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Outcomes in ambulatory chronic systolic and diastolic heart failure:

A propensity score analysis

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Abstract

Background—Prior studies of outcomes in systolic and diastolic heart failure (SHF and DHF) are often limited to mortality in hospitalized acute HF patients, and may be confounded by residual bias. In this analysis, we examined long-term mortality and hospitalization in a propensity score matched cohort of ambulatory chronic SHF and DHF patients.

Methods—Of the 7788 patients in the Digitalis Investigation Group trial, 6800 had SHF (ejection fraction ≤45%) and 988 had DHF (ejection fraction >45%). We restricted our analysis to 7617 patients without valvular heart disease: 916 with DHF and 6701 with SHF. Propensity scores for DHF, calculated for each patient by a non-parsimonious multivariable logistic regression model, were used to match 697 DHF with 2091 SHF patients. Matched Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for outcomes for DHF (versus SHF).

Results—During a median 38-month follow-up, Compared with 32% mortality in SHF, 23% of DHF patients died (HR=0.70; 95%CI=0.59-0.84; when DHF is compared with SHF). Respective HR (95%CI) for cardiovascular and HF mortality were 0.60 (0.48-0.74) and 0.56 (0.40-0.79). All-cause hospitalizations occurred in 64% of SHF and 67% of DHF patients (HR=0.99; 95%CI=0.87-1.11). Respective HR (95%CI) for cardiovascular and HF hospitalizations were 0.84 (0.73-0.96) and 0.63 (0.51-0.77).

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Ali Ahmed conceived the study hypothesis and design, and wrote the first and subsequent drafts of the paper, incorporating contributions from other authors. Ali Ahmed did the statistical analyses, which were verified for accuracy by Thomas Love. All authors interpreted the data, participated in critical revision of the paper for important intellectual content, and approved the final version of the article. Ali Ahmed had full access to the data.

Conclusions—Despite lower mortality and cardiovascular morbidity, ambulatory DHF patients had similar overall hospitalizations as SHF patients. Ejection fraction should be assessed in all HF patients to guide therapy, with special attention to non-cardiovascular morbidity in DHF patients.

Diastolic heart failure (DHF), defined as clinical heart failure (HF) with normal or near normal left ventricular ejection fraction (LVEF), is common.[1-5] With the aging of the US population, the incidence and prevalence of DHF is likely to increase in the coming decades. However, the effects of DHF on mortality and hospitalization have not been adequately defined. In a recent review of outcomes in DHF patients Hogg et al. reported wide variations in mortality and hospitalization in these patients compared to those with systolic heart failure (SHF), defined as clinical HF with low LVEF.[6]

Results from studies comparing outcomes in SHF and DHF patients are often based on multivariable risk-adjusted mortality in hospitalized HF patients.[1, 2, 4, 6, 7] Many of these studies included HF patients with valvular heart disease and arrhythmias (especially atrial fibrillation).[4,8-10] On the other hand, community-based studies of outcomes in DHF suffer from small sample sizes.[1, 2, 7]

Propensity score (PS) methodology is commonly used to reduce the impact of selection bias when comparing exposures and allows for post-risk adjustment evaluation of residual bias using standardized differences between covariates.[11-21] The objective of our study was to compare the effect of DHF versus SHF on mortality and hospitalization in a PS-matched cohort of ambulatory chronic HF patients.

METHODS

Study Design

The randomized DIG clinical trial was conducted in the early 1990's to determine the effects of digoxin on outcomes in HF. DIG enrolled both SHF (LVEF ≤45%) and DHF (LVEF >45%) patients. The detailed design and results of the trial have been published elsewhere.[22-24] We conducted a secondary analysis of the DIG dataset obtained from the National Heart, Lung, and Blood Institute, who sponsored the trial.

Patients

In the DIG trial, of the total of 7788 HF patients in normal sinus rhythm, 6,800 had SHF and 988 had DHF. HF was diagnosed by clinical symptoms, signs, and radiographic evidence of pulmonary congestion. Patients were recruited irrespective of their HF etiology or New York Heart Association (NYHA) functional class. For the present analysis, we excluded 171 patients with valvular heart disease as the primary etiology of their HF. Of the remaining 7617 patients, 916 had DHF. We focused our current analysis on a subset of 2788 patients based on a PS matching.

