Readmission and Death in Patients Admitted with New-onset versus Worsening of Chronic Heart Failure: Insights from a Nationwide Cohort

Running title: *New-onset versus worsening heart failure and outcomes*

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Abstract

Aim: To examine the rates of all-cause mortality and heart failure (HF) readmission in patients hospitalized with decompensated HF according to HF duration – new-onset HF and worsening of chronic HF.

Methods and Results: In this nationwide observational cohort study, 17,176 patients were included at first hospital admission for HF in the period 2013-2015 using data from Danish nationwide registries. In total, 8,860 (51.6%) patients were admitted with new-onset HF and 8,316 (48.4%) with worsening of chronic HF. Patients with worsening of chronic HF were characterized by a greater comorbidity burden compared with patients with new-onset HF. The rates of outcomes were examined by multivariable Cox regression models, adjusted for age, sex, and comorbidity. Worsening of chronic HF was associated with a higher rate of the composite endpoint of all-cause mortality or HF readmission (hazard ratio [HR] 1.37 [95% CI, 1.31-1.43]), all-cause mortality (HR 1.22 [95% CI, 1.16-1.28]), and HF readmission (HR 1.81 [95% CI, 1.69-1.93]) compared with new-onset HF. There was an interaction between atrial fibrillation (AF), HF duration, and outcome: In worsening of chronic HF, the rate of the composite endpoint was higher in patients with AF compared with those without (HR 1.12 [95% CI, 1.07-1.19]), whereas in new-onset HF, the rate of the composite endpoint was lower in patients with AF compared with those without (HR 0.91 [95% CI, 0.85-0.96]) (P-value for interaction < 0.001).

Conclusions: Among patients hospitalized with decompensated HF, worsening of chronic HF was associated with poorer outcomes compared with new-onset HF.

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide and carries a prognosis similar to many cancers.[1-3] Advances in the treatment of chronic HF during the past three decades have led to significant improvements in prognosis and life expectancy.[4] However, despite substantial efforts to improve outcomes of patients hospitalized with decompensated HF, numerous clinical randomized trials evaluating the efficacy of novel pharmacological therapies and management strategies have failed to show benefit.[5-14] Hospitalization with decompensated HF represents a clinically heterogeneous syndrome, and the paucity of novel therapies may partly be attributed to the marked heterogeneity in patient characteristics and etiology. Thus, there is a need to better characterize patients hospitalized with HF and their subsequent outcomes.

Patients presenting with new-onset HF and worsening of chronic HF represent two distinct groups among those hospitalized with HF. However, there has been little investigation of how these groups compare with respect to their characteristics and subsequent outcomes.[15-17] Indeed it is not clear what outcomes might be expected *a priori*. For example, patients with worsening of chronic HF might carry a better prognosis than patients with new-onset HF because they have survived an initial vulnerable phase after diagnosis.[18, 19] Alternatively, longer duration of HF disease, with extended exposure to neurohormonal activation and greater maladaptive cardiac remodeling, may be associated with higher mortality than that faced after the initial HF diagnosis.[19-21] Understanding the characteristics and outcomes of these two distinct subpopulations may have important implications for clinical risk stratification and future trial design. Consequently, we examined the clinical characteristics and rates of all-cause mortality and readmissions in an unselected, nationwide, and contemporary cohort of patients hospitalized with HF, stratifying as to whether the patients presented with new-onset or worsening of chronic HF.

Methods

Data sources

All citizens in Denmark are assigned a unique and personal identification number, which allows accurate linkage of nationwide administrative registries at an individual level. For this study, data from several nationwide administrative registries were obtained. The Danish National Patient Registry holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD) and all surgical procedures according to the NOMESCO Classification of Surgical Procedures.[22] The Danish National Prescription Registry comprises detailed information on dispensing date, strength, and quantity on all claimed drug prescriptions in Denmark.[23] The Danish Civil Registration System contains data on birth date, sex, and vital status (i.e. whether a person is alive and resident in Denmark, disappeared [persons whose residence is unknown to Danish authorities], emigrated, or dead, along with the date of these events).[24] The Danish Registry of Causes of Death holds information about the date, place, and manner of death, as well as the underlying cause.[25]

Study population

The study population comprised all Danish citizens with a hospital admission for HF, defined as a primary discharge diagnosis of HF, with an overnight hospital stay between January 1, 2013 and December 31, 2015. Each patient was included the time of the first hospital admission for HF between January 1, 2013 and December 31, 2015 and each patient was included only once in the study.

