Hospital admissions in the last year of life of patients with heart failure

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Abstract

Aim: To explore the frequency, causes, and pattern of hospitalisation for patients with chronic HF in the 12 months preceding death. We also investigated cause of death.

Methods: Patients referred to a secondary care HF clinic were routinely consented for follow-up between 2001 and 2020 and classified into three phenotypes: i) HF with reduced ejection fraction (HFrEF), ii) HF with preserved ejection fraction (HFpEF) with plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) 125-399 $ng.L^{-1}$, and iii) HFpEF with NT-proBNP ≥400 $ng.L^{-1}$. Hospital admissions in the last year of life were classified as: HF, other cardiovascular (CV), or non-cardiovascular (non-CV). The cause of death was systematically adjudicated.

Results: 4925 patients (38% women; median age at death 81 [75-87] years) had 9127 hospitalisations in the last year of life. The median number of hospitalisations was 2 (1-3) and total days spent in hospital was 12 (2-25). 83% of patients had ≥1 hospitalisation but only 20% had ≥1 HF hospitalisation; 24% had ≥1 CV hospitalisation; 70% had ≥1 non-CV hospitalisation. HF hospitalisations were most common in patients with HFrEF, but in all groups, at least two thirds of admissions were for non-CV causes. There were 788 (16%) deaths due to progressive HF, of which 74% occurred in hospital.

Conclusion: For patients with chronic HF in the last year of life, most hospitalisations were for non-CV causes regardless of HF phenotype. Most patients had no HF hospitalisations in their last year of life. Most deaths were from causes other than progressive HF.

Introduction

Hospitalisation for heart failure (HF) is common and associated with an adverse prognosis.[1] The clinical course of chronic HF is uncertain, and a range of illness trajectories has been described;[2] but advancing disease is often depicted as a stepwise decline with increasingly frequent episodes of decompensation and hospitalisation.[3] Clinical guidelines advise early integration of palliative care support with the care provided by a HF multidisciplinary team, in addition to prognostically beneficial interventions.[4] Current models of end-of-life care are more applicable to conditions with a linear course and a defined terminal phase before death; therefore, a needs-based approach to palliative care is required for patients with HF.[5]

Exploring the use of acute hospital services in the final year of life might improve understanding of the needs of patients with chronic HF, but there are few available data, and it is unclear whether there are differences between HF phenotypes. Health service costs for HF are driven by hospital admissions,[6] which occur mostly in the year following diagnosis and the last year of life.[7] Hospital admissions in the last year of life may often be mainly due to comorbidities rather than HF.[8] Further investigation could help to inform priorities for multidisciplinary services treating patients with HF. We explored the frequency, causes, and pattern of hospitalisation in patients with chronic HF in the 12 months preceding death.

Methods

Study population and patient selection

All patients provided written informed consent for database analyses prior to enrolment. The study adhered to the principles outlined in the Declaration of Helsinki and was approved by Hull and East Rising Local Research Ethics Committee (ref: LREC/ 03/02/044). Public and patient involvement was not appropriate for this study.

Patients were enrolled at a single secondary care HF clinic in Kingston upon Hull, UK. The clinic serves a local population of approximately 500,000 people and receives referrals from both primary

and secondary care. Some patients had no prior diagnosis of HF and required initiation of guideline-recommended treatment; others were known to have HF but required optimization of care; some were found not to have HF. Patient data were systematically recorded in the dedicated Hull LifeLab database, which includes demography, co-morbidities, signs and symptoms, blood results (including N-terminal pro B-type natriuretic peptide (NT-proBNP)), electrocardiograms (ECG), and echocardiograms.

This study is a "follow-back" study from the date of death of patients in the Hull LifeLab who consented for medical research. Patients referred to the clinic between January 2001 and August 2020 were enrolled. Patients who died before August 2020 were considered for inclusion. Those who did not have a diagnosis of HF, had a missing echo, or a missing NT-proBNP (for patients with a normal ejection fraction) were excluded.

