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ORIGINAL RESEARCH ARTICLE

Recurrent heart failure hospitalizations increase the risk of cardiovascular and all-cause mortality in patients with heart failure in Sweden: a real-world study

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Abstract

Aims Heart failure (HF) is a leading cause of hospitalization and is associated with high morbidity and mortality. We examined the impact of recurrent HF hospitalizations (HFHs) on cardiovascular (CV) mortality among patients with HF in Sweden.
Methods and results Adults with incident HF were identified from linked national health registers and electronic medical records from 01 January 2005 to 31 December 2013 for Uppsala and until 31 December 2014 for Västerbotten. CV mortality and all-cause mortality were evaluated. A time-dependent Cox regression model was used to estimate relative CV mortality rates for recurrent HFHs. Assessment was also done for ejection fraction-based HF phenotypes and for comorbid atrial fibrillation, diabetes, or chronic renal impairment. Overall, 3878 patients with HF having an index hospitalization were included, providing 9691.9 patient-years of follow-up. Patients were relatively old (median age: 80 years) and were more frequently male (55.5%). Compared with patients without recurrent HFHs, the adjusted hazard ratio (HR [95% confidence interval; CI]) for CV mortality and all-cause mortality were statistically significant for patients with one, two, three, and four or more recurrent HFHs. The risk of CV mortality and all-cause mortality increased approximately six-fold in patients with four or more recurrent HFHs vs. those without any HFHs (HR [95% CI]: 6.26 [5.24–7.48] and 5.59 [4.70–6.64], respectively). Similar patterns were observed across the HF phenotypes and patients with comorbidities.
Conclusions There is a strong association between recurrent HFHs and CV and all-cause mortality, with the risk increasing progressively with each recurrent HFH.

Keywords Heart failure; Hospitalization; Mortality; HF phenotypes; Comorbidities

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Introduction

Heart failure (HF) is associated with a large burden of disease for the individual, the patient's family, and healthcare systems and is a leading cause of hospitalization among older adults.[1] Worldwide, HF affects at least 26 million people,[2] and the prevalence of HF varies with about 1–2% of the adult population in developed countries and rising over 10% among individuals aged ≥70 years.[3,4] With the increasing prevalence of chronic HF, there is a concomitant increase in the number of related hospitalizations, and as chronic HF progresses, the risk of acute exacerbation increases.

Furthermore, following discharge, patients with HF are at a high risk for re-hospitalization.[5]

Patients with HF, in particular those with HF with preserved ejection fraction, frequently suffer from multiple comorbidities, including ischaemic heart disease, hypertension, diabetes, atrial fibrillation (AF), and kidney and pulmonary diseases, which together may substantially contribute to hospitalizations.[6]

Despite improvements being observed in the survival of patients with HF over recent years, overall prognosis remains poor,[7,8] with survival estimates of approximately 50% at 5 years after initial diagnosis of HF.[9–11] Previous observational studies conducted in the US, Canada, and Finland have found that the number of recurrent hospitalizations is a strong predictor of mortality.[12–14] Similar findings were noted in a post hoc analysis of the CHARM trial where rates of cardiovascular (CV) death or HF hospitalization (HFH) were higher in patients who had previously been hospitalized for HF vs. those with no hospitalization.[15] However, there is scarcity of data globally including both data from the primary and secondary care setting evaluating recurrent hospitalizations and mortality in a contemporary, real-world setting. There are also limited published data analysing the relationships between HFH and mortality in different left ventricular ejection fraction (LVEF) phenotypes, and according to comorbidity status, the latter is considered important given the likely influence of significant comorbidities on patient morbidity and survival.

The objective of this study was to evaluate the association of recurrent HFHs with CV and all-cause mortality among patients with an incident HFH and to examine the change in risk by recurrent hospitalizations. Analyses of subgroups with different HF phenotypes defined based on the LVEF and in strata of patients with HF having comorbid AF, diabetes, and chronic renal impairment (CRI) were also performed.

Methods

This was a retrospective non-interventional cohort study using regional longitudinal, patient-level data from linked national health registers and electronic medical records of patients with HF in Sweden. National registry data covering the entire Swedish population, drawn from the National Population Register (NPR), the National Prescribed Drug Register (NDR), and the Cause of Death Register, were linked to the electronic medical record data from two regions to cover the entire patient pathway. Hence, data were extracted from both primary care and hospital cardiology departments for the counties of Uppsala and Västerbotten. The Pygargus Customized eXtraction Program (CXP 3.0)[16] was used to extract data from electronic medical records of patients in Uppsala (two hospitals and 46 primary care centres) and Västerbotten (three hospitals and 37 primary care centres) and subsequently linked to data from the national health registers.

