpEF, all other comorbidities were more prevalent in patients with HFpEF.

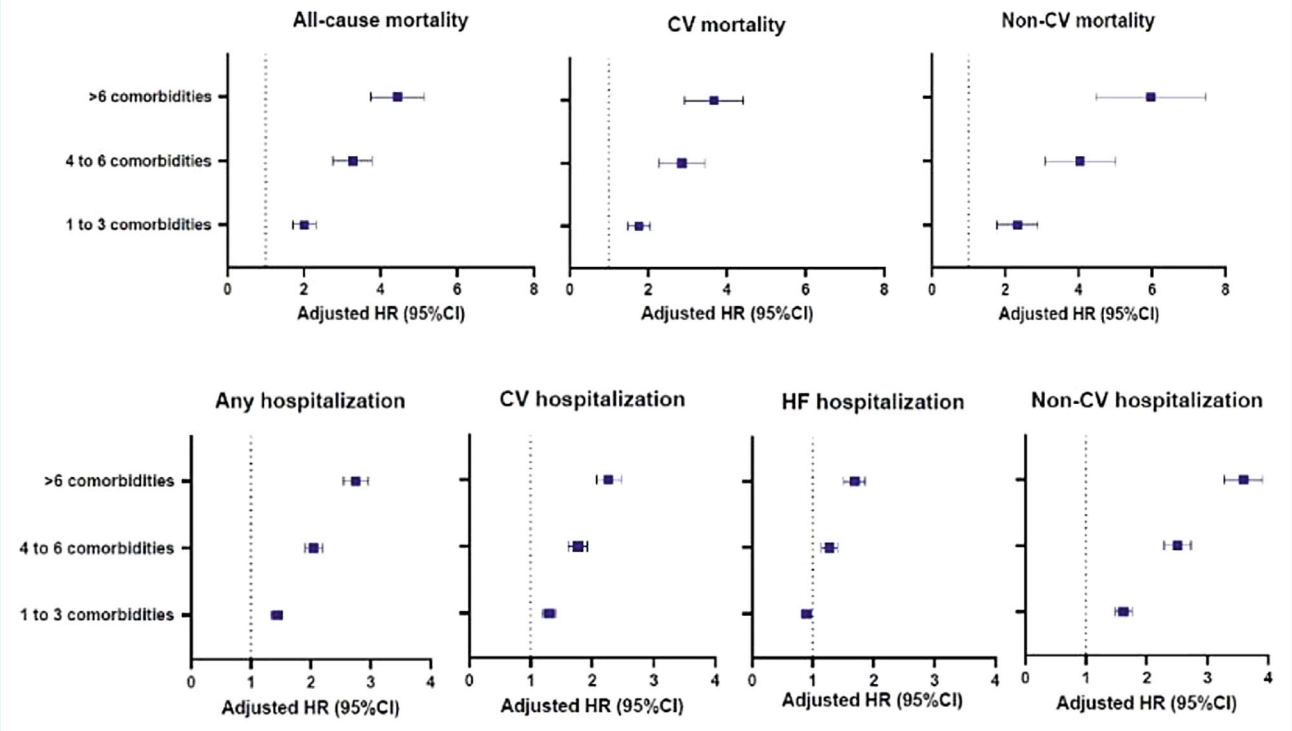


Figure 6 Adjusted hazard ratio (HR) for all-cause mortality and the secondary endpoints according to the number of comorbidities (none vs. 1 to 3 vs. 4 to 6 vs. >6 comorbidities). CI, confidence interval; CV, cardiovascular; HF, heart failure.

Clinical phenotypes according to the number of comorbidities

Patients with multimorbidity were older, with a longer duration and more severe HF as shown by higher NT-proBNP levels, worse NYHA class and more likely diuretic use. Comorbidities were also associated with different patterns in medication use in patients with HFrEF. ACEi/ARB/ARNI were less prescribed in HFrEF patients with the highest burden of comorbidities, whereas diuretics and non-HF drugs (i.e. nitrates) were more frequently used. Lower adherence to and prescription of guideline-directed medical therapy (GDMT) have been previously reported among older and comorbid HFrEF patients,[22,23] and might reflect lower tolerance, higher risk of side effects, higher chance of contraindications but also clinical inertia and more limited evidence from trials in this setting. Severe CKD and risk of hyperkalaemia have been advocated as a reason for under-prescription of mineralocorticoid receptor antagonists (MRAs),[24,25] although the safety of MRA use has recently been shown across the entire eGFR spectrum.[26] A secondary analysis of the STRONG-HF has shown that the achievement of full doses and the benefits of HF therapies were similar regardless of non-CV comorbidity burden.[10]

Outcome

The majority of comorbidities were associated with a worse survival. Atrial fibrillation was independently associated with a higher risk of all-cause death across the EF spectrum, as already shown among incident HFpEF and HFrEF in the Framingham Heart Study, registries and meta-analyses of randomized trials.[27–30] Differently from other studies showing that the association of atrial fibrillation with outcome seems to be mitigated in HFrEF, we rather observed the highest risk in this phenotype.[31,32] VHD has been extensively associated with poorer prognosis.[33–35] We extend previous evidence in a larger and representative cohort of HF patients, confirming the results across the EF spectrum and we also investigated specific (CV or non-CV) causes of death or hospitalization.