HF was defined as the presence of signs and symptoms of the syndrome with **either** left ventricular systolic dysfunction (LVSD) mild or worse (HF with reduced ejection fraction [HFrEF]), **or** no LVSD (trivial or none) and raised levels of NT-proBNP (HF with preserved ejection fraction [HFpEF]). NT-proBNP ≥125 $ng.L^{-1}$ is the diagnostic threshold specified in the European Society for Cardiology (ESC) guidelines.[9] However, the National Institute for Clinical Excellence (NICE) guidance recommends a cut-off of NT-proBNP ≥400 $ng.L^{-1}$.[10] Therefore, analyses were performed according to three phenotypes: (i) HFrEF; (ii) $HFpEF_{125}$: HFpEF with NT-proBNP 125-399 $ng.L^{-1}$; (iii) $HFpEF_{400}$: HFpEF with NT-proBNP ≥400 $ng.L^{-1}$. The flow of patients through the study is shown in *Supplementary Figure 1*.

Study outcomes

The main outcome was hospital admission in the last year of life. The cause of each hospital admission was documented and classified as: HF, other cardiovascular (CV), or non-cardiovascular (non-CV). Hospital admissions were coded using ICD-10 criteria; the primary cause for admission was used in this analysis. The last 12 months of life were reviewed for each patient, irrespective of their clinic enrolment date. All hospital admissions were evaluated, including those that led to death. The cause of death for each patient was adjudicated using a systematic process of death adjudication based on information available from electronic records and used in previous analyses

from the Hull LifeLab.[11] (*Supplementary material*: process of death adjudication); whether the death was an in-patient or out-patient death was also recorded. All deaths in the emergency department were considered sudden deaths unless investigations or correspondence suggested differently. For out-patient deaths, if a patient had recently been seen in clinic or discharged from hospital without warning of a poor prognosis, end-of-life planning or significant abnormality on investigations and then died without other healthcare contact, the mode of death was defined as sudden.

Statistical analyses

Continuous variables are presented as median (quartile [Q] 1 and 3) and categorical data are summarised as percentages. Analysis of variance (ANOVA) was used to compare the means of more than two continuous variables and chi-squared tests were used to compare categorical variables. Analyses were performed using StatView version 5. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Between 2001 and 2020, 10,059 patients were assessed, 8001 of whom consented to participate and were deemed to have heart failure. During a median [25th and 75th centile] follow-up of 4.36 [1.86 – 8.36] years, 4,925 patients died: 3027 (62%) had HFrEF; 514 (10%) had $HFpEF_{125}$; and 1384 (28%) had $HFpEF_{400}$. The baseline characteristics are shown, divided by phenotype, in *Table 1*. The median age at death was 81 (75-87) years; age at death was slightly greater for patients with HFpEF. Patients with HFpEF were more likely to be women. Ischaemic heart disease was common, especially for patients with HFrEF. Diabetes mellitus and chronic obstructive pulmonary disease (COPD) were similarly common across phenotypes. Patients with $HFpEF_{400}$ had the highest prevalence of atrial fibrillation. Median NT-proBNP for $HFpEF_{400}$ was only slightly lower than for HFrEF.

Causes and patterns of hospitalisation

In the last year of life, 83% of patients had at least one hospitalisation (any cause). However, most patients (80%) had no HF hospitalisations in their last year of life; conversely, most patients (70%) had at least one non-CV admission. In the $HFpEF_{125}$ group, 94% of patients had no HF admissions in their last year of life. The combinations of hospitalisations are shown in *Table 2*.

The median number of hospital admissions per patient was 2 (1-3) for each phenotype (*Supplementary Figure 2*). The median number of days spent in hospital during the last year of life was 12 (2-25), which was similar across phenotypes (*Figure 1*). Among those patients who did have a hospitalisation for HF, the median number of days for an individual HF hospitalisation was 10 (4-19) (*Figure 1*). The percentage of patients admitted to hospital increased in the 3 months prior to death, particularly for non-CV causes, for all phenotypes (*Figure 2*).

