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## Natural History of Left Ventricular Ejection Fraction in Patients With Heart Failure

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### Abstract

**Background**—Patients with heart failure (HF) are typically designated as having reduced or preserved ejection fraction (HFREF, HFPEF) because of the importance of left ventricular ejection fraction (LVEF) on therapeutic decisions and prognosis. Such designations are not necessarily static, yet few data exist to describe the natural history of LVEF over time.

**Methods and Results**—We identified 2413 patients from Kaiser Permanente Colorado with a primary discharge diagnosis of HF between January 1, 2001, and December 31, 2008, who had 2 LVEF measurements separated by 30 days. We used multi-state Markov modeling to examine transitions among HFREF, HFPEF, and death. We observed a total of 8183 transitions. Women were more likely than men to transition from HFREF to HFPEF (hazard ratio, 1.85; 95% confidence interval, 1.38–2.47). Patients who were adherent to  $\beta$ -blockers were more likely to transition from HFREF to HFPEF (hazard ratio, 1.53; 95% confidence interval, 1.10–2.13) compared with patients who were nonadherent to  $\beta$ -blockers, whereas angiotensin-converting enzyme or angiotensin II receptor blocker adherence was not associated with LVEF transitions. Patients who had a previous myocardial infarction were more likely to transition from HFPEF to HFREF (hazard ratio, 1.75; 95% confidence interval, 1.26–2.42).

**Conclusions**—In this cohort of patients with HF, LVEF is a dynamic factor related to sex, coexisting conditions, and drug therapy. These findings have implications for left ventricular systolic function ascertainment in patients with HF and support evidence-based therapy use, especially  $\beta$ -blockers.

### Keywords

heart failure; outcomes assessment; prognosis; ventricular ejection fraction

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Heart failure (HF) is a syndrome caused by a wide range of abnormalities of cardiac structure and function. Measurement of left ventricular ejection fraction (LVEF) is central to

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### Disclosures

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the evaluation and management of HF. Patients with the syndrome are typically categorized as having either HF with reduced ejection fraction (HFREF) or HF with preserved ejection fraction (HFPEF). This dichotomy is central to the approach to patients with HF: LVEF is linked to HF pathogenesis and is instructive in diagnosis, directly informs guideline recommended drug and device therapy, and is a determinant of prognosis.<sup>1,2</sup>

Patients are typically designated into LVEF categories of HFREF or HFPEF based on a single measurement at a point in time, although LVEF is not necessarily static. LVEF can worsen over time because of progressive cardiac disease or ventricular remodeling, or it can improve in response to HF therapy or reversal of the underlying pathogenesis. The few existing studies of trends in LVEF are limited by restriction to patients with reduced LVEF<sup>3</sup> or to demographically homogenous populations.<sup>4</sup> Furthermore, existing studies of the natural history of LVEF lack longitudinal data on medical therapy and medication adherence.<sup>3,4</sup> Few randomized controlled trials have focused on the effect of evidence-based therapies on LVEF, and randomized controlled trials in HF typically enroll unrepresentative populations and may have limited follow-up time.<sup>5-7</sup>

The objectives of this study were to examine the natural history of LVEF in a cohort of patients with HF in the community and to identify the factors associated with changes in LVEF and death using a novel analytic method (multi-state modeling). An understanding of the pattern of changes in LVEF over time in a representative cohort of patients with HF and the relationship of clinical factors and treatment to these patterns would help guide decisions about the frequency of follow-up, need for repeat cardiac imaging, and prognostic counseling.

## Methods

### Study Population

Kaiser Permanente Colorado is an integrated health plan, which provides care to >480 000 members in the Denver metropolitan area. Patients aged ≥ 21 years with a primary hospital discharge diagnosis for HF between January 1, 2001, and December 31, 2008, were identified. The diagnosis for HF was based on either *International Classification of Diseases 9th Revision* codes (428.xx, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93) or diagnosis-related group system codes (127 before October 17, 2007, or 291, 292, or 293 after October 17, 2007)<sup>8,9</sup> Patients were excluded if they did not have ≥ 2 LVEF tests that were performed ≥ 30 days apart. To describe the natural history of left ventricular systolic function in patients with HF, subjects were followed from their first LVEF measurement (as early as January 1, 2000) to death, disenrollment, or December 31, 2009, whichever occurred first. The Kaiser Permanente Colorado Institutional Review Board approved the study, and a waiver of consent was obtained because of the study design.

