Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: Recurrent hospitalizations and mortality

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Abstract

Aims: Hospitalizations for heart failure (HF) are common and associated with significant morbidity, mortality and costs. However, precipitating factors leading to HF hospitalization and their importance with respect to subsequent outcomes are not well understood.

Methods and Results: We prospectively collected the symptoms and signs present on admission and investigator-identified factors thought to have contributed to the first adjudicated HF hospitalization in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity program (CHARM), stratified by ejection fraction (EF). Potential precipitants were collected using a specifically designed case report form and then categorized as cardiovascular (CV), non-cardiovascular (non-CV) and unknown. We examined the associations between these factors and subsequent re-hospitalization and mortality rates.

Of 1,668 patients who experienced HF hospitalization, 1,152 had reduced EF (HFrEF; EF ≤40%) and 516 had preserved EF (HFpEF). Overall, 54% had CV, 32% non-CV, and 14% unknown factors thought to have precipitated HF, with similar proportions in HFrEF and HFpEF. The most common precipitants were arrhythmia (15%), other non-CV reasons (11%), and respiratory infection (10%). Subsequent CV re-admission rates were highest in those whose initial HF hospitalization was precipitated by CV factors. However, mortality rates were similar among patients with any of the three categories of precipitating factors. Results were similar in HFrEF and HFpEF.

Conclusions: Among chronic HF patients hospitalized for decompensation, the investigator-reported precipitating factor was not associated with the subsequent mortality rate but was associated with the type of re-admission: re-admissions for CV reasons were more likely when the index precipitant was CV.

Keywords: Heart failure, hospitalization, precipitating factors, ejection fraction, prognosis

Introduction

Heart failure (HF) is a leading reason for hospitalization in Western populations over the age of 65 and is associated with significant cost, morbidity, and subsequent mortality.[1] Precipitating factors leading to HF hospitalization have been identified in prior, mainly retrospective, studies and include arrhythmias, myocardial ischemia, infections, worsening renal function, uncontrolled hypertension and non-compliance with medications or diet.[2-5] However, the relationship between these factors and long-term morbidity and mortality, including recurrent hospitalizations, is not well understood. Similarly, the clinical signs and symptoms on admission in patients hospitalized for HF according to these precipitants are poorly described.

A better understanding of the effect of precipitating factors of HF hospitalizations is important for several reasons. First, the identification of modifiable factors leading to HF hospitalizations may help inform strategies to mitigate recurrent admission. Second, the association of these factors with recurrent hospitalizations may inform the design of future clinical trials, for instance in the selection of high-risk patient populations. Traditionally, only the first hospitalization for HF has been analyzed as an endpoint in clinical trial reports and observational studies. However, this approach does not consider the burden of recurrent events to patients, the healthcare system and payers. Analyses of recurrent hospitalizations among patients with HF are, thus, gaining increasing interest and have the potential to improve the efficiency and reduce cost of future clinical trials.[6, 7]

In this study we examined prospectively collected, investigator-identified, reasons thought to have contributed to the first hospitalization for HF in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity program (CHARM) and the association between these contributors to HF hospitalization and subsequent recurrent admissions, as well as the rate and cause of subsequent death. Since literature on the precipitants of HF hospitalization in individuals with HFrEF and HFpEFis sparse, we also examined these variables stratified by ejection fraction.

Methods

Patient population

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) program randomized 7,599 patients with New York Heart Association (NYHA) class II-IV HF to candesartan or placebo in addition to standard HF therapy. The design and main results of this trial have been previously reported.[8] Briefly, the program consisted of three concurrent trials (March 1999 – March 2003): CHARM-Alternative included HF patients with an EF≤40% who were intolerant to ACE-inhibitors, CHARM-Added included HF patients with an EF≤40% who were being treated with an ACE-inhibitor, and CHARM-Preserved included HF patients with an EF>40% most of whom were not treated with an ACE-inhibitor. The CHARM trials were approved by institutional review boards for each study site and all enrolled patients provided informed consent for study participation. Patients were excluded from this analysis if there was no primary precipitating factor reported for the first adjudicated HF hospitalization (n=7) or if the ejection fraction was not documented (n=1). For the purpose of this analysis, we focused on patients with a first adjudicated HF hospitalization (n=1,668).