HF duration

The duration of HF was determined using in-hospital and out-patient diagnosis codes up to 10 years prior to admission. Based on the duration of HF, patients were assigned to the following groups: New-onset HF, defined as either no history of HF or a history of HF of 30 days or less, and worsening of chronic HF, defined as a history of HF of more than 30 days. The latter group was further classified into 2 categories according to the duration of HF, 31 days to 3 years and more than 3 years. These cutoffs were chosen based on the distribution of HF duration within the study population and a clinical judgment.

Covariates

Comorbidity was obtained using in-hospital and out-patient diagnosis codes up to 10 years prior to admission (eTable 1 for ICD-10 codes). Patients with diabetes were identified using claimed drug prescriptions as described previously.[26, 27] Pharmacotherapy at baseline was defined as claimed prescriptions within 180 days prior to admission (eTable 2 for ATC codes).

Outcomes

The primary outcome was a composite of all-cause mortality or HF readmission. Secondary outcomes were all-cause mortality, HF readmission, and readmission for any cause. A readmission was defined as a hospital admission with an overnight hospital stay. Patients were followed from the date of admission until occurrence of the outcome of interest, death, emigration, or end of the study (December 31, 2016), whichever came first.

Statistics

Descriptive data were reported as frequencies with percentages, medians with 25^{th}-75^{th} percentiles. Differences in baseline characteristics between patients admitted with new-onset and worsening of

chronic HF and between subgroups of worsening of chronic HF were tested with the Chi-squared test for categorical variables and the Mann-Whitney test for continuous variables. Survival curves of the composite endpoint of HF readmission or all-cause mortality and all-cause mortality according to groups were estimated with the Kaplan Meier method, and differences between groups were assessed using the log-rank test. The absolute risk of a HF readmission and readmission for any cause according to groups was estimated using the Aalen-Johansen estimator and differences between groups were assessed using Gray's test.[28] Multivariable Cox regression was used to estimate outcome-specific hazard ratios (HR) with 95% confidence intervals (CI). The models were adjusted for age (categorical variable: <65, 65-74, 75-81, >82 years), sex, history of ischemic heart disease, atrial fibrillation (AF), stroke, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and cancer. Patients admitted with new-onset HF served as the reference group in all analyses. Only the first event was considered in patients experiencing multiple events. Prespecified subgroup analyses of outcomes were performed for the following variables: Age, sex, ischemic heart disease, stroke, AF, and diabetes. In a supplementary analysis, multivariable logistic regression, adjusted for the same covariates as in the Cox regression models, were used to estimate the odds of in-hospital mortality. Further, multivariable Cox regression were used to examine the rates of the primary endpoint among patients discharged alive. In this analysis, patients were followed from the date of discharge. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, North Carolina, USA). The level of statistical significance was set at 5%.

Ethics

The Danish Data Protection Agency approved this study (No. 2007-58-0015; internal reference: *GEH-2014-014,* I-Suite no. 02732). In Denmark, registry-based studies, in which individuals cannot be identified, do not require ethical approval.

Results

From January 1, 2013 to December 31, 2015, 17,176 patients had at least one hospital admission for HF in Denmark. Of these, 8,860 (51.6%) were admitted with new-onset HF and 8,316 (48.4%) with worsening of chronic HF. The median age of the study population was 76 years (25^{th}-75^{th} percentile, 67-84) and 62.9% were men. The baseline characteristics of the patients in the groups of interest are summarized in Table 1. Patients admitted with worsening of chronic HF were more often men, had a greater prevalence of cardiovascular and non-cardiovascular comorbidities, and a higher utilization of medication compared with those admitted with new-onset HF.

Primary outcome

The risk of the primary composite endpoint of HF readmission or all-cause mortality according to duration of HF is shown in Figure 1a. Worsening of chronic HF was associated with a higher rate of the composite endpoint compared with new-onset HF (unadjusted HR 1.54 [95% CI, 1.48-1.60]; adjusted HR 1.37 [95% CI, 1.31-1.43]). There was a graded relationship between HF duration and the rate of the primary endpoint, with longer duration associated with a higher rate (Figure 2).

