Lifetime Analysis of Hospitalizations and Survival of Patients Newly-Admitted with Heart Failure

Chun et al: Lifetime Events in Heart Failure Patients

Soo hun Chun, MD; Jack V. Tu, MD, PhD; Harindra C. Wijeysundera, MD; Peter C. Austin, PhD; Xuesong Wang, MSc; Daniel Levy, MD; Douglas S. Lee, MD, PhD

From the Department of Medicine, University of Toronto (SC, JVT, HCW, DSL), Institute for Clinical Evaluative Sciences (JVT, XW, DSL), Sunnybrook Health Sciences Centre (JVT, HCW), University of Toronto, National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, MA (DL), Center for Population Studies of the National Heart, Lung, and Blood Institute, Bethesda, MD (DL), and the University Health Network and Toronto General Hospital (DSL), University of Toronto, Toronto, Canada.

Correspondence to:
Douglas S. Lee, MD, PhD
Scientist, Institute for Clinical Evaluative Sciences
Associate Professor of Medicine, University of Toronto
Institute for Clinical Evaluative Sciences
Rm G-106, 2075 Bayview Avenue
Toronto, Ontario M4N 3M5
Email: dlee@ices.on.ca
Tel: 416-340-3861
Fax: 416-480-6048

Journal Subject Codes: epidemiology [8], congestive heart failure [110], other heart failure [11], secondary prevention [122], health policy and outcome research [100]
Abstract

Background—Hospital readmissions for heart failure (HF) contribute to increased morbidity and resource burden. Predictors of hospitalization and patterns of cardiovascular events over the lifetime of HF patients have not been elucidated.

Methods and Results—We examined recurrent hospitalizations, cardiovascular events, and survival among patients newly-discharged (April 1999-March 2001) with HF in the Enhanced Feedback For Effective Cardiac Treatment Phase 1 study. During 10-year follow-up, we examined all new cardiovascular hospitalizations and selected predictors of readmission. Among 8543 patients (mean age 77.4 ± 10.5 years, 51.6% women) followed for 22,567 person-years, 60.7% were ischemic etiology and HFrEF (left ventricular ejection fraction ≤45% vs. >45% [HFpEF]) was present in 67.3%. Overall 10-year mortality was 98.8%, with 35,966 hospital readmissions occurring over the cohort’s lifetime. Adjusted hazards ratios (HR) for first cardiovascular hospitalization were 1.36 for ischemic HF (95%CI; 1.28-1.44, p<0.001), 1.10 for HFrEF (95%CI; 1.00-1.20, p=0.045), and 1.00 for men (95%CI; 0.94-1.06, p=0.979). On repeated events time-to-event analysis, ischemic HF was a predictor of cardiovascular (HR 1.24, 95%CI; 1.18-1.29), HF (HR 1.20, 95%CI; 1.13-1.27) and coronary heart disease (HR 2.01, 95%CI; 1.81-2.24) hospitalizations (all p<0.001). Of all recurrent HF hospitalizations, 26.8% occurred in the first and 39.8% in the last deciles of cohort survival duration. Similarly, 29.7% and 52.3% of all cardiovascular readmissions occurred in the first and last deciles of the cohort survival duration, respectively.

Conclusions—Among newly-discharged HF patients, cardiovascular events were clustered at early post-discharge and pre-fatal time periods, and were increased among those with ischemic etiology.

Key Words: heart failure, hospitalization, readmission, cardiovascular disease, ischemic heart disease, epidemiology, outcomes, health services research, prognosis, population
There is increasing interest in the high rates of repeat hospital visits and readmissions for heart failure (HF).\(^1\) Repeat hospitalizations contribute significantly to the increased costs of health care for those with HF,\(^2,3\) and the issue of readmissions has been identified as a priority problem for the health care system.\(^4\) As an ambulatory care sensitive condition, hospital readmissions for HF have also been deemed indicators of reduced quality of care.\(^5,6\)