Outcomes

The primary outcome of the overall program was all-cause mortality and for the component trials it was the composite of cardiovascular (CV) death or hospital admission for HF. First hospitalizations for HF were adjudicated, while subsequent HF hospitalizations were investigator reported, as were non-HF hospitalizations. The median follow up for the overall program was 37.7 months. Due to uncertain discharge dates, 2 patients were excluded from the annual incidence rates for HF, CV, non-CV and all-cause readmissions. For patients with missing discharge dates for the first HF hospitalization (n=141), discharge dates were imputed assuming a 5 day length of stay based on the median hospital length of stay in this trial.

Patients who ended study while hospitalized (n=7) did not contribute to the calculation of annual incidence rates for HF, CV, non-CV and all-cause readmissions.

Identification of precipitating factors

When reporting HF hospitalizations after randomization, investigators were asked to report possible precipitating and aggravating factors and to assign a primary reason for the HF hospitalization to one of several predefined reasons: non-compliance with cardiac medications, inappropriate decrease of anti-failure therapy, excessive salt intake/dietary non-compliance, cardiac arrhythmias, acute myocardial ischemia/myocardial infarction, anemia, febrile illness, other high-output state, excessive alcohol intake, concomitant drug use within previous 48 hours (calcium channel blockers, beta-blockers, antiarrhythmic drugs other than amiodarone, non-steroidal anti-inflammatory drugs), any other non-cardiac precipitating or associated illness or factor, precipitating valvular disease, any other precipitating or aggravating factor(s). Only the primary precipitant identified by investigators was utilized in this analysis. Of those first adjudicated HF hospitalization which were assigned to either “any other non-cardiac precipitating or associated illness or factor” (n=282) or to “any other precipitating or aggravating factor(s)” (n=543) free text descriptions of the primary reason were individually reviewed by a physician and used to reclassify the precipitating factors into specific CV, non-CV and unknown factors.

Statistical analyses

Baseline characteristics for patients according to precipitant factor were compared using chi-squared or Fisher’s exact test, as appropriate, for categorical and ANOVA for continuous variables. In additional analyses, investigator-identified clinical characteristics (HF signs and symptoms) and precipitating factors for HF hospitalizations, stratified by those with reduced

(≤40%) and preserved (>40%) EF, were analyzed using chi-squared or Fisher's exact test, as appropriate.

To assess possible associations between precipitating factors leading to the first HF hospitalization on subsequent hospitalizations and mortality we compared incident all-cause re-admission rates by the 3 precipitating factor groups, stratified by EF group, using chi-squared or Fisher's exact test, as appropriate. To assess the cumulative incidence rates of subsequent HF hospitalization, the crude number of HF hospitalizations per 100 patient-years of follow up after discharge from the initial hospitalization for HF was calculated by dividing the total number HF hospitalizations by the total follow up time of all patients in each group. The resulting incidence rates, 95% confidence intervals (CI) and p-value were based on the Poisson distribution.[9]

All tests were two-sided, and a p-value of <0.05 was considered statistically significant. All analyses were conducted using STATA SE, version 12.1 (College Station, TX).

Results

Baseline characteristics, according to type of precipitant

Overall, 1,668 patients enrolled in the CHARM program who were hospitalized for HF based on adjudication criteria, were included in this analysis. Their baseline characteristics, according to type of precipitant, are presented in **Table 1**. Investigators identified a probable CV precipitant in 54% (n=895) of first HF hospitalizations, a non-CV precipitant in 32% (n=538) and could not identify any precipitant (precipitant unknown) in 14% (n=235). Baseline characteristics were broadly similar across the 3 groups. Of all patients hospitalized for HF, 1,152 (69%) had HFrEF at baseline and 516 (31%) had HFpEF.