### LVEF Tests

LVEF was determined through manual chart review and supplemented by tests found electronically within the medical record. Abstraction was performed on all valid sources, including echocardiography, left ventriculography, radionuclide scanning, cardiac computerized tomography, and cardiac magnetic resonance imaging studies. The LVEF data were presented qualitatively 45% of the time. Therefore, we dichotomized the variable to examine patients with HFPEF or HFREF, consistent with the definitions applied in contemporary practice guidelines for HF. For any single study, if the quantitative and qualitative assessments disagreed, the quantitative measure was used. Quantitative results of LVEF ≥ 40% or qualitative results of normal or mildly reduced left ventricular (LV) systolic

function were categorized as HFPEF. Quantitative results of LVEF <40% or qualitative results of moderately or severely reduced LV systolic function were categorized as HFREF.<sup>10</sup> If an LVEF test was found within 30 days of the last test, the average of the 2 tests was used. If the results were qualitative and separated by only 1 category, then the more severe assessment was used.

## Covariates

Covariates that were static over time included sex, age at first LVEF test, race/ethnicity, coexisting conditions, and socioeconomic status. Coexisting conditions were considered as a continuous indicator variable for those conditions included in the modified Charlson comorbidity index (CCI),<sup>11</sup> except for myocardial infarction and renal disease, which were considered separately because of their direct clinical relevance to LVEF in patients with HF. HF was also not considered in the CCI because by definition all patients had this condition. We also included valvular heart disease and hypertension as additional covariates. Coexisting conditions were identified using *International Classification of Diseases 9th Revision* codes and were collected during the study period at or before the first discharge diagnosis for HF. Socioeconomic status was derived from census data, which categorized patients as having a poor socioeconomic status if they resided in an area with >20% of housing in poverty or if <25% of residents had a high school education. Race/ethnicity was missing for 48% of the patients, so we did not include this covariate in our models.

Because of prior evidence demonstrating the effect of  $\beta$ -blocker therapy on LVEF in patients with HF, we also considered  $\beta$ -blocker therapy as a time-varying covariate.<sup>12-16</sup>  $\beta$ -blocker adherence was assessed for patients every 6 months after their initial  $\beta$ -blocker fill during the study period. Patients were considered adherent during a 6-month period if their percent of days covered during the period was  $\geq 80\%$ .<sup>17</sup> Because patients may also have a period of time after their initial LVEF measurement where they were not prescribed or taking a  $\beta$ -blocker, we introduced a third level to indicate whether a patient was not prescribed the medication. Therefore, there was a 3-level variable to characterize  $\beta$ -blocker therapy: (1) nonadherent if prescribed but percent of days covered <80%, (2) adherent if prescribed and percent of days covered  $\geq 80\%$ , or (3) not prescribed. If patients discontinued filling their prescriptions for  $\beta$ -blockers, they were considered nonadherent thereafter. The reference category was nonadherent.

Similarly, we conducted a secondary analysis, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) drug adherence, in a separate model. We calculated adherence in the same manner as for  $\beta$ -blocker therapy. This model was constructed separately, given instability in the estimates resulting from both time-varying medication adherence variables in 1 model.

## Statistical Methods

We used multi-state Markov models (MSMs) to describe the natural history and evolution of LVEF.<sup>18,19</sup> MSMs model both the rates and predictors of movements between various states of a categorical outcome in time. MSMs have been used to study transitions between disease states in several other conditions and states of hospitalization or death in patients with HF.<sup>20,21</sup> The approach is an extension of survival (time to event) analysis that allows multiple states instead of only 2 (eg, alive or dead), and allows patients to move back and forth between these states except for terminal events (eg, death), which are considered absorbing states. In our study, patients were categorized into 3 states: HFPEF, HFREF, and death. Because LVEF could worsen, improve, or stay the same, patients were allowed to remain in a specific state or could move between HFPEF and HFREF. Death was considered an absorbing state. In MSMs, transitions between states are described by instantaneous

intensity rates. This is analogous to the hazard rate in survival analysis, where future state changes depend only on the current state.<sup>22</sup>