Despite the importance of readmissions in the HF population, many challenges remain. First, the important predictors of readmission among HF patients have not been determined.\(^7,8\) Second, from a methodological standpoint, most prior studies examined occurrence of the first readmission, and did not account for all hospitalizations occurring over the lifetime after the initial HF hospital discharge.\(^9\) While heart failure is commonly classified, based on underlying left ventricular (LV) systolic function, as HF with reduced (HFrEF) or preserved (HFpEF) ejection fraction, it is unknown if this classification is predictive of repeated hospitalizations and death occurring over the lifetime of the patient. Furthermore, it is unknown if classification based on ischemic or non-ischemic etiology is predictive of hospitalization and cardiovascular events over the lifetime of HF patients.\(^10\)

In this study, we examined a patient cohort who was discharged after being newly-hospitalized for HF and we followed them over their lifetime for all cardiac and non-cardiac hospitalizations that occurred until death. These patients, who were originally enrolled in Phase 1 of the Enhanced Feedback For Effective Cardiac Treatment study, have now been followed for up to 10 years. We examined the patterns of hospitalization and recurrent cardiovascular events over the lifetime of patients who were newly-admitted with HF. Furthermore, we examined the
association of sex, presence of HFrEF vs. HFpEF, and ischemic vs. non-ischemic etiology on hospitalizations in this population-based cohort.

**Methods**

**Study Population.** We evaluated patients who were newly-admitted to hospital with HF in Ontario, Canada, in Phase 1 of the Enhanced Feedback For Effective Cardiac Treatment (EFFECT) study, described in detail elsewhere. Briefly, these patients were identified by examining the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) from April 1999 to March 2001 for those with a primary/most responsible diagnosis of HF as indicated by the International Classification of Diseases (ICD-9) code 428.x. In the EFFECT Phase 1 study, primary chart records were abstracted by highly-trained nurse-abstractors from 86 hospital corporations for clinical information, and only those who met the Framingham criteria for HF were included. In this study, we examined mortality among all patients subsequent to the index EFFECT admission and readmissions among those who survived to index hospital discharge. Approval from the ethics review board was obtained from all participating institutions before the study.

**Data Sources.** Using the patients’ unique, encrypted health card number, we linked the EFFECT data to the hospitalization information contained in the CIHI-DAD and examined all subsequent hospitalizations using ICD-9-CM and ICD-10-CA codes. Cardiovascular hospitalizations included those for HF, coronary artery disease, and other cardiac disease as the primary/most responsible diagnosis. Other cardiac disease hospitalizations included admissions for arrhythmia, myo-/peri-/endo-cardial diseases, cerebrovascular disease, hypertensive disease,
pulmonary vascular disease, rheumatic heart disease, shock, syncope, sudden cardiac death, valvular heart disease and other unspecified cardiac diseases. All other reasons for hospitalization were assigned to be non-cardiovascular. In the CIHI-DAD, each hospitalization has one primary diagnosis. However, multiple new conditions could be diagnosed during the course of a single hospitalization. Therefore, we also identified all secondary conditions in any of the 16 CIHI diagnosis fields that were new conditions contributing to the hospital stay. Together, these conditions (primary and new secondary diagnoses) were classified as hospitalization-based cardiovascular or non-cardiac events. To exclude readmissions for day procedures, hospitalizations with length of stay of 1 day or less were not included as an event.

Mortality was determined by linkages with the Registered Persons Database (RPDB) for vital statistics. All hospitalizations and invasive procedures were examined in each HF patient until death occurred or until the date of last available follow-up.

**Study definitions.** We defined the lifetime of the newly-admitted HF patient to begin upon initial hospitalization for HF. Heart failure with reduced (HFrEF) or preserved ejection fraction (HFP EF) was defined by LV ejection fraction (LVEF) ≤45% vs. >45% based on previously-defined thresholds. Ischemic HF was defined by prior coronary artery disease, unstable angina, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery. Morbid outcomes were defined as either hospitalizations (i.e., each admission contributes one primary diagnosis) or hospitalization-based events (i.e., one admission could generate multiple events if new secondary diagnoses are coded). Secondary diagnoses that were chronic, pre-existing conditions were not included, thus, analysis of hospitalization-based events accounted
for multiple *de novo* conditions that could arise during a single hospital admission.