There were 9127 hospital admissions in the last year of life. The majority of hospital admissions were due to non-CV causes, and HF admissions were a minority for all phenotypes (*Figure 2*). The HFrEF group had the highest proportion of HF admissions; but in each group, at least two thirds of the admissions were for non-CV causes. Among hospitalisations for other CV causes, the most common cause was acute myocardial infarction (*Figure 3*). Among hospitalisations for non-CV reasons, the most common cause was infection, followed by cancer (*Figure 3*). Among patients hospitalised for infection, 46% were due to pneumonia, 15% were due to unspecified acute lower respiratory tract infection, 14% were due to urinary tract infection, 13% were due to other septicaemia, 6% were due to cellulitis, and 6% were due to other causes. The distributions of the sub-categories of causes of hospitalisation were similar across phenotypes (*Supplementary Table 1).*

Among hospitalisations during 2020, 13/208 (6%) hospitalisations were for COVID-19, 69% of which were in patients with HFrEF. It is possible that some diagnoses for “pneumonia, unspecified” or “unspecified acute lower respiratory tract infection” (which accounted for 20% of hospitalisations in

2020) could have been due to COVID-19, particularly during the window in which testing for COVID-19 was not routinely performed.

Causes and place of death

In the total cohort, 16% of deaths were due to progressive HF (*Figure 4*). Death from progressive HF was most common in patients with HFrEF, and least common in patients with $HFpEF_{125}$. The median age at death from progressive HF was 81 (75-86) years [HFrEF: 80 (75-86); $HFpEF_{125}$: 85.5 (81-90); $HFpEF_{400}$: 84 (79-88)]. The pattern of hospitalisations was different in the year before death from progressive HF: of those who died of HF, 96% had at least one hospitalisation, 61% had at least one HF hospitalisation, 29% had at least one other CV hospitalisation, and 67% had at least one non-CV hospitalisation.

52% of deaths occurred during a hospital admission and 41% were out of hospital. Place of death was unknown in 7%. For deaths due to progressive HF, 74% of deaths occurred in hospital; for deaths due to non-CV causes, 65% of deaths occurred in hospital; and for CV deaths other than for HF, 33% occurred in hospital. A large proportion of deaths recorded as "sudden" occurred out of hospital. The median age at the time of sudden death was 79 years. For deaths due to other CV causes, most were classified as sudden. For non-CV deaths, the predominant cause was infection, followed by cancer. Among patients who died from infection, 65% were respiratory infection, 20% were other sepsis, 5% were urinary tract infection, 10% were other causes of infection. The distributions for sub-categories of causes of death within other CV and non-CV were similar across phenotypes (*Supplementary Table 2).*

Discussion

Main findings

We have found that about three quarters of hospitalisations among patients with chronic HF during their last year of life are for non-CV reasons, regardless of HF phenotype. HF hospitalisations were

more common among patients with HFrEF than in the other phenotypes, but in each group, at least two thirds of admissions were for non-CV causes. Most patients in all phenotypes had no HF hospitalisations in their last year of life. Most deaths were from causes other than progressive HF, which accounted for only 19% of deaths among patients with HFrEF and even fewer among patients with HFpEF. Most deaths from progressive HF occurred in hospital and most sudden deaths occurred out of hospital, as has been previously reported from clinical trials.[12]

Causes and patterns of hospitalisation

In our cohort, 83% of patients had at least one hospitalisation in the last year of life, with a median of two and an increasing rate in the 3 months before death for all phenotypes.

Our results are consistent with findings from previous studies. In the Rochester Epidemiological Project cohort study (2003 to 2011), among 698 patients from Minnesota, United States (US),[13] 81.5% of patients were hospitalised at least once in their last year of life, with a median of 2 hospitalisations, and hospitalisations increased in the 2 months before death. Among 32,157 patients with HF from Danish nationwide registries,[14] 83% of patients were hospitalised at least once in their last year of life, with a median of 2 hospitalisations and a high rate in the 2 months before death. Non-CV causes also dominated hospitalisations in the Danish cohort. Neither measurements of left ventricular ejection fraction nor natriuretic peptides were available; therefore, HF phenotypes were not known. The absence of phenotype stratification was identified as the main limitation of the study. We have expanded on the findings of Madelaire et al. by showing the similarities and differences between phenotypes of HF in our analyses. In our study, we have analysed highly granular data from a bespoke local database of patients referred to a local HF clinic, but otherwise unselected.