The HF phenotype [i.e. HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF)] was determined based on the LVEF data from local echocardiography registries. Ethical approval was obtained from the regional ethics review board in Uppsala, Sweden (2015-045), before the data were extracted.

Study design and population

Adult patients (aged ≥18 years) with an HF diagnosis and treated in the primary or secondary care setting between 01 January 2005 and 31 December 2014 and with at least one HFH between 01 January 2009 and 31 December 2011 were identified. Because two different NPR extractions were performed for Uppsala and Västerbotten, the data coverage was different for the two regions. For Uppsala, data were available until 31 December 2013, whereas for Västerbotten, data were available until 31 December 2014 (*Figure 1*).

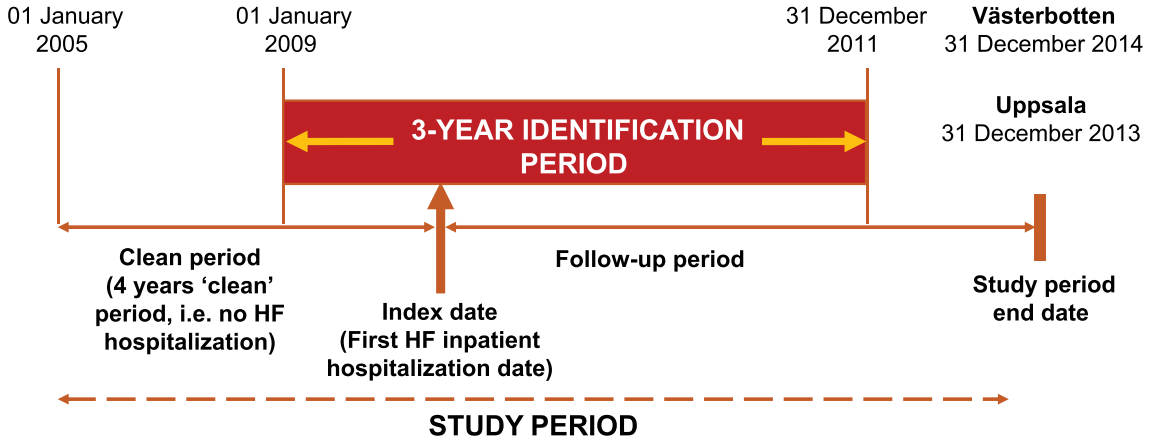
The index HFH was defined as the first HFH recorded in the NPR data with a diagnosis for HF based on the International Classification of Diseases, 10th edition (ICD-10) codes I11.0, I13.0, I13.2, I42.0, I42.1, I42.2, I42.9, or I50.X during the identification period. The date of admission for the first HFH in the identification period was defined as the index date. In order to ensure that all patients were newly diagnosed, patients were excluded if they had experienced an HFH during the 4 year pre-index period (01 January 2005 to 01 January 2009), described as the 'clean period'. Patients were followed until death, transfer out of healthcare region (i.e. Uppsala and Västerbotten), or end of the study period.

A subgroup analysis was performed based on HF phenotypes and across patients with HF by type of comorbidity. Local echocardiography registries were used to determine the HF phenotype. Available LVEF values closest to the index date within 1 year were used for grouping [HFrEF (LVEF <45%), and HFpEF (LVEF ≥50%)]. LVEF cut-offs were based on the availability of the data groups. For subgroups based on comorbidities, patients with HF diagnosed with comorbid AF, diabetes, or CRI prior to the index date were assessed and grouped based on the ICD codes I48, E10-E-14, and N18, respectively; the groups were not mutually exclusive.

Study variables

Patients were grouped according to the number of recurrent HFHs (one, two, three, and four or more) after the index HFH. A patient who died after the index HFH date or who survived until end of follow-up with no subsequent recurrent HFHs was classified as zero recurrent HFH. Baseline characteristics assessed on the index date included age, sex, body mass

Figure 1 Overview of study design. HF, heart failure.



index, estimated glomerular filtration rate, comorbidities, N-terminal pro b-type natriuretic peptide levels, and concomitant medications.

During the study follow-up, all-cause mortality and CV mortality (where CV disease was listed as the primary cause of death) were recorded for the overall HF population and for the subgroups based on HF phenotype and patients with HF having comorbidities of interest, respectively. Among patients with zero recurrent HFHs, mortality outcomes were evaluated from the date of admission. CV disease as the primary cause of death was assessed using ICD-10 codes (i.e. Chapter I00-99) based on the underlying cause of death field in the death certificate.