Assessment of Left Ventricular Ejection Fraction

Data on most recent left ventricular ejection fraction (LVEF) were obtained for all DIG participants before enrollment. LVEF was measured at the time of randomization if the prior LVEF was not measured in the six months prior to randomization.[25] LVEF was calculated using contrast left ventriculography, radionuclide ventriculography, and two-dimensional echocardiography, in that order of preference.[23]

Outcomes

The primary outcomes for this analysis were all-cause mortality and all-cause hospitalization during follow up (median: 37.9 months overall; 37.8 months for SHF and 38.1 months for

DHF). Secondary outcomes included mortality due to cardiovascular causes and worsening HF, and hospitalizations due to cardiovascular causes, including those due to worsening HF, ventricular arrhythmias / cardiac arrest, supra-ventricular arrhythmias, acute myocardial infarction, unstable angina, and coronary revascularization.

Statistical Analysis

Estimation of PS—Because patients do not randomly develop DHF or SHF, there are significant imbalances in baseline covariate distribution between DHF and SHF patients as is evident from Table 1 (pre-match panel; descriptive analysis based on Chi-square and Wilcoxon rank sum tests, as appropriate). To account for this imbalance, we calculated PS for DHF for each patient using a non-parsimonious multivariable logistic regression model, with consideration of clinically plausible interactions. Covariates in that model included all measured baseline patient characteristics shown in Table 1 (except for LVEF and digoxin use by randomization). The PS for DHF estimates the conditional probability that a patient would have developed DHF given the patient's measured baseline characteristics.[11-20] Chronic kidney disease was defined as a glomerular filtration rate <60 ml/1.73 square meter.[26] The model was well calibrated and discriminated effectively between DHF and SHF (c statistic=0.78).

Matching by PS—Matching patients on PS tends to effectively balance the distribution of all measured covariates, thus substantially reducing bias, as is apparent from Table 1 (post-match panel).[21, 27] Although PS are frequently used to balance baseline covariates between two treatment groups,[18-20] they have also been used to balance baseline covariates between two groups of patients with and without certain comorbidity or risk factors.[28-30] Using an SPSS matching macro,[31] we matched 697 (76%) of the 916 DHF patients to three unique SHF patients each, for a total of 2,091 matched SHF patients.

Evaluation of post-match covariate balance—We compared the balance of baseline covariates between SHF and DHF patients before and after matching using standardized differences, which directly describe the observed bias in the means (or proportions) of covariates across two groups, expressed as a percentage of the pooled standard deviation (Figure 1).[15, 17, 19, 20] We also used Chi-square and Wilcoxon rank-sum tests as appropriate to compare baseline characteristics (Table 1).

Estimating the effect of DHF on outcomes—We used Kaplan-Meier survival analyses to compare various outcomes between patients with SHF and DHF in the matched cohort. We then used Cox proportional hazards models to estimate the association of DHF with various outcomes. We accounted for matching by stratifying the model based on a variable that identified the matched groups.[19, 20] We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. We then used multivariable matched Cox regression models to estimate the effect of DHF on various outcomes. Covariates included were the same as those used in the logistic regression model for PS and were entered forward stepwise into the models.

Sensitivity analysis—To address concerns about incomplete matching, we analyzed data from all 7617 patients (pre-match) cohort, using direct regression adjustment for the PS. Then, we estimated the association between DHF and outcomes in bivariate and multivariable Cox regression models adjusting for all covariates used in the PS estimation (forward stepwise entry). Finally, we repeated these analyses using LVEF as a continuous variable.

Subgroup analysis—To examine whether the association of DHF with all-cause mortality was homogeneous across various subgroups of patients, we conducted subgroup analyses in

the pre-match cohort.[32] We first calculated absolute risks, and then formally tested for first-order interactions in Cox proportional hazards models, entering interaction terms between DHF and the subgroups. All statistical tests were evaluated using a two-tailed 95% confidence level. All data analyses were performed using SPSS for Windows version 14.[33]

RESULTS

Baseline Patient Characteristics

Before matching, compared with DHF patients, SHF patients were more likely to be young, male, and have longer duration of HF, ischemic heart disease, receive angiotensin-converting enzyme (ACE) inhibitors, and have higher NYHA class symptoms. Patients in the matched cohort had a mean (±SD) age of 65.8 (±10.1) years, 31.8% were women and 12.9% were non-whites.