Markov models assume that transition probabilities depend only on the current state but not on previous states. The models handle differences in time since previous measurement, down-weighting dependence on the previous state when measurements occur further in the past. To adjust for possible dependence on history of HFREF, we included a 3-level variable in our primary and secondary analyses. The 3 levels were classified as never having a prior LVEF assessment, which was assigned for the first measurement during the study period, never previously having HFREF, or had HFREF at some previous measurement.

Transitions to death were observed exactly, as we obtained exact death dates from the electronic medical record. Although we captured the exact date of LVEF measurement, patients could have changed states any time between the previous assessment and the current assessment. These types of transitions were considered to be interval censored. Because the state transition times into HFPEF and HFREF were interval censored, we used fully parametric models, assuming a constant baseline hazard (or equivalently an exponential baseline time to event distribution) that may depend on time-constant and time-varying covariates. MSMs also allow the calculation of a probability matrix, which provides the probability that a patient with given characteristics and in a given state will be in each of the possible states at a specified future time. We estimated state transition probabilities for 6 months, 1 year, 2 years, and 5 years. The matrix was calculated for a 70-year-old patient with a CCI of 3 and with all other covariates set to their referent values; male, high socioeconomic status, no previous myocardial infarction, no valvular heart disease, no hypertension, and no prior LVEF measurement of HFREF; and while nonadherent to  $\beta$ -blocker therapy.

We carried out several model assessments and sensitivity analyses to ensure that our results for covariate parameters were not driven by the parametric model assumptions (constant baseline hazard functions). We fit a 2-state parametric survival analysis model (alive and dead) using the PROC LIFEREG procedure in SAS 9.2 to compare exponential, gamma, and Weibull lifetime distributions. Because the software does not allow time-varying covariates,  $\beta$ -blocker and ACE/ARB adherence were not included in these analyses. Likelihood ratio tests were conducted, and probability plots were examined to determine which parametric model best fit the data. We also fit a Cox proportional hazard survival model, as well as an unadjusted Kaplan–Meier model, for transitions from the HFREF state to death using SAS software, and compared these results with analyses of the corresponding transitions using MSM in R.<sup>18,19</sup> We chose this transition because the PROC PHREG procedure in SAS cannot address interval censoring. Proportional hazards assumptions were tested, and we found no significant deviations.

## Results

### Patient Characteristics

There were 4232 patients with a primary hospital discharge diagnosis for HF during the study period, of whom 1819 patients (43%) did not have 2 LVEF tests 30 days apart during the study period, resulting in a final cohort of 2413 patients. Of the 2413 patients, 1204 (49.9%) died, 272 (11.3%) were censored because of loss to follow-up, and 937 (38.8%) were censored at the end of the study interval. The mean follow-up time was 4.4 years (SD, 2.4 years). Patients who were excluded from this study were, on average, older, had a similar proportion of patients who had HFPEF or HFREF, had a higher proportion of women (58.4% versus 50.1% in the cohort), had fewer ambulatory and inpatient encounters,

and had a higher mortality rate in follow-up (61.2% versus 49.9%; Table I in the online-only Data Supplement).

For patients in the study cohort, the median time between LVEF assessments was 360 days (interquartile range, 187–683 days). The majority of our diagnostic imaging was derived from echocardiograms (72%). Another 8% were derived from nuclear perfusion, and 4% were from left ventriculography during catheterization. The remaining 16% were derived from other or unknown modalities. Patient characteristics are presented comparing patients with HFPEF with those with HFREF at baseline (Table 1). Patients who had HFPEF at baseline were older and more likely to be women and white. Patients with HFPEF also had a slightly higher CCI and higher percentage of hypertension and valvular heart disease diagnoses, had fewer diagnoses of myocardial infarction and renal disease, and had more ambulatory and inpatient encounters.