Data analysis

Baseline demographics and clinical characteristics were summarized using descriptive analyses. No imputation was carried out for missing data. Continuous variables were summarized as either mean ± standard deviation (SD) or median (interquartile range [IQR]), while all categorical variables were summarized as frequencies and percentages. A time-dependent Cox regression model using a stepwise selection approach was used to estimate adjusted CV and all-cause mortality rates for patients with time-dependent recurrent HFHs vs. patients without recurrent HFHs. Based on the testing for differences in patient characteristics between patients with and without HFHs after the index date, variables showing differences (either in means or proportions) with a significance level of 10% (i.e. P value <0.1) were included as adjusting covariates in the model. In this analysis, the referent group included those patients with no recurrent HFH after the index HFH. Patients who died before the end of the follow-up or patients who survived until the end of the follow-up, all of them without any other HFH, were included in the same group because their outcome is the same. However, the time they contribute into the analyses is different and the opportunity to have a recurrent HFH disappears; therefore, a time-dependent model is being used, and competing risks were also addressed.

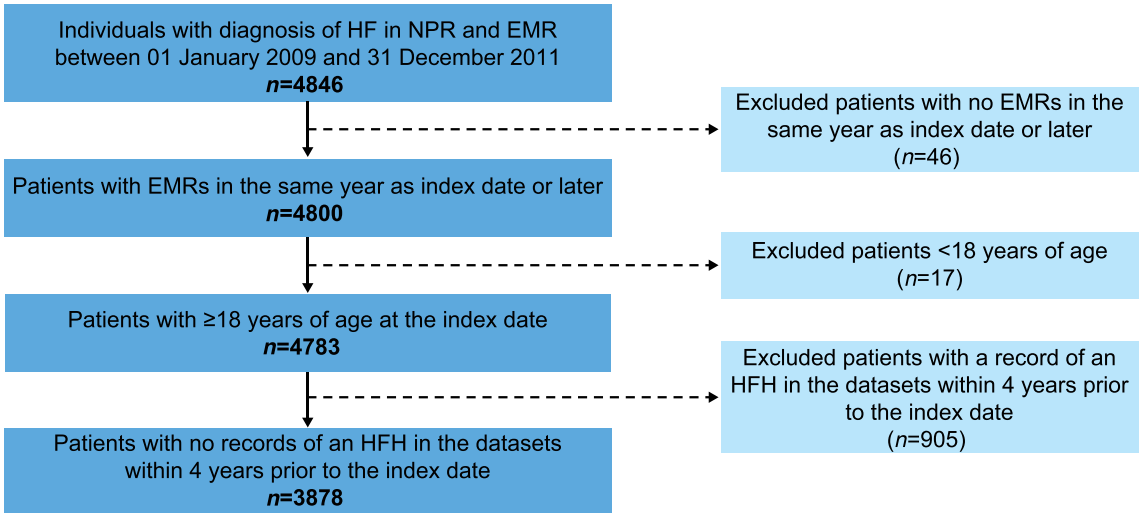
The model variables were demographics, clinical characteristics, common comorbidities, treatments, and laboratory measures. Time to CV mortality from index date and from one, two, three, and four or more recurrent HFHs was calculated by using the non-parametric estimate of the cumulative incidence. Differences in the survival distributions between different time points were calculated using a pairwise log-rank test. Time to immediate next recurrent HFH from the previous recurrent HFH (one to two, two to three, three to four or more) was described using the non-parametric estimate of the cumulative incidence. Competing risks were addressed using the Fine–Gray sub-distribution hazard function in SAS.[17]

Similar analyses were carried out for the subgroups based on HF phenotypes (HFrEF and HFpEF) and among patients with HF having AF, diabetes, or CRI prior to the index date.

Results

A total of 4846 patient records between 01 January 2009 and 31 December 2011 were considered for this study. After applying the selection criteria (*Figure 2*), 3878 patients with HF with an index HFH were included in the analysis, leading to a total of 9691.9 patient-years of follow-up (mean ± SD follow-up per patient: 2.5 ± 1.7 years). For the majority of the study population, the HF phenotype was unknown (n = 2458, 63.4%). Among patients with known HF phenotypes (n = 1420, 36.6%), HFrEF was the most prevalent phenotype (n = 771, 19.9%), followed by HFpEF (n = 487, 12.6%). Of 3878 patients, 2078 patients (54%) did not have

Figure 2 Patient selection process. EMR, electronic medical record; HF, heart failure; HFH, HF hospitalization.



any recurrent HFH, while 1800 (46%) had at least one recurrent HFH.