A significant interaction between EF and each comorbidity for the risk of mortality could be assessed. For example, CAD was associated with a higher risk of mortality in patients with HFrEF and HFmrEF but not in those with HFpEF. This could be related to the different severity of the disease. Indeed, patients experiencing myocardial infarction or delayed treatment may develop left ventricular dysfunction, worsening their prognosis. We also found that hypertension was protective in patients with preserved EF, whereas non-significant associations were found in patients with HFmrEF and HFrEF. The protective role of hypertension in HFpEF might be related to the different prognosis of different HFpEF phenotypes, e.g. cardiac amyloidosis (which is not captured in our data set) that represents a high-risk phenotype characterized by low blood pressure.[36] Also, we cannot exclude a residual confounding role for renin–angiotensin system inhibitors (RASi) even if we adjusted

Table 3 Outcome according to the number of cardiovascular and non-cardiovascular comorbidities

	CV comorbidities			Non-CV comorbidities			
	No CV comorbidities	1 to 3 CV comorbidities	4 to 6 CV comorbidities	No non-CV comorbidities	1 to 3 non-CV comorbidities	4 to 6 non-CV comorbidities	>6 non-CV comorbidities
All-cause mortality							
Crude HR (95% CI), *p*-value	Ref	2.22 (2.09–2.35), <0.001	4.17 (3.91–4.44), <0.001	Ref	2.57 (2.47–2.68), <0.001	4.65 (4.44–4.86), <0.001	6.98 (5.81–8.38), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.55 (1.45–1.64), <0.001	2.12 (1.98–2.27), <0.001	Ref	1.64 (1.57–1.71), <0.001	2.20 (2.09–2.30), <0.001	2.52 (2.08–3.06), <0.001
CV mortality							
Crude HR (95% CI), *p*-value	Ref	3.06 (2.79–3.35), <0.001	6.44 (5.86–7.07); <0.001	Ref	2.41 (2.29–2.54); <0.001	3.82 (3.61–4.05), <0.001	4.08 (3.05–5.45), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.96 (1.78–2.15), <0.001	2.90 (2.62–3.20), <0.001	Ref	1.44 (1.37–1.52), <0.001	1.65 (1.56–1.76); <0.001	1.35 (1.01–1.82); 0.046
Non-CV mortality							
Crude HR (95% CI), *p*-value	Ref	1.59 (1.46–1.72), <0.001	2.46 (2.25–2.68), <0.001	Ref	2.86 (2.67–3.07), <0.001	6.25 (5.80–6.74), <0.001	12.74 (10.03–16.18), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.24 (1.14–1.35), <0.001	1.48 (1.35–1.63); <0.001	Ref	2.02 (1.88–2.16), <0.001	3.37 (3.12–3.64), <0.001	5.25 (4.10–6.72), <0.001
Any hospitalization							
Crude HR (95% CI), *p*-value	Ref	1.56 (1.50–1.61), <0.001	2.42 (2.32–2.51), <0.001	Ref	1.63 (1.60–1.67); <0.001	2.76 (2.68–2.84), <0.001	3.98 (3.36–4.70), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.33 (1.28–1.38), <0.001	1.68 (1.61–1.75), <0.001	Ref	1.34 (1.31–1.37), <0.001	1.86 (1.81–1.92), <0.001	2.36 (1.99–2.80), <0.001
CV hospitalization							
Crude HR (95% CI), *p*-value	Ref	1.76 (1.68–1.84), <0.001	2.88 (2.74–3.02), <0.001	Ref	1.48 (1.44–1.52), <0.001	2.25 (2.17–2.32), <0.001	3.01 (2.49–3.65), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.46 (1.39–1.53); <0.001	1.91 (1.81–2.02), <0.001	Ref	1.19 (1.15–1.22), <0.001	1.48 (1.42–1.53), <0.001	1.81 (1.49–2.20), <0.001
HF hospitalization							
Crude HR (95% CI), *p*-value	Ref	1.39 (1.32–1.47), <0.001	2.37 (2.24–2.51), <0.001	Ref	1.78 (1.71–1.84), <0.001	3.04 (2.91–3.18), <0.001	4.49 (3.62–5.57), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.08 (1.02–1.14), 0.006	1.36 (1.28–1.45), <0.001	Ref	1.32 (1.27–1.37), <0.001	1.78 (1.70–1.86), <0.001	2.40 (1.93–2.99), <0.001
Non-CV hospitalization							
Crude HR (95% CI), *p*-value	Ref	1.54 (1.48–1.60), <0.001	2.35 (2.25–2.46), <0.001	Ref	1.90 (1.84–1.95), <0.001	3.59 (3.47–3.71), <0.001	5.59 (4.68–6.68), <0.001
Adjusted HR (95% CI), *p*-value	Ref	1.27 (1.22–1.32), <0.001	1.57 (1.50–1.65), <0.001	Ref	1.55 (1.50–1.59), <0.001	2.42 (2.34–2.51), <0.001	3.29 (2.74–3.94), <0.001