Investigator-identified precipitating factors leading to HF hospitalization

Among the CV precipitants, the five most commonly reported were: 1) an arrhythmia (HFrEF 15% vs. HFpEF 16% of all precipitants; 27% vs. 31% of CV precipitants), 2) non-

compliance/inappropriate decrease in HF therapy (11% vs. 7.6%), 3) dietary indiscretion/excessive oral or IV fluids (8.3% vs. 8.5%), 4) myocardial ischemia/angina (7.4 vs. 8.7%) and 5) worsening HF/disease progression (9.0% vs. 3.3%; p<0.001) (**Table 2**). Although uncommon, uncontrolled hypertension was more often identified as a precipitant in patients with HFpEF (in 3.1% of admissions) compared with HFrEF (1.2%; p=0.007).

Among the non-CV reasons for admission, respiratory infection was by far the most common individual precipitant (10% vs. 11% of all precipitants; 32% vs. 33% of non-CV precipitants), with worsening renal function (3.1% vs. 4.8%), other infection (1.9% vs. 2.5%) and anemia (1.4% vs. 3.1%; p=0.018) the other most commonly identified precipitants. Although less common, a diabetes-related reason was more commonly reported as a precipitating factor in HFpEF (0.2% vs. 1.4%; p=0.005) and physical exertion more frequently in HFrEF (1.1% vs. 0%; p=0.013). There was also a large category of “other” non-CV precipitants (11% vs.10%).

The proportion of patients with an unknown reason for HF hospitalization was similar in the two HF groups (14% vs 13%).

Investigator–identified clinical evidence of HF, according to type of precipitant

Investigator-identified symptoms and signs at the time of the first hospitalization for HF were similar among the precipitating factor groups, both in HFrEF and HFpEF, with the exception of pulmonary edema which was more commonly reported in patients with HFpEF when the precipitating factor was thought to be CV (39.7% CV, 29.4% non-CV, 24.6% unknown precipitant; p=0.016) (**Figure 1**). The proportions of patients receiving intravenous diuretics (92% HFrEF, 91% HFpEF, p=0.496) and intravenous vasodilators (16% both groups, p=0.935) were similar, but patients with HFrEF were more likely to have received intravenous inotropic agents than patients with HFpEF (21% vs. 13%, p<0.001).

Precipitating causes and subsequent mortality

CV precipitants of hospital admission did not selectively identify patients more likely to die from a CV cause (annual incidence rate: 39 (95% CI: 35, 44) per 100 patient-years for HFrEF, 29 (95% CI: 24, 35) for HFpEF) and a non-CV precipitant of hospitalization (annual incidence rate: 39 (95% CI: 34, 45) per 100 patient-years for HFrEF, 32 (95% CI: 26, 40) for HFpEF) didn't make a subsequent non-CV death more likely than a CV death (**Table 3**). Patients with an unknown precipitant were at slightly lower risk of death (both all-cause and CV) and this was also true for both types of HF (HFrEF and HFpEF).

Precipitating causes and subsequent re-hospitalization

The picture regarding re-admission was different than that for mortality. The overall re-admission rate was similar in patients with HFrEF (annual incidence rate: 179 (95% CI: 172, 186) per 100 patient-years) and HFpEF (173 (95% CI: 164, 184) per 100 patient-years) and highest among those with a CV precipitant of their index hospitalization for both HFrEF (187 (95% CI: 177, 197) per 100 patient-years) and HFpEF (181 (95% CI: 168, 196) per 100 patient-years)). Compared to patients with a non-CV precipitant of their index admission, those with a CV precipitant were relatively *more* likely to have a subsequent HF (and any CV) admission and relatively *less* likely to have a subsequent non-CV admission. This pattern was apparent in both HFrEF and HFpEF (**Table 3**).

Discussion

Our main findings were: 1) CV reasons were thought to be the precipitant for HF admissions in more than half of cases and non-CV reasons in one third, with the remainder of admissions having no prospectively identified precipitant. 2) Among the CV and non-CV precipitants, there was no single very common and only a few common causes. 3) The precipitants that were identified were largely similar for HFrEF and HFpEF, although there were a few differences. 4)

The type of precipitant (CV or non-CV) was not associated with the subsequent cause of death but was associated with re-admission type.