Baseline characteristic

The included patients with HF were relatively old, had a median (IQR) age of 80.0 (69–86) years at index, and were more likely to be male (55.5%). The most common comorbidities observed at baseline were hypertension (71.7%), ischaemic heart disease (51.7%), and AF (50.6%). More than half of the patients were receiving β-blockers (62.3%), while 45% and 21.6% of patients were receiving angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, respectively, at the index date. The median (IQR) age in the HFrEF/HFpEF cohorts was 72 (63–81)/78 (68–86) years and the proportion of male patients was 71.2%/46.8% (*Table 1*). The most common comorbidities in the HFrEF/HFpEF cohorts were hypertension (61.5%/76%), ischaemic heart disease (54.9%/37.8%), and AF (41.4%/56.7%). The proportions of patients with HF having AF, diabetes, and CRI as comorbidities were 50.6%, 28.7%, and 49.3%, respectively. The most widely received concomitant medication was β-blocker, followed by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in the HFrEF and HFpEF cohorts (63%/47.9%/23.9% and 65.3%/42.9%/23.6%, respectively). Baseline characteristics with regards to number of HF hospitalizations stratified for HF phenotype and comorbidities are found in Table *2*.

Annualized mortality rates

The annualized all-cause mortality rates increased with the first three recurrent HFHs (*Figure 3*).

In all patients with HF, there was an increase in the annualized mortality rates after each recurrent HFH up to three recurrent HFHs. Among patients with one recurrent HFH, the annualized mortality rate for CV mortality was 29 deaths per 100 person-years at risk, which increased to 53 deaths per 100 person-years at risk for patients with three recurrent HFHs. Similarly, the annualized mortality rate for all-cause mortality increased from 32 deaths per 100 person-years at risk for one recurrent HFH to 57 deaths per 100 person-years at risk for three recurrent HFHs. Compared with the group with three recurrent HFHs, the group with four or more recurrent HFHs had a decline in both CV and all-cause mortality.

Similar patterns were observed in patients with HFrEF and among patients with HF having comorbid AF and CRI: the annualized CV mortality rates and all-cause mortality rates increased from one recurrent HFH to three recurrent HFHs, and a decline was observed in patients with four or more recurrent HFHs. In patients with HF and diabetes or with HFpEF, the annualized CV mortality rates increased with each recurrent HFH from one to four or more recurrent HFHs. Recurrent HFHs were associated with a statistically significant impact on CV and all-cause mortality (*Figure 3*). The adjusted hazard ratios (HRs) for CV mortality as well as for all-cause mortality were statistically significant for patients with one, two, three, and four or more recurrent HFHs compared with patients without recurrent HFHs (*Figure 4A*). Compared with patients without recurrent HFHs, the risk of CV mortality and all-cause mortality increased approximately six-fold in patients with four or more recurrent HFHs (HR [95% confidence interval; CI]: 6.26 [5.24–7.48] and 5.59 [4.70–6.64], respectively).

A similar pattern was observed across the HF phenotype subgroups and patients with HF having comorbid AF, diabetes, and CRI, with a lack of statistical significance observed

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Table 1 Baseline characteristics of the overall HF population and across subgroups