**Statistical Analysis.** Continuous variables were reported as mean ± standard deviation and compared using Student’s t-test. Categorical variables were compared between groups using the $\chi^2$ statistic. A descriptive analysis of hospitalizations was initially performed by counting the number of hospitalizations occurring during follow-up. In these analyses, each hospitalization was categorized as due to HF, coronary heart disease, other cardiac, or non-cardiovascular, based on the primary diagnosis in the CIHI-DAD. The effect of clinical categories on time-to-first hospitalization was assessed using adjusted Cox proportional hazards models, accounting for patients clustered within hospitals. These models were adjusted for sex, ischemic vs. non-ischemic etiology, and HFrEF vs. HFpEF, and censored at death or upon last follow-up date of March 31, 2009. Those without documented LVEF were included in the regression analyses as a separate category (e.g., unknown LVEF). We also adjusted for the following covariates based on a previously validated model: age, serum sodium, hemoglobin, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, hepatic cirrhosis, dementia, cancer, systolic blood pressure, respiratory rate, and blood urea nitrogen. We constructed survival curves adjusted for the aforementioned covariates using the corrected group prognosis method. The proportional hazards assumption was tested for Cox regression models using a Kolmogorov supremum-type test on 1000 resamplings of the cumulative sums of martingale residuals.

Repeat hospitalization outcomes were examined using Cox regression analysis for recurrent events accounting for the possibility of multiple readmissions occurring over time in the same patient. To further explore the patterns of hospitalizations over the lifetime of the HF cohort,
we divided the lifetime (after the index HF discharge) of each patient into deciles and counted
the number of hospitalizations occurring in each time fraction of the survival duration. Similarly,
the lifetime of each patient was divided into tertiles (early, middle, late), and hospitalizations that
occurred in each of the three periods were examined for all new hospital-based events. In
sensitivity analyses, we treated hospitalizations and mortality as competing events, and jointly
modeled the cause-specific hazard functions of these two outcomes. A p-value <0.05 was
considered statistically significant. Analyses were performed using SAS version 9.2 (Cary, NC).

Results

Study Cohort. We examined 8543 HF patients (mean age 77.4±10.5 years) of whom 60.7%
were ischemic, 67.3% had HFrEF, and 51.6% were female. The baseline characteristics of the
study cohort are shown in Table 1. Those with ischemic HF were younger than those with non-
ischemic HF, and had significantly higher rates of hypertension, hyperlipidemia, diabetes,
smoking, and greater comorbidity burden. Among the subcohort with LV functional assessment
performed (42.5%), those with HFpEF were older and had higher prevalence of hypertension and
atrial fibrillation than those with HFrEF. While women were older and had more hypertension,
they also had lower rates of chronic obstructive pulmonary disease than men.

Time to Death. We examined a total of 22,567 person-years of follow-up. Overall 10-year
mortality was 98.8%, with median survival 1.75 years. Benchmark survival rates of 25%, 10%,
and 5% occurred after 4.25, 6.94, and 8.34 years of follow-up respectively. The adjusted hazards
ratio [HR] for mortality was 1.17 (95% CI; 1.08-1.26, p<0.001) for HFrEF compared to HFpEF
(Figure 1). The adjusted HR for ischemic vs. non-ischemic HF was $1.07$ (95% CI; 1.02-1.13, 
p=0.004). Compared to those with LV function testing performed, those with unknown LVEF 
had shorter median survival (1.52 vs. 2.16 years, p<0.001) and HF hospitalization-free survival 
(2.76 vs. 3.19 years, p=0.01). There was an increased risk of death among men as demonstrated 
by an adjusted HR of $1.06$ (95% CI; 1.01-1.11, p=0.019) compared to women.