Investigator-identified precipitating factors leading to HF hospitalization

A number of precipitating factors believed to be associated with HF hospitalizations have previously been reported but these have almost exclusively been collected retrospectively. One exception was the RESOLVD pilot study, in which, among 768 patients with HFrEF, the most common primary causes leading to HF hospitalizations were thought to be non-adherence to salt restriction (15%), other non-cardiac causes (15%), and inappropriate reductions in HF therapy (9%).[2] Within the "other" and "other non-cardiac" precipitating factor categories, investigators noted respiratory infections, use of a beta-blocker (the study drug metoprolol) and excessive fluid intake as most common causes. While the proportion of non-cardiac causes and inappropriate reductions in HF therapy were similar in our study, non-adherence in salt restriction was reported less frequently in CHARM. This difference could be due to either patient education efforts regarding salt restriction in the CHARM cohort or alternative primary precipitants (e.g. arrhythmia) which were more commonly identified in CHARM. Although both CHARM and RESOLVD were multi-site international trials, geographic variability in salt intake may contribute to this difference. In the OPTIMIZE-HF registry of 48,612 patients hospitalized for HF (mean EF 39%) in the USA, 61.3% patients had one or more pre-specified precipitating factors identified, with pneumonia/respiratory process (15.3%), myocardial ischemia (14.7%), and an arrhythmia (13.5%) being most frequent.[4] The OPTIMIZE-HF report did not differentiate between patients with HFrEF and HFpEF. A more recent international AHF registry (GREAT) of 15,828 patients hospitalized for HF in Europe and Asia identified one precipitating factor in 49% of patients, multiple factors in 6% and no known precipitants in 44%. Of those with a single precipitating factor, the most common reported precipitants were acute coronary syndrome (52%), atrial fibrillation (16%) and infection (14%).[10] The higher rates of precipitant infection and

myocardial ischemia in the AHF registries as compared with CHARM may be related to the difference between an AHF registry and a chronic HF clinical trial dataset. Since our analysis is based on adjudicated HF hospitalizations, myocardial infarctions complicated by AHF would have been adjudicated as myocardial infarction rather than HF hospitalization based on the pre-defined event definitions and respiratory infections without significant concomitant volume overload may not have qualified as HF admission.

Recently, registry data from the US Get With The Guidelines-HF database, a prospective observational study of patients hospitalized for HF with documented EF, reported that the most common factors thought to precipitate HF hospitalizations included pneumonia/respiratory problem (28.2%), arrhythmia (21.7%), medication non-compliance (15.8%), worsening renal failure (14.7%), and uncontrolled hypertension (14.5%).[5] Some of these factors varied by EF group (EF <40%, 40-49%, ≥50%) and were independently associated with hospital length of stay and inpatient mortality. Long term outcomes were not reported. This registry also identified higher rates of respiratory infection, arrhythmias, medication non-compliance, worsening renal function and hypertension than ours. Although the leading precipitating factors were similar to ours, the proportions in these groups were higher than in CHARM. Registry cohorts may differ from clinical trial cohorts due to exclusion criteria which may select a patient population with generally better renal function, blood pressure control and medication compliance, for instance.

Our findings extend those from prior reports. We identified a broad spectrum of CV and non-CV reasons thought to have precipitated the index HF hospitalization, with only small differences between patients with HFrEF and HFpEF. Several of these factors, both CV and non-CV related, are potentially modifiable and could be addressed through close outpatient monitoring, patient education and engagement. Based on our data, these strategies should include improved management of co-morbidities (atrial fibrillation, hypertension, COPD, diabetes), and strategies to improve adherence to evidence based HF therapies. Comprehensive in-hospital

and post-discharge programs that focus on these aspects have demonstrated reductions in the rate of subsequent readmissions for HF, although no single intervention alone may be sufficient to address this complex issue.[11] In addition, the number of respiratory infections leading to HF exacerbations, which was one of the leading non-CV reasons in our study, could potentially be reduced through vaccination programs for influenza and pneumococcal infections.[12, 13] Given the chronicity and trajectory of HF, some hospitalizations for HF will be unavoidable. However, novel strategies for outpatient management through home visits or clinics for IV diuretics have the potential to further reduce hospitalizations for HF even in the setting of worsening HF.[14]

Investigator–identified clinical evidence of HF

There were no important differences with respect to symptoms and clinical signs between the precipitant factor groups with the exception that pulmonary edema was more commonly reported in HFpEF patients with a CV precipitant. This may be an indicator of a higher degree of volume overload in this subgroup of patients.