Characteristics	Overall HF (*N* = 3878)	HF phenotypes		HF with comorbidities		
		HFrEF (LVEF <45%) *N* = 771	HFpEF (LVEF ≥50%) *N* = 487	AF *N* = 1961	Diabetes *N* = 1114	CRI *N* = 1910
Age, years, median (IQR)	80.0 (69.0–86.0)	72.0 (63.0–81.0)	78.0 (68.0–86.0)	81.0 (74.0–87.0)	78.0 (69.0–84.0)	83.0 (76.0–88.0)
Sex, male, *n* (%)	2151 (55.5)	549 (71.2)	228 (46.8)	1060 (54.1)	674 (60.5)	955 (50.0)
Follow-up time from hospital admission date, years, mean (SD)	2.5 (1.7)	2.7 (1.5)	2.5 (1.4)	2.4 (1.6)	2.5 (1.7)	2.1 (1.7)
BMI category						
BMI, kg/m^2, median (IQR)	26.3 (23.3–30.5)	26.2 (23.5–29.9)	26.6 (23.6–29.9)	26.2 (23.4–30.6)	28.1 (24.9–32.8)	26.5 (23.7–30.9)
Missing/unknown, *n* (%)	1808 (46.6)	232 (30.1)	81 (16.6)	874 (44.6)	399 (35.8)	858 (44.9)
eGFR category, *n* (%)						
eGFR ≥60 mL/min/1.73 m^2	1485 (38.3)	389 (50.5)	230 (47.2)	708 (36.1)	375 (33.7)	0 (0.0)
Missing/unknown	483 (12.5)	100 (13)	33 (6.8)	214 (10.9)	153 (13.7)	—
NT-proBNP, *n* (%)						
≥3000 pg/mL	1359 (35.0)	358 (46.4)	171 (35.1)	746 (38.0)	361 (32.4)	813 (42.6)
Missing/unknown	1281 (33.0)	193 (25.0)	75 (15.4)	581 (29.6)	369 (33.1)	593 (31.0)
Comorbidities, *n* (%)						
Hypertension	2780 (71.7)	474 (61.5)	370 (76)	1508 (76.9)	973 (87.3)	1481 (77.5)
Ischaemic heart disease	2004 (51.7)	423 (54.9)	184 (37.8)	1041 (53.1)	711 (63.8)	1102 (57.7)
AF	1961 (50.6)	319 (41.4)	276 (56.7)	1961 (100.0)	548 (49.2)	1039 (54.4)
Diabetes	1114 (28.7)	219 (28.4)	138 (28.3)	548 (27.9)	1114 (100.0)	586 (30.7)
Anaemia	998 (25.7)	153 (19.8)	136 (27.9)	543 (27.7)	338 (30.3)	640 (33.5)
CRI	377 (9.7)	85 (11.0)	62 (12.7)	201 (10.2)	179 (16.1)	324 (17.0)[a]
Any concomitant medication, *n* (%)						
ACEi	1745 (45.0)	369 (47.9)	209 (42.9)	975 (49.7)	558 (50.1)	866 (45.3)
ARB	838 (21.6)	184 (23.9)	115 (23.6)	473 (24.1)	308 (27.6)	444 (23.2)
BB	2416 (62.3)	486 (63.0)	318 (65.3)	1411 (72.0)	767 (68.9)	1223 (64.0)
MRA	729 (18.8)	206 (26.7)	94 (19.3)	436 (22.2)	242 (21.7)	370 (19.4)
Use of cardiac device[b]	605 (15.6)	202 (26.2)	55 (11.3)	279 (14.2)	177 (15.9)	179 (9.4)
PCI (coronary revascularization)	131 (3.4)	42 (5.4)	11 (2.3)	55 (2.8)	65 (5.8)	48 (2.5)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; BB, β-blocker; BMI, body mass index; CRI, chronic renal impairment; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCI, percutaneous coronary intervention; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a]The HF with CRI subgroup has been defined as per clinical impairment (eGFR <60 mL/min/1.73 m^2).

[b]Cardiac device includes cardiac resynchronization therapy, pacemaker, defibrillator, implantable cardioverter defibrillator.

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Table 2 Baseline characteristics of the overall HF population and across the subgroups according to recurrent HF hospitalization status

Number of recurrent HFHs during follow-up	Overall (*N* = 3878)	HF phenotypes			HF patient with comorbidities		
		HFrEF [LVEF <45%], (*N* = 771)	HFpEF [LVEF≥50%] (*N* = 487)	Unknown (*N* = 2458)	AF (*N* = 1961)	T2DM (*N* = 1114)	CRI (*N* = 1910)
0	2078 (53.6)	331 (42.9)	276 (56.7)	1382 (56.2)	1026 (52.3)	550 (49.4)	1044 (54.7)
1	882 (22.7)	202 (21.2)	105 (21.6)	534 (21.7)	435 (22.2)	246 (22.1)	450 (23.6)
2	397 (10.2)	105 (13.6)	42 (8.6)	233 (9.5)	202 (10.3)	130 (11.7)	187 (9.8)
3	190 (4.9)	38 (4.9)	24 (4.9)	121 (4.9)	106 (5.4)	68 (6.1)	89 (4.6)
4+	331 (8.5)	95 (12.3)	40 (8.2)	188 (7.6)	192 (9.8)	120 (10.7)	140 (7.3)
At least one HFH	1800 (46.4)	440 (57.1)	211 (43.3)	1076 (43.8)	935 (47.7)	564 (50.6)	866 (45.3)

Abbreviations: AF, atrial fibrillation; CRI, chronic renal impairment; HF, heart failure; HFH, HF hospitalization; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; T2DM, type 2 diabetes mellitus.

Figure 3 Annualized mortality rates according to number of recurrent HFHs in the overall population and across subgroups. CRI, chronic renal impairment; CV, cardiovascular; HF, heart failure; HFH, HF hospitalization; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction.