### Probabilities of Transitions Between States

The median follow-up time from the time of first LVEF assessment to death, disenrollment, or to the end of the study period was 4.1 years (fifth percentile 0.8 years, 95th percentile 8.8 years). We observed 5358 visits with an assessment indicating HFPEF, of which 588 (11.0%) were followed by the next assessment indicating HFREF, 745 (13.9%) were followed by death, and there were 3147 transitions remaining in HFPEF at the next assessment. There were 2825 visits with an assessment indicating HFREF, of which 598 (21.2%) were followed by the next assessment indicating HFPEF, 459 (16.2%) were followed by death, and there were 1437 transitions remaining in HFREF at their next LVEF assessment (Table 2). The estimated transition probabilities at several follow-up times are shown in Table 3. For similar patients with HFPEF, after 5 years, there was a 15% probability they would remain as HFPEF (95% confidence interval [CI], 11%–19%), a 33% probability they would decline to HFREF (95% CI, 26%–40%), and a 52% probability they would die (95% CI, 43%–61%). For similar patients with HFREF, after 5 years, there was a 13% probability they would improve to HFPEF (95% CI, 10%–17%), a 31% probability they would remain as HFREF (95% CI, 23%–38%), and a 56% probability they would die (95% CI, 47%–66%).

### Covariate Effects on Transition Rates

Estimates of covariate associations with state changes are shown in Table 4. Women were more likely than men to transition from HFREF to HFPEF. CCI score and renal disease were not significantly associated with transitions between HFPEF and HFREF; however, patients who had a history of valvular heart disease were less likely to transition between the HFPEF and HFREF states. Patients with a history of myocardial infarction were more likely to transition from HFPEF to HFREF, and patients who had a history of hypertension were more likely to transition from HFREF to HFPEF. Patients who had a history of HFREF were less likely to transition from HFPEF to HFREF and more likely to transition from HFREF to HFPEF compared with those with no history of HFREF.

Analysis of  $\beta$ -blocker therapy indicated that patients were more likely to transition from HFREF to HFPEF during periods when they were  $\geq 80\%$  adherent to the drug compared with periods when they were  $<80\%$  adherent. Analysis of ACE/ARB adherence showed that patients who were adherent were not significantly associated with transitions between HFREF and HFPEF states; however, patients who were not prescribed an ACE/ARB were less likely to transition from HFPEF to HFREF.

Patients in the HFREF state with renal disease were more likely to die, but there was no significant association of renal disease with death for patients in the HFPEF state. Previous



history of HFREF was associated with a greater likelihood of death in HFPEF but a decreased likelihood of death in HFREF. We also found that patients in either HFPEF or HFREF states were less likely to die during periods when they were  $\geq 80\%$  adherent to  $\beta$ -blockers or ACE/ARB drugs than when they were  $<80\%$  adherent but were more likely to die in the HFREF states if they were not prescribed the drug compared with those who were on drug but were  $<80\%$  adherent. Patients adherent to  $\beta$ -blockers were also more likely to die in HFPEF if they were not prescribed the drug compared with those who were on drug but were  $<80\%$  adherent.

### Model Fit Assessment and Sensitivity Analyses

Parametric survival analysis showed that both Weibull and gamma baseline time to event distributions provided statistically better fits than the exponential distribution ( $P < 0.0001$  for both); however, with large sample sizes, even small differences in model fit are typically highly significant. Covariate parameter estimates and CIs were similar among the 3 models (Table II in the online-only Data Supplement), providing confidence that the lack of fit in the baseline hazard function did not substantially affect estimation of covariate effects, our primary interest. Survival plots, including Kaplan–Meier–unadjusted, Cox-adjusted for covariates, and MSM-adjusted for covariates, demonstrated similar shapes, indicating that the exponential survival time assumption made by MSM is not unreasonable (Figure I in the online-only Data Supplement). Analysis of transitions from HFREF to death for Cox regression, the 2-state MSM, and the full MSM using all states also yielded similar hazard ratios and significance levels for each covariate (Table EI in the onlineonly Data Supplement). Thus, the sensitivity analyses suggest that the primary MSM approach was robust.