Recurrent hospitalizations and mortality

Prior data on the long term outcomes based on precipitants leading to an initial hospitalization for HF are sparse. We found that patients with a CV precipitant of their index HF hospitalization had the highest annual incidence rate of CV readmissions adding information to the previous report about subsequent risk following a hospitalization for HF.[15] This insight may be relevant both clinically and for research purposes. If a specific CV cause, such as uncontrolled hypertension, can be addressed, subsequent hospitalization could potentially be prevented. Few other studies have investigated the relationship between potential HF hospitalization precipitating factors and risk of re-admission and mortality. In the OPTIMIZE-HF registry (n=5,791, mean EF 37%), myocardial ischemia and worsening renal function were associated with a higher risk of 60- to 90-day all-cause mortality whereas uncontrolled hypertension as a

precipitating factor was associated with lower rates of post-discharge death or readmission. In the GREAT registry (n=15,828, mean EF 38%) 90-day all-cause mortality was highest in patients in whom AHF was thought to have been precipitated by acute coronary syndrome or infection (HR 1.69, 95% CI 1.44-1.97 and HR 1.51, 95% CI 1.18-1.92).[10] Analyses were not stratified by EF. In CHARM, rates of CV and all-cause mortality were similar among the three precipitating factor categories in patients with HFrEF and HFpEF but were overall higher in those with HFrEF, in concordance with prior analyses stratified by EF.[7]

Our findings suggest that precipitating factors leading to the initial HF hospitalization may be associated with the rate of recurrent admissions rather than subsequent mortality. This finding could be due to a number of reasons but it may be that CV precipitants are more persistent or likely to recur (e.g. atrial fibrillation, myocardial ischemia) than non-CV causes, e.g. respiratory infection. It is also possible that based on the precipitant, certain conditions may be more or less likely to be amendable to outpatient management in patients with known HF so that patients re-presenting with CV problems, e.g. arrhythmias, are more likely to be admitted, whereas non-CV problems, e.g. certain infections, may be managed in the outpatient setting.

Limitations

These data should be interpreted in the context of their limitations. First, only the initial HF hospitalization was adjudicated by an independent committee, all subsequent hospitalizations were investigator reported. It is possible that some of these events would not meet the criteria used by an endpoint committee. In addition, subsequent hospitalizations may have been influenced by the type of precipitant (CV vs. non-CV) whereas mortality was adjudicated in all cases. However, the same data collection forms were used for all events and should have led to consistent data collection for subsequent events. Removal of additional events would have led to an underestimation of the number of recurrent hospitalizations in this cohort. Second, this analysis focused on the primary factor leading to the first adjudicated hospitalization for HF,

additional secondary factors were not analyzed in this manuscript and precipitating factors leading to subsequent HF hospitalizations were also not analyzed with respect to CV, non-CV and unknown factors. It is possible that both during the initial and subsequent hospitalizations multiple factors contributed to patients' worsening HF. In addition, patient-identified precipitating factors for HF hospitalizations may differ from investigator-identified reasons for admission but these were not collected in this trial.[16, 17] Third, EFs were reported by the study sites and not verified by an independent core imaging laboratory. Fourth, the cut off values for HFrEF (EF≤40%) and HFpEF (EF>40%) in this analysis were based on the study design of CHARM. Due to the small size of the group with an EF ≥40% we were unable to further divide this group into the recently proposed HFmrEF (EF 40-50%) and HFpEF (>50%) classifications.[18] Future investigations in larger cohorts should describe precipitating factors based on the new classifications. Finally, although our analyses were stratified by EF, we did not adjust for potential additional confounders in this hypothesis-generating report.