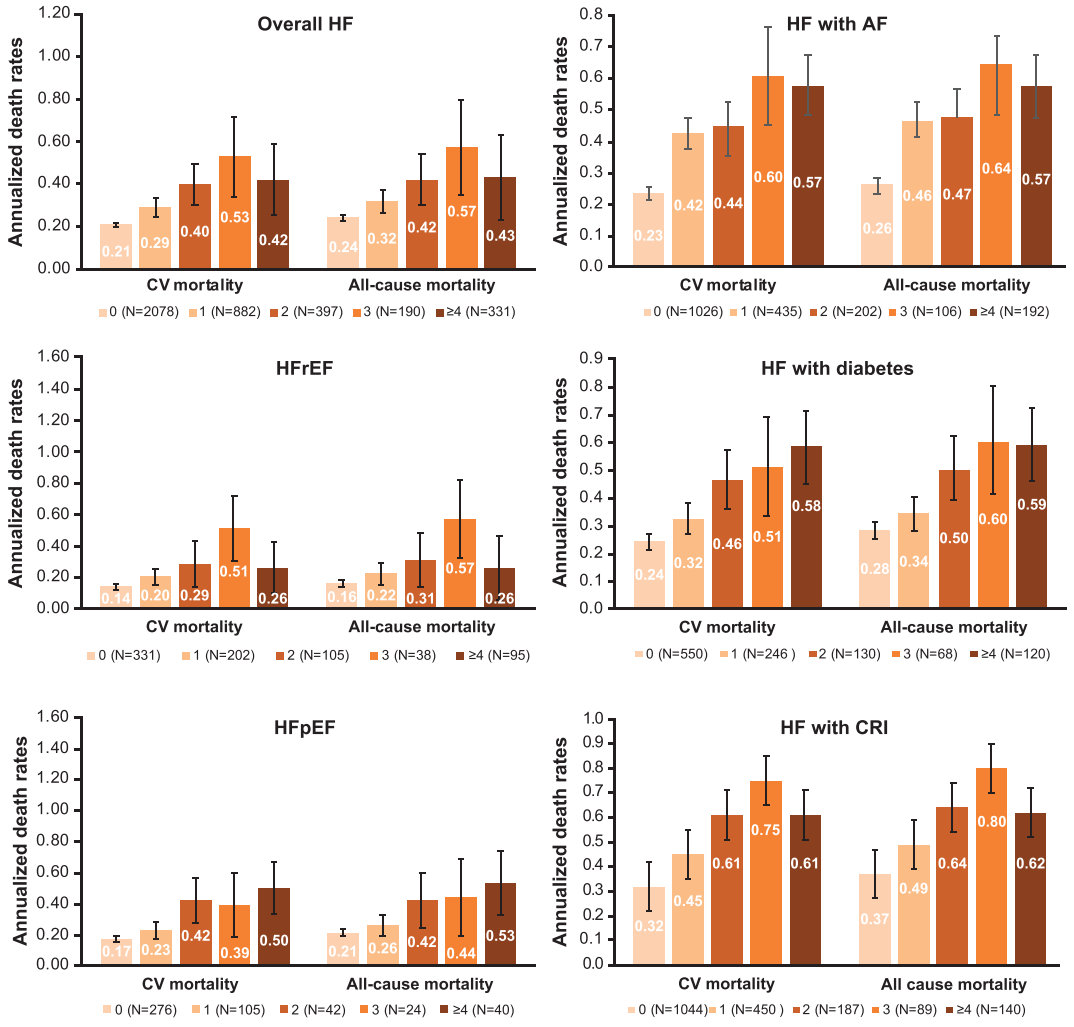

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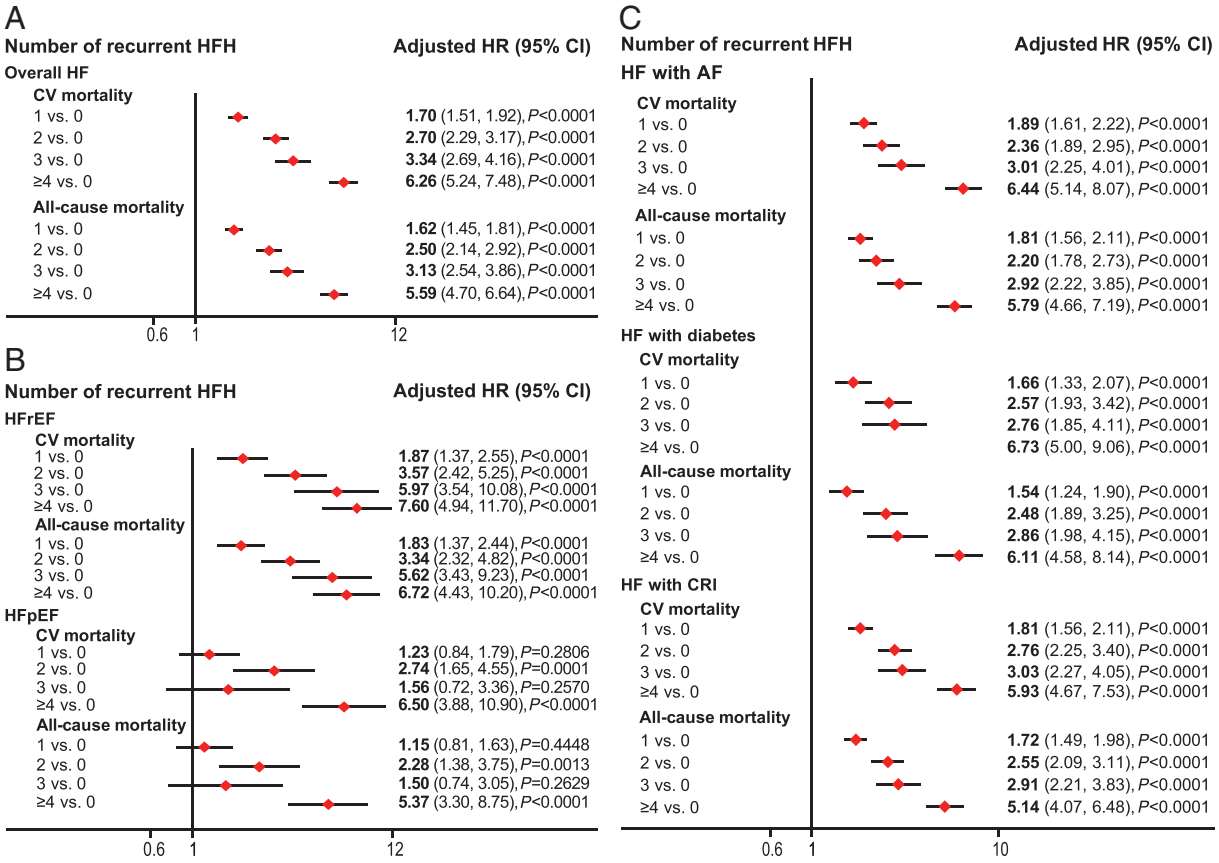
Figure 4 Hazard ratios for mortality in patients with recurrent HFHs vs. none in (A) overall patients with HF, (B) HFrEF and HFpEF subgroups, and (C) Patients with HF having comorbid AF, diabetes, and CRI. AF, atrial fibrillation; CI, confidence interval; CRI, chronic renal impairment; CV, cardiovascular; HF, heart failure; HFH, HF hospitalization; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; HR, hazard ratio.



in the HFpEF subgroup for patients with one or three recurrent HFHs vs. those without any HFH (*Figure 4B,C*).

Time to cardiovascular mortality

Time to CV mortality from index date and from one, two, three, and four or more recurrent HFHs for the overall population is presented in *Figure S1*. The incidence of CV mortality was high after each hospitalization, and the Grey's test (P = 0.8748) showed that the time to CV mortality did not significantly differ by cumulative number of hospitalizations. Similar findings were observed across the HFrEF and HFpEF subgroups and patients with HF having comorbid AF, diabetes, and CRI.

Time to immediate next recurrent heart failure hospitalization

The cumulative incidence of an immediate next recurrent HFH was highest for patients with more recurrent HFHs (*Figure S2*), reflecting decreasing time to subsequent hospitalization. Patients with three recurrent HFHs had the highest risk for an additional hospitalization, whereas patients with one recurrent HFH had the lowest risk for a subsequent hospitalization. A similar trend was observed in the cumulative incidence of one, two, three, and four or more recurrent HFHs from index date for the HF phenotypes and patients with HF having comorbid AF, diabetes, and CRI.

Discussion

This retrospective analysis of 3878 patients with incident HFH highlights that recurrent HFHs are associated with an increased risk of CV mortality and all-cause mortality. Compared with patients with no recurrent HFH, the adjusted risk of CV mortality and all-cause mortality was approximately two-fold higher in patients with one recurrent HFH and six-fold higher in patients with four or more recurrent HFHs. The findings of this study further strengthen the existing