The median length of stay for HF hospitalisation was 10 days. The UK National Heart Failure Audit reports that median length of stay for a HF hospitalisation (all years of life) is 9 days on a cardiology ward, or 6 days on a general medical ward.[15] Our findings suggest a similar length of stay for a HF hospitalisation in the last year of life. The duration of the admission alone offers few clues that a patient might be in their last year of life.

Infection was the most common cause of non-CV hospitalisation. In patients with HFrEF, median survival following hospitalisation for infection is similar to that of survival following hospitalisation for decompensated HF.[16] Prevention of non-CV hospitalisation should, therefore, be taken as seriously as the prevention of HF hospitalisation. However, poor control of heart failure and pulmonary congestion may predispose to, and increase mortality from, respiratory infections.[17] Respiratory infection and decompensated heart failure commonly co-exist. Perhaps clinical trials of heart failure should include hospitalisations or deaths due to respiratory infection amongst their endpoints. Further efforts to increase implementation of pneumococcal, influenza and now COVID-19 vaccination might have an important effect on the prognosis of HF.[18]

Most discussions about the care of patients with HF are focused on the treatment of the syndrome itself with emphasis placed on the need to maximise medical and device therapy for HF. However, most hospital admissions in the last year of life are for non-CV causes, suggesting that the needs of patients with HF extend far beyond the optimisation of treatment for HF. Our findings point to a need for care that is multidisciplinary, patient-centred and co-ordinated between the hospital and community. Integrated palliative care, with its cornerstones of holistic assessment, medication reviews, symptom management, and person-centred (including family) care planning, improves quality of life and symptoms in patients with advanced HF,[19] as well as reducing rehospitalisation. [20] The co-speciality palliative care program for HF patients in Cardiff, Wales (UK) reduced all cause hospitalisations as well as HF hospitalisations,[21] suggesting that such a strategy could play a vital role in the management of patients with HF and comorbidities. A similar approach can be seen in geriatric cardiology, with its focus on comprehensive geriatric assessment, medication review, and optimisation of patient goals.[22] Perhaps the optimal multidisciplinary care of people with advanced HF should include cardiology, geriatrics, and palliative care, underpinned by primary care.

Causes and place of death

In our cohort, only 16% of deaths were from progressive HF. Our findings are similar to other studies suggesting a minority of patients with HF die from progressive HF. Among 55,595 patients with HF who died between 2000 and 2017 in a UK population cohort study, 7.2% of patients had HF recorded as the primary cause of death (42.4% had HF listed as a contributory cause).[23] Among 399 patients with HF (data from 23 general practices) who died between 2001 and 2006 in the

Netherlands, 23% of patients died from progressive HF.[24] Non-CV mortality accounts for 45% of deaths in our cohort (of which infection was the predominant cause): this aligns with findings from the UK biobank cohort study, where approximately half of deaths in patients with HF were due to non-CV causes.[25]

The median age at death from progressive HF was identical to the median age at death from all causes (81 years). This perhaps reflects how good our treatments for HF have become. Comprehensive guideline-recommended therapy has a profound prognostic benefit in patients with HFrEF.[26] Survival has improved substantially amongst younger patients with HFrEF over the last 15 years, accompanied by a marked increase in non-cardiac mortality.[27] In a well-run clinical service, HF might be becoming something that patients die with, rather than something that patients die from.

Just over half of the deaths in our study occurred during a hospital admission, including the great majority (74%) of deaths from progressive HF. Many patients with chronic disease would prefer to die at home,[28] but most die in hospital; and palliative care and hospice care is underused in advanced HF in the UK and worldwide.[29] Advance care planning improves quality of life and satisfaction with end-of-life care for patients with HF;[30] the challenge is how to overcome implementation barriers to provide this effectively and equitably. We hope that our work will prompt further research into the relations between patients' individual preferences and hospitalisation toward the end of like. Addressing the challenges in implementing advance care planning and ensuring equitable access to palliative and hospice care would be valuable in improving end-of-life care for patients with chronic HF.