Analysis of Time to First Hospitalization. HFrEF was associated with an increased age- and 
sex-adjusted risk of first hospitalization for HF and coronary heart disease (Table 2). Ischemic 
HF was associated with the largest risks of hospitalization for HF, coronary heart, and 
cardiovascular disease (Table 2). Heart failure hospitalization-free survival curves are shown in 
Figure 2a for HFrEF vs. HFpEF and Figure 2b for ischemic vs. non-ischemic HF. For those with 
HFrEF vs. HFpEF, adjusted HRs for first HF hospitalization were $1.16$ (95% CI; 1.04-1.30, 
p=0.008) and $1.47$ (95% CI; 1.26-1.72, p<0.001) for first coronary heart disease hospitalization  
(Table 2). There were no differences in adjusted rehospitalization outcomes among men vs. 
women (Table 2). In sensitivity analyses, we accounted for competing risks in which the effects  
of sex, ischemic vs. non-ischemic status, and HFrEF vs. HFpEF on the cause-specific hazard  
function for the readmission outcomes were estimated. Results similar to those above were  
observed.

Analyses of Repeat Hospitalizations. The rates of repeat hospitalizations per 100 person-years 
of follow-up are shown in Table 3. Accounting for multiple possible hospitalizations per patient, 
those with ischemic HF were far more likely than those with non-ischemic HF to experience  
repeat cardiovascular, HF, and coronary heart disease hospitalizations. There were smaller
differences in repeat hospitalizations when compared by HFrEF vs. HFpEF, and by sex.

Repeated events Cox regression analysis (Table 4) demonstrated attenuated effect sizes compared to the analysis of time-to-first events shown in Table 2. Despite this, ischemic HF etiology remained predictive of cardiovascular readmissions over the post-HF onset lifetime, with 24% increased risk after multivariable adjustment. Ischemic etiology also increased the risk of HF hospitalizations by 20% and doubled the risk of coronary heart disease hospitalizations after multivariable adjustment.

Timing of Hospitalizations Relative to Initial Discharge and Death. Repeat hospitalizations for HF occurred in 61.3% of patients, while cardiovascular events occurred in 66.5% of patients within the first year after discharge. Among patients who were rehospitalized for HF or for cardiovascular disease, the largest proportion of initial readmissions occurred within the first and last deciles of the post-discharge survival duration (Figure 3), where each decile was a median of 63 days in length. Considering any rehospitalization, accounting for multiple hospitalizations per patient, the greatest proportion of hospital admissions occurred in the decile of survival time just prior to death followed by the immediate post-discharge period (Figure 4). Noncardiovascular hospitalizations demonstrated an early peak for the first readmission and prominent increases in the last decile for the first or any readmission.

Timing of Repeat Hospitalization-Based Events. Repeat hospitalization-based events occurred more frequently prior to death. In the 18 months prior to death, there were 6924 hospitalizations with a new diagnosis of recurrent HF – 14.2%, 19.4%, and 47.5% of the entire
cohort experienced recurrent HF events during the periods 12-18 months, 6-12 months, and <6 months prior to death, respectively. In a similar time frame, there were 9314 hospitalizations with recurrent CVD events in the last 18 months prior to death, with the majority of events occurring near the end of the lifespan: 20.8% at 12-18 months, 26.2% at 6-12 months, and 62.1% within 6 months before death. Non-cardiovascular events (total 6924) also exhibited a similar time course with 16.7%, 20.7%, and 43.7% of patients diagnosed within 12-18, 6-12, and <6 months prior to death.

Examining the number of repeat hospitalization-based events that occurred in the first (early), second (middle), and third (late) tertiles of the total survival duration, cardiovascular causes (primarily recurrent HF) were predominant in all three time periods. Frequency distribution of events were very consistent in those with one, two, and three or more admissions occurring over the lifetime after the index HF hospitalization.