literature[18] evaluating the relationship between mortality and recurrent HFHs.

A significant increase in the annualized mortality rates after each recurrent HFH was noted from one to three recurrent HFH; however, a decline in the annualized mortality rate was observed with four or more recurrent HFHs. This might be attributed to the variability in number of patients with recurrent HFHs, that is, there was a decrease in the number of patients from one to three recurrent HFHs, while the number of patients with four or more recurrent HFHs was higher as this group included all patients who had up to four or more recurrent HFHs. As patients with four or more HFHs were grouped together, the lower annualized mortality rates in this group may be due to inclusion of patients who had survived for a relatively long time while experiencing multiple hospitalizations. Thus, the number of HFHs was a strong predictor of CV mortality and all-cause mortality in real-world data setting, which is in line with previous studies reporting that the risk of death increases progressively with each HFH.[12–15,18]

Further, in this study, the impact of subsequent re-hospitalizations on mortality was also assessed across HF phenotypes and across subgroups with major comorbidities. Overall, the highest hazard for death was found in patients with HFrEF, which is in line with previous literature reporting highest all-cause mortality in patients with HFrEF.[19,20] Similar to the overall population, patients with HFrEF and HFpEF experiencing more recurrent HFHs had a higher risk of death compared with patients with HF without any recurrent HFH. Unlike patients with HFrEF, the cumulative number of recurrent HFHs in patients with the HFpEF phenotype was not consistently associated with CV and all-cause mortality. This was most likely due to the lower number of patients with HFpEF than HFrEF. Furthermore, compared with patients in the HFrEF group, patients in the HFpEF group were older and had more comorbidities, yielding a more complex pattern in this group. Additionally, owing to multiple comorbidities, there are further competing risks of mortality among HFpEF patients, which contribute to the observed pattern of mortality across recurrent HFHs.