Conclusions

Among chronic HF patients hospitalized for decompensation, the investigator-reported precipitating factor was not associated with the subsequent mortality rate (or cause of death) but was associated with the type of re-admission: re-admissions for CV reasons were more likely when the index precipitant was CV. These findings may have implications for developing strategies to prevent readmissions and inform the design of future trials.

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Conflict of Interest

Dr. Platz reports grants from NIH/NHLBI, personal fees from Sanofi and Parexel, outside the submitted work. Dr. Jhund and Dr. Claggett have nothing to disclose. Dr. Pfeffer reports grants from AstraZeneca, during the conduct of the study; personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, DalCor, Gilead, GlaxoSmithKline, Janssen, Lilly USA, The Medicines Company, and Merck, grants and personal fees from Novartis, personal fees from Novo Nordisk, and Relypsa, grants and personal fees from Sanofi, personal fees from Thrasos, Genzyme, and Teva, outside the submitted work. In addition, Dr. Pfeffer has a patent and The Brigham and Women's Hospital has patents for the use of inhibitors of the RAS in selected survivors of MI with Novartis. Dr. Pfeffer is a co-inventor. His share of the licensing agreement is irrevocably transferred to charity. Dr. Swedberg reports grants from AstraZeneca, during the conduct of the study; personal fees from Novartis, grants and personal fees from Servier, outside the submitted work. Dr. Granger reports grants and personal fees from Astra Zeneca, during the conduct of the study. Dr. Yusuf has nothing to disclose. Dr. Solomon reports grants and personal fees from Astra Zeneca, during the conduct of the study; grants and personal fees from Novartis, grants and personal fees from Amgen, grants and personal fees from Bayer, grants and personal fees from GlaxoSmithKline, grants and personal fees from Alnylam, grants from Gilead, Ionis, and Boston Scientific, personal fees from Merck, and Bristol-Myers Squibb, outside the submitted work. Dr. McMurray has nothing to disclose.

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Table 1. Baseline characteristics (n=1,668)

	CV reasons (n=895)	Non-CV reasons (n=538)	Unknown reason (n=235)	P
Demographics				
Age (years)	68 (11)	68 (11)	67 (11)	0.199
Men	614 (69)	360 (67)	168 (72)	0.449
Ethnicity				**<0.001**
European	786 (88)	488 (91)	193 (82)	**0.003**
Black	55 (6.2)	22 (4.1)	9 (3.8)	0.163
Other	54 (6.0)	28 (5.2)	33 (14)	**<0.001**
Clinical characteristics				
NYHA class				0.559
II	290 (32)	160 (30)	81 (35)	
III	557 (62)	348 (65)	138 (59)	
IV	48 (5.4)	30 (5.6)	16 (6.8)	
Mean LVEF (%)	35 (15)	37 (15)	35 (14)	0.281
Heart rate (bpm)	75 (14)	74 (12)	76 (14)	0.403
Systolic BP (mmHg)	129 (20)	130 (20)	127 (20)	0.269
Diastolic BP (mmHg)	75 (11)	74 (11)	75 (11)	0.277
BMI (kg/m2)	28 (6)	29 (6)	27 (6)	**0.021**
Clinical evidence of HF				
Dyspnea when walking on level ground	634 (71)	401 (75)	178 (76)	0.167
Orthopnea	246 (28)	158 (29)	62 (26)	0.631
PND	168 (19)	101 (19)	41 (18)	0.889
JVD	126 (14)	69 (13)	34 (15)	0.751
Crackles (any)	202 (23)	127 (24)	59 (25)	0.696
S3	143 (16)	100 (19)	34 (15)	0.279
Peripheral edema	306 (34)	202 (38)	77 (33)	0.316
Medical history				
Hospital admission for HF	749 (84)	449 (84)	204 (87)	0.463
Myocardial infarction	481 (54)	286 (53)	129 (55)	0.906
Stroke	98 (11)	59 (11)	23 (10)	0.866
Diabetes mellitus	352 (39)	239 (44)	94 (40)	0.155
Hypertension	530 (59)	318 (59)	124 (53)	0.181
Atrial fibrillation	309 (35)	191 (36)	81 (35)	0.924
Pacemaker/ICD	133 (15)	82 (15)	44 (19)	0.338
ECG: Bundle branch block	279 (31)	175 (33)	74 (32)	0.698
Current smoker	108 (12)	72 (13)	40 (17)	0.134
Cancer	72 (8.0)	46 (8.6)	10 (4.3)	0.099
HF etiology				
Ischemic	538 (60)	329 (61)	151 (64)	0.510
Idiopathic dilated cardiomyopathy	157 (18)	87 (16)	43 (18)	0.715
Hypertensive	113 (13)	70 (13)	23 (9.8)	0.426
Valvular	33 (3.7)	18 (3.4)	5 (2.1)	0.549
Diabetes	3 (0.3)	0	4 (1.7)	**0.007**