Discussion

We conducted a comprehensive, long-term analysis of hospitalizations of newly-discharged HF patients who were followed until nearly the entire study cohort had died. During 10 year follow-up, approximately 99% of the cohort had died and the median survival was 1.8 years. We found that those with ischemic HF demonstrated increased mortality, experienced earlier readmission for cardiovascular disease, and exhibited greater risk of repeat hospitalizations over their lifetime. Over the lifetime, survival was marginally but statistically significantly higher among women and those with HFpEF. Patients with HFrEF were more likely to experience marginally
increased risk of early cardiovascular readmissions, with an increase in hospitalizations for HF and coronary artery disease. Those with ischemic HF were significantly more likely to experience repeat cardiovascular disease admissions of all subtypes.

Cardiovascular readmissions occurred frequently, and these repeat hospitalizations were largely due to episodes of recurrent HF. Examining the first readmission, 66.5% were hospitalized for cardiovascular disease and 61.3% were readmitted for HF within the first year. Most first readmissions occurred in the initial and final deciles of the cohort’s lifespan. When all hospitalizations were examined, cardiovascular disease and recurrent HF comprised the majority of events in the early, middle, and late periods of the survival duration. Repeat hospitalizations occurred most frequently within a few months (i.e., final lifespan decile) prior to death. In multivariable analysis, repeat cardiovascular admissions occurred more frequently among younger patients and those with ischemic HF. When we further dissected cardiovascular events, ischemic HF remained the only significant predictor of repeat admissions for HF and cardiovascular disease. LVEF and gender did not predict repeat HF, coronary heart disease, or cardiovascular readmissions.

Our study contributes new data by examining the full range of outcomes over the lifetime of patients in a population-based setting, exploring outcomes by HF subtype, and examining time to first rehospitalization vs. recurrent events. The cross-sectional associations were consistent with previously-published data which found greater frequency of women, elderly, hypertension, and atrial fibrillation among patients with HFP EF.10,20 Our findings also support prior community-based epidemiologic studies which reported greater risks of coronary heart disease-related deaths
in men compared to women, and in those with HFrEF compared to HFrEF.21,22 The distribution of cardiovascular vs. non-cardiovascular readmissions was consistent with a long-term HF follow-up study from Olmstead County.23 However, our study extended prior literature by examining events occurring over the lifetime and the prognostic implications of HF subtypes, in particular, classification based on ischemic vs. non-ischemic HF and LV systolic function.

A novel aspect of our study was the examination of patterns of hospitalization and cardiovascular events occurring over the post-HF lifetime with death occurring in nearly all patients during the study. Prior reports evaluating mortality found few differences or non-significant trends in short- or near-term events when contrasted by HFrEF vs. HFrEF or by sex.24,25 Prior studies comparing ischemic and non-ischemic HF did not explore the impact on hospitalizations, were limited to shorter follow-up duration, or were performed in a selected subset of enrollees.26,27 Some studies comparing ischemic vs. non-ischemic HF reported no differences in death or hospitalizations when limited to near-term follow-up.28 Our analysis extended the literature by examining a broad range of events occurring over the lifetime of HF patients, and by identifying significant mortality and morbidity differences in extended follow-up.

Methodologically, we also examined readmissions using an approach that accounted for repeat events. Unlike prior studies of HF morbidity, which focused on occurrence of the first event without regard for the possibility of multiple readmissions per patient, results differed when we examined multiple events occurring over the lifetime. Ischemic HF was a ubiquitous predictor of repeat hospitalizations, time-to-first hospitalization, and death, which may be attributable to the potentially destabilizing impact of coronary ischemia.7,29 While patients with HFrEF were more
likely to be rehospitalized early, this increased risk was not observed for repeat events over the lifetime relative to those with HFrEF. The reduction in risk of repeat events among those with HFrEF over the lifetime may be attributed in part to the availability of medical therapies which can reduce hospitalizations among those with reduced LV systolic function. In contrast, there are few efficacious pharmacologic therapies that have demonstrably reduced repeat hospitalizations in those with HFpEF.