### Discussion

In this contemporary, community-based HF cohort who underwent routine, clinically based cardiac imaging on  $>1$  occasion, we found that LVEF changed to the extent that the classification of preserved and reduced LVEF was not static in a substantial proportion of patients. Specifically, during a 5-year period, we estimated that the probability was  $>1$  in 3 that patients with HFPEF would experience a transition to HFREF, and conversely the estimated probability was  $>1$  in 8 that patients with HFREF would experience a transition to HFPEF. Patient demographics and clinical characteristics were correlated with changes between HFPEF and HFREF. Female sex, hypertension, and  $\beta$ -blocker adherence were all associated with a tendency toward HFPEF through higher rates of transition from HFREF to HFPEF and lower rates of transition from HFPEF to HFREF. These findings significantly enhance our understanding of the natural history of LVEF in patients with HF and have implications for the diagnostic and therapeutic approach to patients with HF.

Although creating a diagnostic dichotomy of HFPEF and HFREF in populations with HF is convenient for defining evidence-based therapy and characterizing prognosis, this study adds to the literature, suggesting that the epidemiology of this important clinical characteristic is more nuanced than traditionally presented. Clinical trials evidence, primarily from studies of  $\beta$ -blockers in HFREF, suggest that evidence-based therapy with  $\beta$ -blockers has the potential to improve LV systolic function.<sup>12,13</sup> However, these trials were restricted to patients with HFREF at baseline, and it is well known that clinical trial populations often bear little resemblance to those treated in practice.<sup>6</sup>

Our study complements and expands on recent observational studies assessing changes in LV systolic function in community populations. The Registry to Improve the Use of Evidence-based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) study found that  $>1$  in 4 outpatients with HF experienced more than a 10% improvement in LVEF

in a 2-year period.<sup>3</sup> Women, patients without ischemic heart disease, and those treated with digoxin were most likely to experience an improvement in LVEF. However, it only focused on patients with HFREF, precluding assessment of changes in LVEF among patients with HFPEF. Furthermore, this study only included patients who survived 2 years from enrollment and underwent subsequent testing, introducing the possibility of important survival bias. Similarly, in a cohort study of 1233 patients in Olmsted County, MN,  $\approx$ 40% of patients with baseline HFREF experienced an improvement in LVEF, whereas a similar proportion of those with baseline HFPEF experienced a decline in LVEF.<sup>4</sup> Women, younger patients, those without coronary disease, and those receiving evidence-based therapies were most likely to experience improvements in LVEF. Changes in LVEF were also important to prognosis, with declines associated with higher mortality and improvements associated with better survival. However, this study was conducted in a socio-demographically homogenous population during a period of time when HF therapy was evolving (1984–2009), potentially limiting the applicability of the findings to more diverse cohorts of patients treated in clinical practice today. In addition, therapy in this cohort was characterized only by treatments at baseline rather than during follow-up.

Our study identified important demographic and clinical characteristics associated with changes in LVEF over time. Compared with men, women with HFPEF were less likely to experience a decline in LVEF, and those with HFREF were more likely to improve. This is concordant with the epidemiological finding in cross-sectional studies in cohorts with HF that the female sex is strongly correlated with preserved LVEF.<sup>23</sup> The reasons for this finding are unclear but may relate to differential ventricular responses to stimuli such as pressure overload.<sup>24</sup> We also found that patients with hypertension were more likely to experience an improvement from HFREF to HFPEF. This finding supports the hypothesis that LV systolic dysfunction attributable to hypertension is more likely reversible than that of other causes.<sup>25</sup> In identifying characteristics associated with changes in LVEF, or the lack thereof, our study has possible implications for decision making on subsequent imaging in patients with HF.