Limitations

Kingston upon Hull is a major seaport and although the population is predominantly White, European ancestry may be more diverse than many other British cities; however, our results might be less applicable to more diverse populations. Patients referred to our clinic may not represent the entire spectrum of patients with chronic HF, although we are the only clinic locally. For example, patients who were very frail might not have been referred to the service and some patients may have died between referral for assessment and their clinic visit.

We classified HFpEF as signs and symptoms of HF with an NT-proBNP ≥125 ng.L^{-1}; however, ESC guidance recommends the use of a second criterion (diastolic dysfunction or structural heart disease) in clinical practice. Biomarker-based categorisation for research purposes may overclassify HF but avoids variability in clinical diagnoses and enables inclusion of patients where detailed echocardiographic information is unavailable. Because we have excluded patients with a missing Nt-proBNP for patients with a normal ejection fraction, it is possible we might have omitted some patients with heart failure from the analysis.

Co-morbidities were recorded at the patient's initial visit; it is possible that additional co-morbidities developed between recruitment and death. Measurements of ejection fraction were missing for some patients, but visual assessment of systolic function was available for almost all. The use of ICD-10 codes is susceptible to misclassification; however, this error is likely to be evenly distributed.

We were unable to determine whether out-patient deaths occurred at home or in a hospice. We are here presenting in-patient events during the last year of life and do not have information regarding out-patient visits or primary care visits. We cannot speculate on the effect of possible interventions made during hospitalisations. We do not have information on patients' preferred place of death, which may have an impact on the pattern of hospitalisation toward the end of life.

We recorded cause of death through a systematic process of death adjudication but were unable to view death certification for patients who died outside hospital; cause of death is thus susceptible to misjudgment. The high proportion of deaths classified as "sudden" reflects the nature of an adjudication process outside the confines of a clinical trial. Where a patient died outside hospital, with no evidence of severe infection or terminal illness, and without indication of poor prognosis from most recent health care contact, the primary mode of death was classed as sudden.

Conclusion

In the last year of life, among patients with chronic HF, most hospitalisations were for non-CV causes regardless of HF phenotype. Most patients in all phenotypes had no HF hospitalisations in their last year of life. Most deaths were from causes other than progressive HF. The predominance of non-CV causes of hospitalization and mortality points towards a need for co-specialty care for people with advanced HF, including cardiology, geriatrics, and palliative care, underpinned by primary care. Most HF deaths occurred in hospital, suggesting there may be a role for better advance planning in HF care.

CRediT author statement:

AAIA: Conceptualisation, Formal Analysis, Investigation, Writing – Original Draft; **NAS**: Investigation; **JJC**: Data Curation; **OIB**: Writing – Review and Editing; **SK**: Software, Data Curation; **JGFC**: Writing – Review and Editing; **MJJ**: Writing – Review and Editing; **ALC**: Conceptualisation, Methodology, Writing – Review and Editing, Supervision.