Our study has important implications for HF care because repeat hospitalizations reflect a progressive illness where the cumulative effects of increasing morbidity may eventually result in heightened mortality risk.30, 31 Our findings suggest that determining the presence of ischemia is of critical importance, since it was the most robust predictor of repeat HF and cardiovascular admissions, and may also be amenable to anti-ischemic therapeutic interventions. As reported in the Surgical Treatments for Ischemic Heart failure (STICH) trial, judicious use of coronary revascularization procedures may have beneficial effects on reducing hospitalizations,32 which are prominent outcomes over the lifetime of patients with HF. Before the policy of broad use of revascularization interventions is enacted, however, further studies are required to better characterize patient subsets who would most benefit from medical therapy or intervention.33

While the initial readmission often occurred early after the index HF discharge, cardiovascular causes were prominent reasons for hospitalization in early, middle, and late phases of the survival duration. Thus, our results suggest that interventions to reduce hospitalizations should: a) be provided early after HF discharge, b) be sustained over the patient’s lifetime, and c) consider both cardiac and non-cardiac aspects of care.
Our study had several strengths including complete, extended follow-up for a wide range of outcome events, and all patient deaths recorded in a cohort where almost all patients had died. While this study provided new insights into the HF syndrome, there were several limitations. LV function, laboratory abnormalities, and concomitant comorbidities were evaluated at the index admission, and we did not account for changes that may have occurred during follow-up. However our group has shown previously that adjustment for covariates at baseline predicted long-term risk even after stratification by LVEF. Cross-over of some initially non-ischemic patients to ischemic categorization may have occurred, potentially attenuating differences in outcomes between those with ischemic and non-ischemic HF. As with all epidemiologic studies there may be additional impacts of regional variations in care and outcomes, and thus confirmatory studies in other jurisdictions are needed. Finally, our examination of morbidity was limited to hospitalization events, and clinical worsening that was treated purely in the ambulatory setting was not evaluated. However, symptomatic worsening that requires hospitalization increases mortality risk in a graded manner and has substantial implications from the standpoint of the health care system.

In conclusion, among heart failure patients who were discharged from hospital, readmissions for recurrent HF and cardiovascular disease most often occurred in the months early post-discharge or late, prior to death. Over the lifetime of HF patients, recurrent hospital-based events were often attributable to cardiovascular disease and were frequently HF-related. While those with HFrEF were marginally more likely to experience earlier rehospitalization for HF and coronary heart disease when examined over the lifetime, ischemic HF was the most potent predictor of repeat hospitalizations and earlier readmission to hospital for all cardiovascular causes in the
population. Identification of HF patients with ischemic heart disease coupled with appropriate therapeutic interventions may improve survival and reduce the burden of this leading cause of hospitalization and health care costs.

Sources of Funding

Supported by operating grant MOP 114937 from the Canadian Institutes of Health Research (CIHR), Career Investigator award from the Heart and Stroke Foundation of Ontario (JVT, PCA), a Canada Research Chair in Health Services Research (JVT), and a CIHR Clinician-Scientist Award (DSL). The Institute for Clinical Evaluative Sciences is supported in part by a grant from the Ontario Ministry of Health and Long Term Care. The opinions, results and conclusions are those of the authors and no endorsement by the Ontario Ministry of Health and Long Term Care or by the Institute for Clinical Evaluative Sciences is intended or should be inferred.