Consistent with the literature from clinical trials, we found that  $\beta$ -blocker therapy was associated with improvements in LVEF among patients with HFREF, as well as improved survival. Indeed, the benefits of  $\beta$ -blocker therapy may be partially exerted by their effects on systolic function.<sup>12,13</sup> These findings further emphasize the importance of providing  $\beta$ -blockers to those patients with HFREF without contraindications, as well as the importance of patient adherence to evidence-based HF therapy. In contrast, ACE/ARB adherence was not associated with improvements in LVEF, despite some evidence from trials suggesting that such therapy may slow or reverse LV systolic dysfunction.<sup>26</sup> For both  $\beta$ -blockers and ACE/ARB, therapy in our cohort was associated with significantly lower mortality, supporting the importance of evidence-based HF therapies in patients seen in real-world practice.

From a methodological standpoint, this study illustrates the value of the MSM approach in analyzing data involving the potential for multiple changes in health states. Indeed, prior observational studies of this topic used either generalized estimating equations or linear mixed effects regression to assess the clinical characteristics associated with changes in LVEF.<sup>3,4</sup> Those approaches are constrained in their ability to account for multiple changes in LVEF over time or to include qualitative assessments of HF status, thus potentially obscuring important information in many patients.

## Limitations

Although this is the largest contemporary cohort study to examine changes in LVEF in patients with HF, certain factors should be considered in the interpretation of these results.

First, these data are observational, and the times of ascertainties of LVEF were clinically driven rather than because of a fixed protocol. In particular, patients may be more likely to receive LVEF assessments when they are less well, which could result in some upward bias in the estimated hazard of transitions from HFPEF to HFREF, or less likely to receive LVEF assessments when they are nearing end of life, which could result in some downward bias. Such a link between the observed time and outcome processes is not easily included in the model used in the analysis. We would not expect this to affect estimates of hazard ratios for covariates. In addition, assessments of LVEF are based on estimates, which like all measurements are subject to some degree of variability. This variability could amplify the proportions of patients who experienced a change in LVEF category. However, presuming that the variability in measurement is unrelated to the patient's clinical profile, such misclassification would likely bias our estimates of those factors related to changes in LVEF toward the null, resulting in an underestimate of the strength of these relationships. Second, because we focused on changes in LVEF, we were required to limit the study to patients with 2 documented measurements of LVEF. However, the measurements used were those applied in clinical practice in a diverse clinical cohort of patients with both HFPEF and HFREF with detailed follow-up on clinical outcomes and clinical factors including changes in therapy over time.

We had limited capacity to collect data on some clinical characteristics that could influence changes in LVEF over time, including alcohol or drug abuse or resynchronization therapy, as well as interval clinical events (eg, incident myocardial infarction). Because adherence was assessed by prescriptions filled and because we do not have adequately detailed clinical data in follow-up to identify medication discontinuation, some patients whose medications were discontinued may be misclassified as nonadherent. Finally, because we did not have detailed clinical data in follow-up, we were unable to determine changes in symptom status and confirm whether the patients continued to have HF signs or symptoms.

## Conclusions

During serial follow-up of LVEF in clinical practice in a representative cohort of patients previously hospitalized with HF, changes between HFREF and HFPEF are common. Adherence to  $\beta$ -blocker therapy, age, sex, and coexisting conditions, particularly prior myocardial infarction, are important predictors in determining state changes in LVEF in patients with HF. These findings highlight the limitations of considering patients with HF according to a simple dichotomy of systolic function at a single point in time and have implications for surveillance and therapy in the clinical care of patients with HF.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**WHAT IS KNOWN**

- The dichotomy of left ventricular ejection fraction (LVEF) into reduced and preserved ejection fraction is central to the evaluation and management of heart failure.
- LVEF informs drug and device therapy and is a determinant of prognosis.
- Previous studies examining changes in LVEF over time have largely focused on patients with reduced LVEF or have been limited to homogenous populations.

**WHAT THE STUDY ADDS**

- Changes in LVEF in this diverse community-based cohort of patients with heart failure were common: 22% of the cohort of 2413 patients experienced a transition from preserved to reduced LVEF, and 23% of patients experienced a transition from reduced LVEF to preserved LVEF.
- Women, patients with hypertension, and adherence to  $\beta$ -blocker medications were associated with improvements in LVEF.
- A greater understanding of the patterns of change in LVEF help guide clinicians in decisions about the frequency of follow-up, drug therapy, and prognostic counseling.