Similar to the overall population, patients with HF having comorbid AF, diabetes, and CRI experiencing more recurrent HFHs had a higher risk of death compared with patients without any recurrent HFH, indicating the importance of HFH as a marker of disease progression regardless of comorbidity status.

With repeated hospitalizations, the time to each subsequent re-hospitalization became shorter, highlighting the progressive nature of the disease and emphasizing the importance of risk assessment and management of HF at each HF worsening and subsequent hospitalization. Notably, the time from the final HFH to mortality did not differ significantly between patients who died after one or four or more HFHs, highlighting the period following hospitalization as a period of high risk for patients, requiring close monitoring and potentially optimisation of HF therapies. Overall, this study indicates that each recurrent HFH is associated with an increased risk of death, pointing at the need for prompt intervention in hospitalized patients with HF and for introduction and use of effective treatments that can reduce recurrent hospitalization and thereby help reduce the overall disease burden. To the best of our knowledge, this is the first study to quantify the magnitude of risk between recurrent HFH and mortality among patients with HF and across HF phenotypes in a real-world setting in Sweden. The baseline characteristics of patients in the current study were in line with other studies evaluating the relationship of recurrent HFHs on mortality or re-admissions following incident HFH.[1,12,14,18]

The results of this study should be interpreted in light of some limitations. First, our analysis included only patients with a 4 year clean period, which is reasonable to assume as the study identified actual first HFH. Hospitalization for HF prior to this clean period was not considered. Another limitation concerned missing data for LVEF, where a large proportion of patients had missing values due to the absence of information on an echocardiogram. This is partly due to the extraction method used, where not all patient records presented echocardiograms, and in some cases, the EF value was not reported despite an echocardiogram being available. Further, patients were grouped into HF phenotypes based on the available LVEF values, and the LVEF cut-off values used for grouping of HF phenotypes varied slightly from guideline recommendations. We cannot exclude that missing values may have been unevenly distributed across the LVEF phenotypes and that this could have led to bias in assessment by LVEF phenotype. The data on medication that were presented should be interpreted with caution as this was based on filled prescriptions at the index date and does not take into account uptitration of treatment. This is an area that requires more scrutiny in the future. Lastly, there were inherent limitations associated with retrospective study design and with secondary use of data, including missing data and selection bias, among others.

Conclusion

Mortality increased with increasing number of recurrent HFHs. Moreover, patients with HF with more than one recurrent HFH were more likely to experience another HFH than those without recurrent HFH. Our real-world findings highlight the importance of the prognostic information based on re-hospitalization rates and suggest the need to improve management of HF and the importance to treat underlying diseases, including adequate follow-up strategies to reduce re-hospitalizations among patients with HF, including those with HFpEF and HFrEF with or without AF, diabetes, or CRI.

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Conflict of interest

Krister Lindmark has received lecture grants and consultant fees from Novartis. Kurt Boman, Jan Stålhammar, and Mona Olofsson have received reimbursement from Novartis via IQVIA for performing the study. Kurt Boman and Mona Olofsson have also received lecture grants from Novartis. Raquel Lahoz, Rachel Studer, Clare Proudfoot, Stefano Corda, and Ana Filipa Fonseca are employees of Novartis Pharma AG, Basel, Switzerland. Madlaina Costa-Scharplatz is an employee of Novartis, Sweden. Michael Törnblom and Anna Castelo-Branco of IQVIA, Sweden. Aaron Levine and Eleni Kopsida were part of IQVIA at the time of this study. IQVIA was commissioned to conduct the study (data extraction and analysis) on behalf of Novartis Pharma AG and has ongoing consulting and research relationships with Novartis Pharma AG. Gerhard Wikström has no conflicts of interest to declare; however, his affiliation Uppsala University received research funding from Novartis for conducting this study.

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Supporting information

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

Figure S1. Cumulative incidence of CV mortality from index date and from 1, 2, 3 and ≥4 recurrent HFHs in overall HF population.

Figure S2. Cumulative incidence of immediate next recurrent HFH from 1, 2, and 3 HFHs in overall HF population.

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