Disclosures

None.
References


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ischemic</th>
<th>Non-ischemic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5185</td>
<td>3358</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>77.0 (9.9)</td>
<td>77.9 (11.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>2601 (50.2%)</td>
<td>1475 (43.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n(%)</td>
<td>1260 (24.3%)</td>
<td>257 (7.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>2020 (39.0%)</td>
<td>981 (29.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking history, n(%)</td>
<td>1991 (38.4%)</td>
<td>1096 (32.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease, n(%)</td>
<td>1012 (19.5%)</td>
<td>485 (14.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, n(%)</td>
<td>885 (17.1%)</td>
<td>310 (9.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dialysis, n(%)</td>
<td>75 (1.4%)</td>
<td>48 (1.4%)</td>
<td>0.948</td>
</tr>
<tr>
<td>Chronic obstructive lung disease, n(%)</td>
<td>978 (18.9%)</td>
<td>575 (17.1%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>1633 (31.5%)</td>
<td>955 (28.4%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HFrEF</th>
<th>HFP EF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2448</td>
<td>1190</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>74.6 (10.4)</td>
<td>77.9 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>1187 (48.5%)</td>
<td>667 (56.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n(%)</td>
<td>583 (23.8%)</td>
<td>178 (15.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>926 (37.8%)</td>
<td>384 (32.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking history, n(%)</td>
<td>1085 (44.3%)</td>
<td>433 (36.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease, n(%)</td>
<td>398 (16.3%)</td>
<td>207 (17.4%)</td>
<td>0.388</td>
</tr>
<tr>
<td>Peripheral vascular disease, n(%)</td>
<td>405 (16.5%)</td>
<td>140 (11.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dialysis, n(%)</td>
<td>23 (0.9%)</td>
<td>13 (1.1%)</td>
<td>0.622</td>
</tr>
<tr>
<td>Chronic obstructive lung disease, n(%)</td>
<td>381 (15.6%)</td>
<td>225 (18.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>690 (28.2%)</td>
<td>448 (37.6%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men</th>
<th>Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4133</td>
<td>4410</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>75.2 (10.6)</td>
<td>79.4 (9.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>1811 (43.8%)</td>
<td>2265 (51.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n(%)</td>
<td>843 (20.4%)</td>
<td>674 (15.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>1554 (37.6%)</td>
<td>1447 (32.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking history, n(%)</td>
<td>2012 (48.7%)</td>
<td>1075 (24.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease, n(%)</td>
<td>714 (17.3%)</td>
<td>783 (17.8%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Peripheral vascular disease, n(%)</td>
<td>737 (17.8%)</td>
<td>458 (10.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dialysis, n(%)</td>
<td>70 (1.7%)</td>
<td>53 (1.2%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Chronic obstructive lung disease, n(%)</td>
<td>859 (20.8%)</td>
<td>694 (15.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>1238 (30.0%)</td>
<td>1350 (30.6%)</td>
<td>0.508</td>
</tr>
</tbody>
</table>
Table 2. Association between sex, ischemic etiology, and HFrEF on time to first readmission

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Analysis</th>
<th></th>
<th>Adjusted Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1.07 (1.02,1.13)</td>
<td>0.008</td>
<td>1.39 (1.33,1.46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.08 (1.01,1.15)</td>
<td>0.016</td>
<td>1.33 (1.24,1.42)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.12 (1.03,1.23)</td>
<td>0.008</td>
<td>2.34 (2.13,2.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other cardiac disease</td>
<td>1.13 (1.05,1.21)</td>
<td>&lt;.001</td>
<td>1.29 (1.20,1.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>0.98 (0.93,1.02)</td>
<td>0.322</td>
<td>1.07 (1.02,1.13)</td>
<td>0.004</td>
</tr>
<tr>
<td>Death</td>
<td>1.03 (0.99,1.08)</td>
<td>0.117</td>
<td>1.12 (1.07,1.17)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* HRs for men vs. women adjusted for ischemic vs. non-ischemic, HFrEF vs. HFpEF, hospital-level clustering, and EFFECT-HF risk score covariates

† HRs for ischemic vs. non-ischemic HF adjusted for HFrEF vs. HFpEF, men vs. women, hospital-level clustering, and EFFECT-HF risk score covariates

‡ HRs for HFrEF vs. HFpEF adjusted for ischemic vs. non-ischemic, men vs. women, hospital-level clustering, and EFFECT-HF risk score covariates

* EFFECT-HF risk score covariates: age, serum sodium, hemoglobin, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, hepatic cirrhosis, dementia, cancer, systolic blood pressure, respiratory rate, and blood urea nitrogen
Table 3. Hospital admission rate per 100 person-years of follow-up