Secondary outcomes

Figure 1b-d displays the risks of all-cause mortality, HF readmission, and readmission for any cause, respectively, according to HF duration. Worsening of chronic HF was associated with a higher rate of all-cause mortality (unadjusted HR 1.37 [95% CI, 1.31-1.44]; adjusted HR 1.22 [95% CI, 1.16-

1.28]), HF readmission (unadjusted HR 2.13 [95% CI, 2.01-2.27]; adjusted HR 1.81 [95% CI, 1.69-1.93]), and readmission for any cause (unadjusted HR 1.34 [95% CI, 1.29-1.39]; adjusted HR 1.18 [95% CI, 1.13-1.22]) compared with new-onset HF. There was a graded relationship between HF duration and the rate of death, HF readmission, and readmission for any cause, as for the primary outcome (Figure 2). The number of all HF readmissions during follow-up according to HF duration is displayed in eTable 3. Among patients who had a HF readmission during follow-up, the median time to first HF readmission was 128 days (25^{th}-75^{th} percentile, 42-340 days) in the new-onset HF group and 123 days (25^{th}-75^{th} percentile, 43-345 days) in the worsening of chronic HF group.

Subgroup analysis

The results of the prespecified subgroup analyses for the primary composite outcome are displayed in Figure 3 and for the secondary outcomes in eTable 4. In all subgroups, worsening of chronic HF was associated with a higher rate of the composite endpoint of all-cause mortality or HF readmission compared with new-onset HF. There was an interaction between AF, HF duration, and and the primary outcome: In worsening of chronic HF, the rate of the composite endpoint was higher in patients with AF compared with those without (unadjusted HR 1.02 [95% CI, 0.96-1.08]; adjusted HR 1.12 [95% CI, 1.07-1.19]), whereas in new-onset HF, the rate of the composite endpoint was lower in patients with AF compared with those without (unadjusted HR 1.20 [95% CI, 1.14-1.27]; adjusted HR 0.91 [95% CI, 0.85-0.96]) (P-value for interaction < 0.001). This interaction was also present for the secondary outcomes (eTable 4). In addition, there was an interaction between age, HF duration, and the primary outcome: Age above the median age, as compared with age below the median age, was associated with a higher rate of the composite endpoint in both new-onset HF (unadjusted HR 2.16 [95% CI, 2.03-2.30]; adjusted HR 2.09 [95% CI, 1.96-2.23]) and worsening of chronic HF (unadjusted HR 1.61 [95% CI, 1.53-1.70]; adjusted HR 1.56 [95% CI, 1.47-1.64]), but

the association was significantly stronger in the new-onset HF group (P-value for interaction < 0.001). This interaction was also present for the secondary outcomes except for HF readmission (eTable 4). In addition, the interaction with age was also present for all outcomes when age was computed as a continuous variable and a categorical variable in the Cox regression models (P-value for interaction < 0.001). Figure 4 depicts the risk of the primary outcome according to HF duration and AF. eFigure 1 displays the risk of the primary outcome according to HF duration and age.

In-hospital mortality and post-discharge outcomes

In-hospital mortality was 6.4% (N=570) and 6.9% (N=577) in patients with new-onset and worsening of chronic HF, respectively. Worsening of chronic HF was associated with a similar in-hospital mortality compared with new-onset HF (unadjusted OR 1.08 [95% CI, 0.96-1.22]; adjusted OR 1.01 [95% CI, 0.89-1.15]).

The risks of the composite endpoint and all-cause mortality according to HF duration among those discharged alive are shown in eFigure 2a-b. Worsening of chronic HF was associated with a higher rate of the composite endpoint (unadjusted HR 1.61 [95% CI, 1.54-1.68]; adjusted HR 1.41 [95% CI, 1.35-1.48] and all-cause mortality (unadjusted HR 1.43 [95% CI, 1.36-1.50]; adjusted HR 1.25 [95% CI, 1.19-1.32]) compared with new-onset HF.

Sensitivity analyses

A number of sensitivity analyses were performed to test the robustness of our findings: 1) We restricted the definition of new-onset HF from a history of HF of 30 days or less to no history of HF. Thus, new-onset HF was defined as patients who were diagnosed with HF for the first time at the time of admission. In line with the main analysis, worsening of chronic HF was associated with a higher rate of the composite endpoint (unadjusted HR 1.71 [95% CI, 1.64-1.78]; adjusted HR 1.49