Table 1

## Patient Characteristics at Time of First LVEF Test

Variable	HFPEF n (%) or Mean (SD) or Median (p5, p95) (n=1613)	HFREF n (%) or Mean (SD) or Median (p5, p95) (n=800)	P Value*
Age,y	72.60020(10.5)	69.1 (11.1)	<0.0001
Female sex	913 (56.6%)	297 (37.1%)	<0.0001
Race/ethnicity			0.0044
White	703 (43.6%)	299 (37.4%)	
Non-white or Hispanic	149 (9.2%)	98 (12.2%)	
Unknown	761 (47.2%)	403 (50.4%)	
Socioeconomic status			0.649
Above poverty	1220 (75.6%)	598 (74.8%)	
Below poverty	302 (18.7%)	161 (20.1%)	
Unknown	91 (5.6%)	41 (5.1%)	
Charlson comorbidity index <sup>†</sup>	3 (0,7)	2(0,5)	<0.0001
Cerebrovascular disease	419(26.0%)	136 (17.0%)	<0.0001
Chronic pulmonary disease	1214 (75.3%)	498 (62.3%)	<0.0001
Dementia	64 (4.0%)	12 (1.5%)	0.0011
Diabetes mellitus	758 (47.0%)	338 (42.3%)	0.0276
Diabetes mellitus with chronic complications	509 (31.6%)	218 (27.3%)	0.03
Hemiplegia or paraplegia	41 (2.5%)	13 (1.6%)	0.1517
Hypertension	1481 (91.8%)	630 (78.8%)	<0.0001
Malignancy, including leukemia and lymphoma	281 (7.4%)	89 (11.1%)	<0.0001
Metastatic solid tumor	69 (4.3%)	16 (2.0%)	0.0043
Mild liver disease	88 (5.5%)	31 (3.9%)	0.0914
Myocardial infarction	525 (32.5%)	347 (43.4%)	<0.0001
Peptic ulcer disease	137 (8.5%)	37 (4.6%)	0.0005
Peripheral vascular disorder	460 (28.5%)	170 (21.3%)	0.0001
Renal disease	588 (36.5%)	229 (28.6%)	0.0001
Rheumatologic disease	120 (7.4%)	45 (5.6%)	0.0964
Valvular heart disease	889 (55.1%)	358 (44.8%)	<0.0001
Median no. of ambulatory encounters per Patient	112 (32,308)	80 (18,227)	<0.0001
Median no. of inpatient encounters per Patient	10 (2,31)	7 (1,25)	<0.0001

CCI indicates Charlson comorbidity index; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

\* *t* test,  $\chi^2$ , Mantel-Haenszel  $\chi^2$ , or Wilcoxon rank sum as appropriate.

<sup>†</sup> Modified CCI does not include congestive heart failure, hypertension, myocardial infarction, renal disease, or valvular heart disease. All other components of the modified CCI are listed, with the exception of AIDS and moderate/severe liver disease because of <5 patients having these conditions.

**Table 2**

Observations During the Study Period

	New State		
	HFPEF	HFREF	Death Censored
Prior State HFPEF	3147	588	745
HFREF	598	1437	459
			331

HFPEF indicates heart failure preserved ejection fraction; and HFREF, heart failure reduced ejection fraction.



**Table 3**

Estimated Transition Probability Matrices at Several Points of Follow-Up for the Primary Model

	<b>6 mo (95% CI)</b>	<b>1 y (95% CI)</b>	<b>2 y (95% CI)</b>	<b>5 y (95% CI)</b>
HFPEF→HFPEF	0.63(0.51–0.74)	0.44(0.31–0.57)	0.27(0.21–0.38)	0.15(0.11–0.19)
HFPEF→HFREF	0.32(0.21–0.44)	0.45 (0.33–0.57)	0.50(0.41–0.56)	0.33 (0.26–0.40)
HFPEF→Death	0.05 (0.04–0.07)	0.11 (0.08–0.15)	0.23(0.18–0.28)	0.52(0.43–0.61)
HFREF→HFPEF	0.13(0.08–0.18)	0.18(0.13–0.23)	0.20(0.15–0.24)	0.13(0.10–0.17)
HFREF→HFREF	0.78 (0.72–0.83)	0.65(0.59–0.71)	0.51 (0.44–0.58)	0.31 (0.23–0.38)
HFREF→Death	0.09(0.07–0.12)	0.16(0.12–0.22)	0.29 (0.23–0.36)	0.56 (0.47–0.66)

Modeled for a 70-y-old patient with Charlson comorbidity index of 3 and all other covariates set to their referent value. CI indicates confidence interval; HFPEF, heart failure preserved ejection fraction; and HFREF, heart failure reduced ejection fraction.