<table>
<thead>
<tr>
<th>Hospitalization Type‡</th>
<th>Ischemic</th>
<th>Non-Ischemic</th>
<th>HFrEF</th>
<th>HFpEF</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular†*</td>
<td>96.7</td>
<td>62.1</td>
<td>83.8</td>
<td>72.9</td>
<td>84.4</td>
<td>80.9</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>49.9</td>
<td>33.3</td>
<td>42.9</td>
<td>34.9</td>
<td>45.0</td>
<td>41.3</td>
</tr>
<tr>
<td>Coronary heart disease*</td>
<td>24.5</td>
<td>8.7</td>
<td>19.4</td>
<td>14.7</td>
<td>18.1</td>
<td>17.4</td>
</tr>
<tr>
<td>Other cardiac disease*</td>
<td>29.9</td>
<td>23.0</td>
<td>28.9</td>
<td>28.1</td>
<td>27.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Non-cardiovascular*</td>
<td>154.0</td>
<td>137.0</td>
<td>137.3</td>
<td>132.2</td>
<td>149.9</td>
<td>146.0</td>
</tr>
</tbody>
</table>

† Includes HF, coronary artery disease, or other cardiac disease
* Age/sex-adjusted p<0.001 for ischemic vs. non-ischemic, HFrEF vs. HFpEF, and age-adjusted p<0.001 for men vs. women
‡ Rates are hospital admissions per 100 person-years of follow-up
Table 4. Repeated events Cox regression analysis

Cardiovascular vs. Non-cardiovascular Hospitalizations

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Cardiovascular</th>
<th>Non-cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR* (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (0.96,1.04)</td>
<td>0.962</td>
</tr>
<tr>
<td>Ischemic (vs. non-ischemic)</td>
<td>1.24 (1.18,1.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HFrEF (vs. HFpEF)</td>
<td>1.03 (0.96,1.10)</td>
<td>0.418</td>
</tr>
</tbody>
</table>

Type of Cardiovascular Hospitalization

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Heart Failure</th>
<th>Coronary Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR* (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (0.94,1.05)</td>
<td>0.892</td>
</tr>
<tr>
<td>Ischemic (vs. non-ischemic)</td>
<td>1.20 (1.13,1.27)</td>
<td>&lt;=.001</td>
</tr>
<tr>
<td>HFrEF (vs. HFpEF)</td>
<td>1.05 (0.96,1.15)</td>
<td>0.254</td>
</tr>
</tbody>
</table>

* Covariates in the multivariable model: age, sex, ischemic vs. non-ischemic etiology, HFrEF vs. HFpEF, unknown LVEF, serum sodium, hemoglobin, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, hepatic cirrhosis, dementia, cancer, systolic blood pressure, respiratory rate, and blood urea nitrogen
Figure Legends

Figure 1. Adjusted survival curve: HFrEF vs. HFrEF

Figure 2a. Adjusted HF hospitalization-free survival: HFrEF vs. HFrEF

Figure 2b. Adjusted HF hospitalization-free survival: Ischemic HF vs. Non-ischemic HF

Figure 3. First readmission timing over HF patient lifespan

Figure 4. Timing of any readmission over HF patient lifespan
Figure 1. Survival by left ventricular function

$P < 0.001$
Figure 2a. Effect of HFrEF on HF hospitalization-free survival

P = 0.007
Figure 2b. Effect of Ischemia on HF hospitalization-free survival

P < 0.001
Figure 3. First readmission timing over HF patient lifespan

% of Patients Hospitalized

Decile of Post-Discharge Survival Duration

- Heart Failure
- Cardiovascular
- Non-Cardiovascular

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Figure 4. Timing of any readmission over HF patient lifespan

- Heart Failure
- Cardiovascular
- Non-Cardiovascular

% of Patients Hospitalized

Decile of Post-Discharge Survival Duration
Lifetime Analysis of Hospitalizations and Survival of Patients Newly-Admitted with Heart Failure
Soo hun Chun, Jack V. Tu, Harindra C. Wijeysundera, Peter C. Austin, Xuesong Wang, Daniel Levy and Douglas S. Lee

Circ Heart Fail. published online May 2, 2012;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2012/05/02/CIRCHEARTFAILURE.111.964791