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

for these treatments. Indeed, we observed a higher prescription of RASi in patients with HFpEF and hypertension. Hypertension is frequently associated with other comorbidities, e.g. diabetes and CKD, that can benefit from RASi.[37] Anaemia, CKD, diabetes, COPD, liver disease, stroke and PAD were also confirmed as independent predictors of poorer survival, irrespective of EF.[5,7,38–44]

Furthermore, our study has the potential to inform clinical trial design, with detailed data on cause-specific outcomes for each comorbidity. We showed that CV comorbidities increased more the risk of CV rather than non-CV outcomes. CAD and VHD were associated with a higher risk of CV mortality but not non-CV mortality. On the other hand, cancer and musculo-skeletal disease increased the risk of non-CV mortality but not CV mortality. COPD was associated with a higher risk of non-CV mortality rather than CV mortality.

In contrast with previous findings, depression was not independently related with prognosis in our study, whereas dementia strongly predicted a higher risk of mortality in all HF phenotypes.[20,21]

The so-called 'obesity survival paradox' has recently been questioned. In a post-hoc analysis of PARADIGM-HF trial, enrolling patients with HFrEF, Butt *et al.*[45] found a lower risk of all-cause mortality in patients with a BMI ≥25 kg/m^2, but this disappeared when adjusting for other prognostic variables. Furthermore, the paradox was even more attenuated when considering the waist to height ratio. In the present study we confirmed that obesity was independently associated with better survival in HF, regardless of EF.[46,47] However, as already observed by Butt *et al.*, obesity was associated with a higher risk of HF hospitalizations. Also, compared with non-obese patients, obese patients were more likely to receive HF therapies and achieved the full target dose.[48]

Importantly, our study highlights the impact of multimorbidity on all-cause mortality, CV and non-CV mortality and hospitalizations. We found a consistent and strong association between the number of comorbidities and all long-term outcomes irrespective of EF category and irrespective of older age and more severe HF, in line with previous studies in patients with both chronic and acute HF.[2,5,7,49,50]

It is recommended to identify and treat the underlying risk factors, aetiology, and coexisting comorbidities in HF since the treatment of comorbidities and the underlying phenotypes leads to improved outcomes.[1,19] This is even more crucial in patients with HFpEF, being the burden of comorbidities higher compared to HFmrEF and HFrEF patients and options for the medical treatment of HFpEF patients limited to sodium–glucose cotransporter 2 inhibitors.[51]

The increased risk of events related to CV and non-CV comorbidities should also be considered when assessing frailty in HF patients, to improve their management, considering further strategies including telemonitoring and post-discharge care management or rehabilitation programmes.[6,52,53]

Limitations

We performed many statistical comparisons, but we performed no adjustment for multiple comparisons. Therefore, there is a potential risk of Type I error (false positive results). Also, despite the extensive adjustments, the role of residual unmeasured confounders cannot be ruled out. Furthermore, some comorbidities are captured through the National Patient Register, that does not include primary care, so that diagnoses might be missed. On the other hand, a higher number of comorbidities might be registered in patients with a history of hospitalization. Generalizability of our results is partially limited since patients enrolled in SwedeHF have different characteristics compared with the overall HF population.[54] This analysis was conducted in a nationwide registry and therefore also generalizability to other geographical areas should be considered.

Conclusions

In this nationwide cohort of patients with HF regardless of EF, we showed a very high burden of both CV and non-CV comorbidities, with almost the totality of patients presenting at least one comorbidity. Overall, 14% of patients had >6 comorbidities and multimorbidity was associated with a very poor prognosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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