[95% CI, 1.42-1.56]) and all-cause mortality (unadjusted HR 1.54 [95% CI, 1.47-1.61]; adjusted HR 1.33 [95% CI, 1.27-1.40]) compared with new-onset HF. 2) We restricted the worsening of chronic HF population to patients who had at least one hospitalization and found a similar association as the main analysis with respect to the composite endpoint (unadjusted 1.52 [95% CI, 1.46-1.58]; adjusted HR 1.36 [95% CI, 1.30-1.42]) and all-cause mortality (unadjusted 1.34 [95% CI, 1.28-1.40]; adjusted HR 1.20 [95% CI, 1.14-1.26]). 3) We examined the risk of cardiovascular (defined as a cardiovascular diagnosis code according to ICD-10 codes: I01-I99) and non-cardiovascular death according to HF duration. The absolute risk of cardiovascular and non-cardiovascular death, respectively, are displayed in eFigure 3a and 3b. Compared with new-onset HF, worsening of chronic HF was associated with a significantly higher rate of cardiovascular death (adjusted HR 1.35, 95% CI [1.26-1.44]), but not non-cardiovascular death (adjusted HR 1.06, 95% CI [0.98-1.14]). 4) We examined the relationship between HF duration, modelled as a continuous variable (30-day intervals), and the rate of the composite endpoint. Increasing duration of HF was associated with a higher rate of the composite endpoint (unadjusted HR 1.004 [95% CI, 1.003-1.004]; adjusted HR 1.002 [95% CI, 1.002-1.003]).

Discussion

In this cohort study of all patients admitted to hospital in Denmark with HF in a three-year period, we examined the rates of all-cause mortality and readmission, individually and as a composite, according to HF duration. Specifically, we compared patients presenting with new-onset HF to those with a diagnosis before admission. Our study yielded 4 major findings: First, patients admitted with worsening of chronic HF were more often men and had a greater prevalence of cardiovascular and non-cardiovascular comorbidities compared to those presenting with new-onset HF. Second, despite a similar in-hospital mortality, worsening of chronic HF was associated with a higher rate of the

composite endpoint of all-cause mortality or HF readmission, all-cause mortality, and HF readmission during follow-up compared with new-onset HF. Third, there was a graded relationship between increasing HF duration and the rate of these outcomes, with longer duration of HF associated with higher rates. Fourth, there was an interaction between duration of HF, heart rhythm and outcomes. In patients with worsening of chronic HF, outcomes were worse in patients with AF compared with those without. In patients with new-onset HF, outcomes were better in patients with AF.

In the ACEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), 27% of patients hospitalized with HF presented with new-onset or recently diagnosed HF (defined as a HF duration of less than 4 weeks),[15] while observational studies have reported proportions up to 50%.[16, 17] In line with these studies, we found that approximately 50% of patients hospitalized with HF presented with new-onset HF.

Little attention has been paid to understanding the potential implications of the duration of HF on clinical characteristics and prognosis in patients hospitalized with HF. The only other substantial information comes from a *post-hoc* analysis of the 5,741 patients enrolled in ASCEND-HF. Patients presenting with worsening of chronic HF (defined as a HF duration of at least 4 weeks) had a higher 180-day rate of all-cause mortality compared with those presenting with new-onset or recently diagnosed HF.[15] However, a limitation of this analysis was the exclusion of approximately 20% of the ASCEND-HF population due to lack of data on the date of the HF diagnosis. Patients participating in randomized trials are also selected and in ASCEND-HF there was not a clear, graded relationship between HF duration and outcomes among patients presenting with worsening of chronic HF. We are only aware of two small observational studies, which are both limited by absence of data on the duration of HF.[16, 17] In each of these other studies, patients with worsening of chronic HF in general were more comorbid and had worse baseline kidney

function compared with those with new-onset HF. To our knowledge, our study is the first to examine the long-term risk of both all-cause mortality and readmissions in a large unselected nationwide and contemporary cohort of patients hospitalized with HF according to HF duration. Patients presenting with worsening of chronic HF were more often men and had a greater comorbidity burden despite a 1-year age difference compared with those admitted with new-onset HF. However, even after rigorous adjustment for age, sex, and several comorbidities, we found that worsening of chronic HF was associated with higher rates of all-cause mortality and HF readmission when compared with new-onset HF. Considering the marked heterogeneity in patients characteristics and event rates, a distinction between new-onset and worsening of chronic HF should be considered when designing future trials in hospitalized HF. It is possible that duration of HF may influence the efficacy of an investigational drug. This notion is supported by the *post-hoc* analysis of ASCEND-HF, which revealed that patients with longer duration of HF were more likely to have persisting dyspnea at 24 hours than patients with recently diagnosed HF.[15]

An interesting finding in the present study was the graded relationship between HF duration and rates of all-cause mortality and HF readmission. Although this finding may seem intuitive due to the greater comorbidity burden of patients with longstanding HF, the association between increasing HF duration and subsequent risk of outcomes was independent of age and comorbidities. Instead, the relationship may be due to prolonged exposure to neurohormonal activation and greater maladaptive cardiac remodeling and may reflect the natural course of the disease. However, our findings contrast with those of ASCEND-HF, where this graded relationship was not found.[15] The reasons for this are not clear but may include important differences in patient characteristics including age (mean age 65 years in ASCEND-HF), ethnicity, and prevalence of diabetes, hypertension, and previous myocardial infarction.