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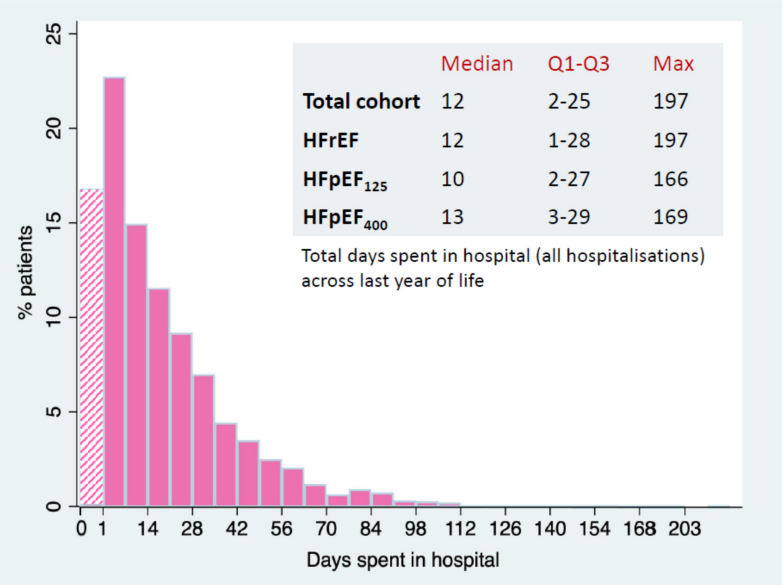
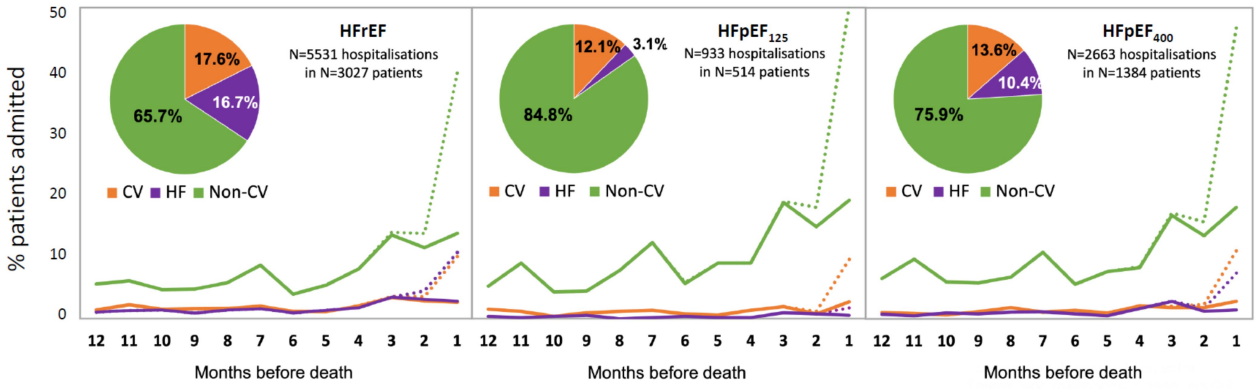


Figure 1

Figure 1. **Days spent in hospital in the last year of life (histogram shows total cohort). The dashed pink bar represents the patients who had 0 admissions in their last year of life**. NT-proBNP: N-terminal pro B-type natriuretic peptide; HF: heart failure; HFrEF: HF with reduced ejection fraction; $HFpEF_{125}$: HF with preserved ejection fraction and NT-proBNP 125-399 $ng.L^{-1}$; $HFpEF_{400}$: HF with preserved ejection fraction and NT-proBNP ≥400 $ng.L^{-1}$.



Bold lines: hospitalisations that resulted in discharge.
Dotted lines: hospitalisations where the patient died during admission.
Inset: Pie charts show the causes of admissions in the last year of life for each phenotype.

Figure 2

Figure 2. Percentage of patients admitted each month prior to death (Bold lines: hospitalisations that ended in discharge; dotted lines: hospitalisations where the patient died during admission). Inset: pie charts showing the proportion of total admissions by cause. Abbreviations as previously defined. CV: other cardiovascular; non-CV: non-cardiovascular.