Alcohol related	8 (0.9)	3 (0.6)	0	0.369
Atrial fibrillation	24 (2.7)	12 (2.2)	4 (1.7)	0.715
Other	19 (2.1)	19 (3.5)	5 (2.1)	0.268
Medical treatment				
ACE inhibitor	414 (46)	258 (48)	112 (48)	0.804
Betablocker	409 (46)	236 (44)	108 (46)	0.768
Diuretic	839 (94)	504 (94)	226 (96)	0.337
Spironolactone	186 (21)	120 (22)	54 (23)	0.679
Digoxin	491 (55)	287 (54)	117 (50)	0.376
Calcium channel blocker	169 (19)	120 (22)	34 (15)	**0.035**
Long acting nitrates	381 (43)	204 (38)	88 (38)	0.137
Oral anticoagulants	353 (39)	204 (38)	84 (36)	0.559
Aspirin	439 (49)	279 (52)	120 (51)	0.567

Legend:

Categorical variables are presented as counts (percentages), continuous variables as means (SD), unless otherwise specified.

NYHA: New York Heart Association class, LVEF: Left ventricular ejection fraction, BP: Blood pressure, BMI: Body mass index, HF: Heart failure, PND: Postural nocturnal dyspnea, JVD: Jugular venous distension, ICD: Implanted cardiac defibrillator, ECG: Electrocardiogram, ACE: Angiotensin converting enzyme.

Table 2. Physician-identified primary reason for worsening heart failure leading to first heart failure hospitalization

n (%)	All patients (n=1,668)	EF≤40% (n=1,152)	EF>40% (n=516)	P*
Cardiovascular reasons	895 (54)	628 (55)	267 (52)	0.294
Arrhythmia	252 (15)	169 (15)	83 (16)	0.456
Non-compliance/inappropriate decrease in HF therapy	160 (9.6)	121 (11)	39 (7.6)	0.059
Dietary indiscretion/excessive oral fluid intake/IV fluids	139 (8.3)	95 (8.3)	44 (8.5)	0.848
Myocardial ischemia/angina	130 (7.8)	85 (7.4)	45 (8.7)	0.344
Worsening HF/disease progression	121 (7.3)	104 (9.0)	17 (3.3)	**<0.001**
Valvular disease	42 (2.5)	25 (2)	17 (3.3)	0.175
Uncontrolled hypertension	30 (1.8)	14 (1.2)	16 (3.1)	**0.007**
Other CV reasons	21 (1.3)	15 (1.3)	6 (1.2)	0.814
Non-cardiovascular reasons	538 (32)	358 (31)	180 (35)	0.124
Respiratory infection	174 (10)	115 (10)	59 (11)	0.370
Worsening renal function/renal failure	61 (3.7)	36 (3.1)	25 (4.8)	0.084
Other infection	35 (2.1)	22 (1.9)	13 (2.5)	0.422
Anemia	32 (1.9)	16 (1.4)	16 (3.1)	**0.018**
COPD/asthma	16 (1.0)	13 (1.1)	3 (0.6)	0.417
Exertion/increased exercise	13 (0.8)	13 (1.1)	0	**0.013**
Depression/anxiety/emotional stress	10 (0.6)	7 (0.6)	3 (0.6)	0.949
Diabetes/diabetes medication related reasons	9 (0.5)	2 (0.2)	7 (1.4)	**0.005**
NSAID use	9 (0.5)	7 (0.6)	2 (0.4)	0.729
Other non-CV reasons	179 (11)	127 (11)	52 (10)	0.564
Unknown reason	235 (14)	166 (14)	69 (13)	0.573

Legend:

*Chi squared or Fisher's exact test comparing two EF groups, as appropriate.