Table 4

## Estimated Hazard Ratios for Predictors of State Changes

	HFPEF to HFREF (95% CI)	HFPEF to Death (95% CI)	HFREF to HFPEF (95% CI)	HFREF to Death (95% CI)
Female (male, referent)	0.93 (0.69–1.26)	0.97 (0.79–1.18)	1.85 (1.38–2.47)	1.01 (0.8–1.26)
Age(per 10-yr increase)	0.91 (0.80–1.03)	1.58 (1.42–1.76)	0.89 (0.79–1.00)	1.64 (1.46–1.84)
Charlson comorbidity index	1.02(0.93–1.12)	1.05 (1.00–1.1)	1.05(0.95–1.16)	1.09(1.03–1.15)
Myocardial infarction	1.75 (1.26–2.42)	0.87 (0.70–1.10)	0.8(0.58–1.10)	0.96 (0.77–1.20)
Renal disease	1.32 (0.93–1.87)	1.11 (0.91–1.37)	1.37 (0.97–1.93)	1.32 (1.06–1.65)
Hypertension	1.11 (0.75–1.65)	0.82 (0.59–1.15)	1.68(1.18–2.39)	0.99 (0.74–1.33)
Valvular heart disease	0.65 (0.48–0.87)	0.98 (0.81–1.18)	0.67(0.51–0.90)	1.04 (0.85–1.28)
Past HF history (no HFREF referent)				
Has had HFREF in past	0.36 (0.25–0.53)	1.63 (1.03–2.57)	3.08 (2.07–4.56)	0.65 (0.44–0.96)
Has not had any prior assessment	0.84 (0.58–1.20)	...	3.19(2.25–4.53)	...
SES* (above poverty referent)				
Below poverty	1.17(0.80–1.72)	0.82 (0.63–1.07)	1.01 (0.70–1.47)	0.93 (0.72–1.20)
Unknown	0.53 (0.29–0.99)	0.73 (0.48–1.12)	0.60 (0.34–1.07)	0.81 (0.48–1.36)
$\beta$ -Blocker adherence (not adherent, PDC <sup>†</sup> <0.80 referent)				
Adherent (PDC = 0.80)	0.97 (0.69–1.35)	0.62 (0.50–0.78)	1.53(1.10–2.13)	0.68 (0.54–0.85)
Not prescribed $\beta$ -blocker	0.94 (0.63–1.40)	1.55 (1.24–1.94)	0.94 (0.63–1.40)	1.34 (1.01–1.77)
ACE/ARB adherence <sup>‡</sup> (not adherent, PDC <0.80 referent)				
Adherent (PDC = 0.80)	0.72(0.51–1.00)	0.45 (0.36–0.55)	1.07(0.76–1.51)	0.49 (0.40–0.61)
Not prescribed ACE/ARB	0.47 (0.30–0.73)	1.05 (0.81–1.37)	0.95 (0.62–1.46)	1.81 (1.14–2.88)

All covariates are time constant except  $\beta$ -blocker and ACE/ARB adherence, which were time varying. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; HF, heart failure; HFPEF, heart failure preserved ejection fraction; HFREF, heart failure reduced ejection fraction; and PDC, percent of days covered.

\* Socioeconomic status: below poverty if patient resided in area with >20% of housing in poverty or if <25% of residents had a high school education.

<sup>†</sup> Percent days covered: adherent if PDC was = 80% and nonadherent if PDC <80%.

<sup>‡</sup> ACE/ARB adherence was examined in a separate model.