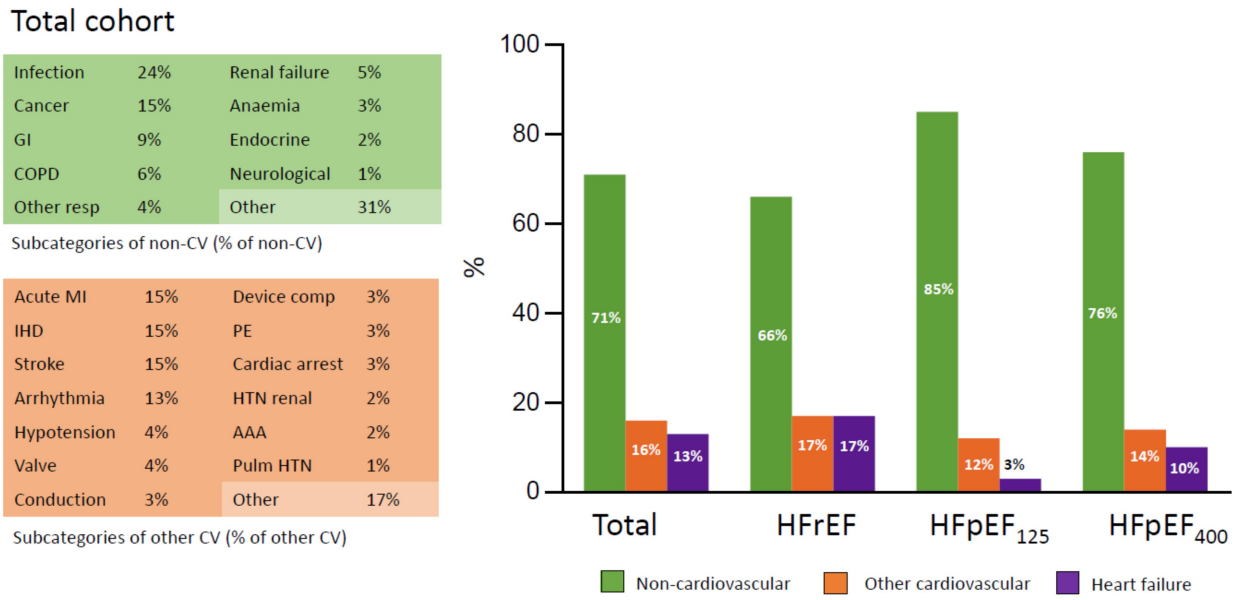


Figure 3

Figure 3. Causes of hospital admissions. Abbreviations as previously defined; NK: not known; MI: myocardial infarction; IHD: ischaemic heart disease; Device comp: complications of cardiac and vascular prosthetic devices and implants and grafts; Pulm HTN: pulmonary hypertension; PE: pulmonary embolism; AAA: abdominal aortic aneurysm and dissection; Other resp: other respiratory causes; COPD: chronic obstructive pulmonary disease; GI: gastrointestinal.