EF: Ejection fraction, HF: Heart failure, CV: Cardiovascular, COPD: Chronic obstructive pulmonary disease, NSAID: Non-steroidal anti-inflammatory drugs

Table 3. Events following first heart failure hospitalization

	First hospitalization for HF EF≤40%					First hospitalization for HF EF>40%				
	All HFrEF patients (n=1,152)	**Group A: CV reasons for HF (n=628)**	**Group B: Non-CV reasons for HF (n=358)**	**Group C: Unknown reasons (n=166)**	**P**	**All HFpEF patients (n=516)**	**Group A: CV reasons for HF (n=267)**	**Group B: Non-CV reasons for HF (n=180)**	**Group C: Unknown reasons (n=69)**	**P**
Readmissions following 1st HF hospitalization										
Annual incidence rate of all-cause readmissions (per 100 pt-yrs; 95% CI)*	179 (172, 186)	187 (177, 197)	174 (162, 187)	162 (146, 180)	**0.032**	173 (164, 184)	181 (168, 196)	165 (149, 182)	166 (143, 193)	0.273
Annual incidence rate of HF readmissions (per 100 pt-yrs; 95% CI)*	79 (75, 84)	86 (80, 93)	70 (62, 78)	74 (64, 87)	**0.005**	59 (54, 65)	61 (53, 69)	52 (44, 62)	71 (57, 90)	0.103
Annual incidence rate of CV readmissions (per 100 pt-yrs; 95% CI)*	127 (121, 133)	138 (130, 147)	111 (102, 121)	120 (107, 136)	**<0.001**	108 (101, 116)	118 (108, 130)	94 (82, 107)	106 (88, 128)	**0.020**
Annual incidence rate of non-CV readmissions (per 100 pt-yrs; 95% CI)*	52 (48, 56)	49 (44, 54)	63 (56, 71)	42 (34, 51)	**<0.001**	65 (59, 71)	63 (55, 72)	71 (61, 82)	60 (47, 78)	0.433
Mortality following 1st HF hospitalization										
Annual incidence of all-cause death (per 100 pt-yrs; 95% CI)**	39 (36, 42)	39 (35, 44)	39 (34, 45)	36 (29, 45)	0.913	28 (25, 33)	29 (24, 35)	32 (26, 40)	19 (13, 30)	0.136
Annual incidence of CV death (per 100 pt-yrs; 95% CI)**	35 (32, 38)	35 (31, 40)	34 (29, 40)	33 (27, 42)	0.963	22 (19, 26)	22 (17, 27)	25 (20, 33)	17 (11, 28)	0.360

Legend:

* P value: Global chi squared or Fisher's exact test, as appropriate, comparing groups A, B and C stratified by EF group.

** P value: Log rank test comparing groups A, B and C stratified by EF group.

HF: Heart failure, CV: Cardiovascular, pt: Patient, yrs: Years, CI: Confidence interval

Figure 1. Investigator-identified clinical evidence of worsening heart failure at time of first HF hospitalization

Panel A: Patients with HFrEF (EF≤40%) (n=1,152)

Panel B: Patients with HFpEF (EF>40%) (n=516)

Legend:

* P<0.05 for comparison between precipitating factor groups

HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, CV: Cardiovascular, JVP: Jugular venous pressure, CXR: Chest x-ray

Figure 2. Annual incidence rates of events following first heart failure hospitalization

Panel A: HFrEF (EF≤40%) (n=1,152)

Panel B: HFpEF (EF>40%) (n=516)

Legend:

HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, CV: Cardiovascular