Another interesting finding of this study was the interaction between duration of HF, heart rhythm and outcomes. In patients with worsening of chronic HF, outcomes were worse in patients with AF compared with those without, whereas outcomes were better in patients with new-onset HF and AF. It is well-known that AF is both a cause and a consequence of HF. HF facilitates the initiation and maintenance of AF by several mechanisms, including neurohormonal imbalance and activation of the renin-angiotensin-aldosterone system, increased filling pressures and afterload, atrial stretch and fibrosis, and dysregulation of calcium homeostasis.[29, 30] On the other hand, AF promotes the development of HF by a number of mechanisms, including loss of atrial systole which impairs left ventricular filling and decreases cardiac output, particularly in patients with diastolic dysfunction, and irregular or rapid ventricular conduction which may lead to left ventricular dysfunction and tachyarrhythmia-induced cardiomyopathy.[29, 30] The finding that patients with new-onset HF and AF have better outcomes than those without AF may reflect that HF hospitalization to a higher degree is a consequence of AF in patients with new-onset HF than in those with worsening of chronic HF and that appropriate rate or rhythm control in tachyarrhythmia-induced HF may improve hemodynamics and myocardial function and thus subsequent outcomes.

We also found that the association between HF duration and the rates of subsequent outcomes was significantly stronger in younger patients compared with older patients. It is possible that this association may in part be explained by the longer life expectancy in younger patients in general. Therefore, HF duration in older patients who presumably have a shorter life expectancy may be of less importance.

Clinical implications

The present study demonstrates significant differences between patients admitted with new-onset HF as compared to worsening of chronic HF. Despite a similar in-hospital mortality, the long-term

rates of adverse events were higher in patients presenting with worsening of chronic HF. These findings may have important implications for future clinical trial design and underline that patients with worsening of chronic HF should receive even more attention after discharge. However, continued efforts to further improve outcomes in patients with worsening of chronic HF should not only focus on a greater adoption to guideline-directed medical therapy in outpatient clinics, but also on initiation of these agents during hospitalization.[31, 32]

Strengths and limitations

The main strength of this study is the completeness of data in a large nationwide cohort of patients hospitalized with HF followed in a real-world setting. The findings of this study should be viewed in the context of a number of limitations. The observational nature precludes the assessment of cause-effect relationships and the possibility of residual confounding cannot be excluded despite adjustment for potential confounders. Although the Danish administrative registries are validated and of high quality with high positive predictive values for the HF diagnosis and other diseases, our findings rely on the coding in these registries. Data on important clinical parameters, such as natriuretic peptides, estimated glomerular fraction, and other laboratory measurements, vital signs, body mass index, and smoking habits, as well as symptoms, including New York Heart Association functional class, were not available. Echocardiographic data (e.g. left ventricular ejection fraction, left ventricular mass) at baseline or during follow-up were also not available. Thus, a differentiation between HF with reduced and preserved ejection fraction was not possible and the degree of cardiac recovery during follow-up could not be assessed. Further, the cause-specific mortality analysis is dependent on the classification of causes of death, and the quality of the data relies mainly upon the correctness of the physicians' notification. Finally, it is difficult to determine the exact cause for HF

readmissions in administrative registries, i.e. whether it reflects a true deterioration of the disease, lack of compliance, or occurrence of e.g. AF or an ischemic event.

Conclusions

In this nationwide cohort study including an unselected contemporary cohort of patients hospitalized with HF, worsening of chronic HF was associated with poorer outcomes compared with new-onset HF. These findings may have important implications for risk stratification and future clinical trial design.

Sources of Funding

None.

Acknowledgements

None.

Conflict of Interest

None declared.

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Figure legends

Figure 1. Absolute risk of outcomes according to duration of heart failure

Figure 1a. Composite of all-cause mortality or heart failure readmission

Figure 1b. All-cause mortality

Figure 1c. Heart failure readmission

Figure 1d. All-cause readmission

Figure 2. Adjusted hazard ratios of outcomes according to duration of heart failure

Figure 3. Adjusted hazard ratios of the composite of all-cause mortality or heart failure readmission for worsening versus new-onset HF within subgroups

CI, confidence interval; DOAC, direct oral anticoagulants; VKA, vitamin K antagonists.

Figure 4. Absolute risk of the primary outcome according to HF duration and rhythm