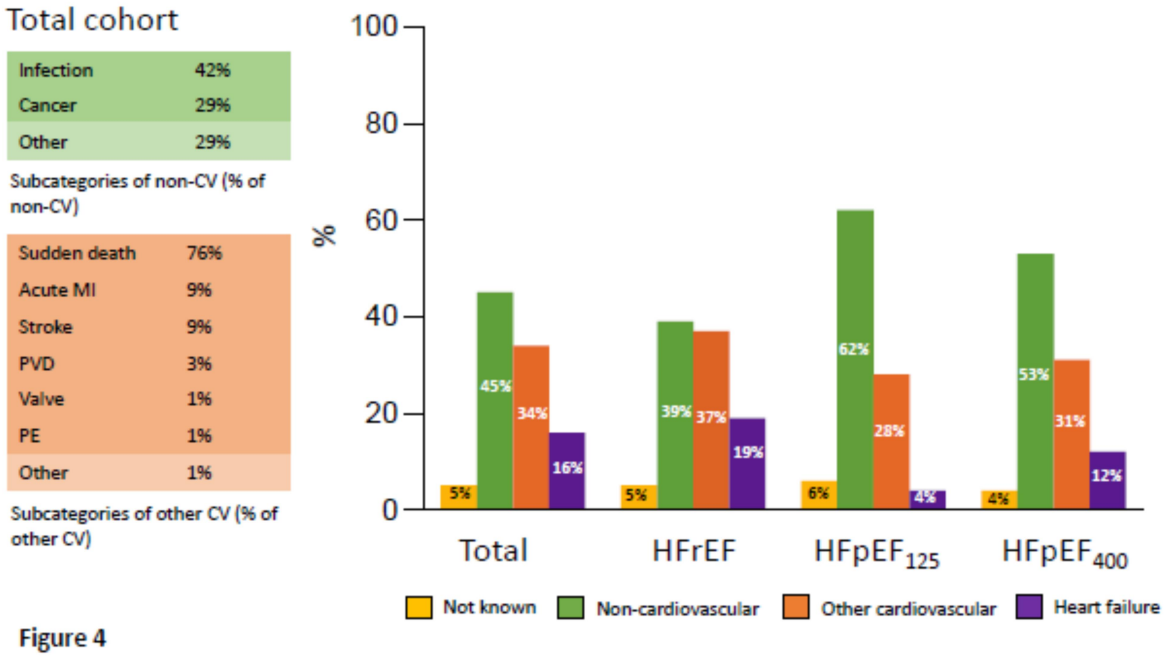


Figure 4. Causes of death. Abbreviations as previously defined; PVD: peripheral vascular disease.

	HFrEF	$HFpEF_{125}$ (125-399 $ng.L^{-1}$)	$HFpEF_{400}$ (≥400 $ng.L^{-1}$)	P value
N	3027	514	1384	
Age at baseline (y)	75 (68-81)	76 (70-81)	79 (74–84)	**<0.0001**
Age at death (y)	80 (73-85)	84 (77-88)	84 (78-88)	**<0.0001**
Female (%)	30	54	51	**<0.0001**
Follow up (months)	42 (16-81)	79.5 (39-127)	38 (16-73)	**<0.0001**
Pre-existing HF (%)	42	48	43	0.11
NT-proBNP ($ng.L^{-1}$)	1998 (841-4290)	228 (164-298)	1419 (778-2696)	**n/a**
BMI (kg/m^2)	27.0 (23.9-30.9)	28.6 (25.3-32.3)	27.7 (24.1-32.0)	**<0.0001**
NYHA I (%)	13	36	19	**<0.0001**
II	47	45	46	0.64
III	36	17	32	**<0.0001**
IV	3	1	3	0.10
Oedema (%)	34	22	42	**<0.0001**
Systolic BP (mmHg)	130 (115-148)	154 (138-170)	145 (129-166)	**<0.0001**
Diastolic BP (mmHg)	75 (66-85)	81 (72-90)	77 (67-88)	**<0.0001**
IHD (%)	68	31	29	**<0.0001**
Hypertension (%)	21	38	34	**<0.0001**
DM (%)	25	23	25	0.47
COPD (%)	11	11	12	0.67
HR (bpm)	74 (63-87)	68 (60-79)	74 (63-86)	**<0.0001**
AF (%)	28	3	47	**<0.0001**
QRS width (msec)	112 (96-142)	90 (82-100)	94 (84-108)	**<0.0001**
Any diuretic (%)	82	50	74	**<0.0001**
Loop diuretic (%)	81	42	69	**<0.0001**
Thiazide (%)	4	9	9	**<0.0001**
Creatinine (umol/L)	110 (89-140)	89 (77-105)	102 (82-134)	**<0.0001**

Table 1. Baseline characteristics. NT-proBNP: N-terminal pro B-type natriuretic peptide; HF: heart failure; HFrEF: HF with reduced ejection fraction; $HFpEF_{125}$: HF with preserved ejection fraction and NT-proBNP 125-399 $ng.L^{-1}$; $HFpEF_{400}$: HF with preserved ejection fraction and NT-proBNP ≥400 $ng.L^{-1}$; BMI: body mass index; NYHA: New York Heart Association; BP: blood pressure; IHD: ischaemic heart disease; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation.

	HFrEF	$HFpEF_{125}$ (125-399 ng/L)	$HFpEF_{400}$ (≥400 ng/L)	Total
≥1 admission	81	85	87	83
≥1 HF admission	24	6	17	20
≥1 CV admission	25	19	23	24
≥1 non-CV admission	65	79	75	70
HF + CV admission	3	1	1	2
HF + CV + non-CV	3	1	2	3
Non-CV alone	39	61	51	44
CV alone	7	5	7	7
HF alone	6	1	3	5
No HF admissions	76	94	83	80

Table 2. Combinations of admissions in the last year of life (% of patients in each group). Abbreviations as previously defined; CV: other cardiovascular; non-CV: non-cardiovascular.