PS Matching and Covariate Balance

The distributions of baseline covariates between DHF and SHF patients before and after matching are displayed in Table 1 and Figure 1. After matching, standardized differences for all observed covariates were below 10% in absolute value, suggesting substantial improvement in covariate balance between DHF and SHF patients (Figure 1). Mean PS for unmatched and matched SHF (0.0698 vs. 0.1720; p <0.0001) and DHF (0.1718 vs. 0.5250; p <0.0001) patients and a graphical assessment (not shown) indicate that patients excluded in the matching process were at the extremes of the PS distribution, as is usual.

Outcomes

During 38 months of median follow up, 836 (30%) of the 2788 PS matched patients died from all causes, 637 (23%) died from cardiovascular causes, and 262 (9%) died due to worsening HF. During the same follow up period, 1805 patients (64.7%) were hospitalized from all causes, with an average 1.8 hospitalizations for each patient. There were 1375 (49.3%) hospitalizations due to cardiovascular causes, and 684 (24.5%) due to worsening HF.

Matched Pairs Mortality

Compared with 32% mortality in SHF patients during a median follow up of 37.8 months, 23% of DHF patients died during a median follow up of 38.1 months (hazard ratio {HR} =0.70; 95% confidence interval {CI} =0.59-0.84); p <0.0001; Table 2). Death due to cardiovascular causes occurred in 25% of SHF and 17% of DHF patients (HR =0.60; 95% CI =0.48-0.74); p <0.0001; Table 2). HF mortality occurred in 11% of SHF and 6% of DHF patients (matched pairs HR =0.56; 95% CI =0.39-0.79); p =0.001; Table 2). Kaplan-Meier plots for all-cause, cardiovascular and HF mortality for SHF and DHF patients are displayed in Figures 2a, 2b, and 2c. The associations between DHF and various causes of mortality remained essentially unchanged after multivariable adjustment for covariates (Table 2).

Multivariable Risk-Adjusted Mortality

In the pre-match cohort of 7617 patients, compared with 35% of SHF patients, 23% of DHF patients died (unadjusted HR =0.62; 95% CI =0.54-0.71; p <0.0001). Adjustment for PS alone (adjusted HR =0.76; 95% CI =0.66-0.88; p <0.0001) or multivariable adjustment for other covariates (adjusted HR = 0.82; 95% CI = 0.71 - 0.95; p =0.008) weakened the association, but it remained significant. The association remained significant when LVEF was used as a continuous variable (adjusted HR =0.983; 95% CI =0.980 - 0.987; p <0.0001).

Matched Pairs All-Cause Hospitalizations

Compared with 64% all-cause hospitalizations in SHF patients during a median 44.8 months of follow up, 66% of DHF patients were hospitalized from all causes during a median follow up of 48 months (HR =0.99; 95% CI =0.87-1.11). Kaplan-Meier plots for time to first hospitalization due to all causes are displayed in Figure 3a. The association between DHF and all-cause hospitalization remained essentially unchanged after multivariable covariate adjustment (Table 3). There was no difference in the number of hospitalizations between the two groups (mean, 1.8 for each group, p =0.906).

Multivariable Risk-Adjusted All-cause Hospitalization

In the pre-match cohort of 7617 patients, compared with 66% of SHF patients, 67% of DHF patients were hospitalized from all causes (unadjusted HR =0.97; 95% CI =0.89-1.05; p =0.405). The association remained essentially unchanged after adjustment for PS alone (adjusted HR =1.02; 95% CI =0.93-1.12; p =0.673), multivariable covariate adjustment (adjusted HR = 1.08; 95% CI = 0.99 - 1.18; p =0.096), or when LVEF was used as a continuous variable (adjusted HR =0.999; 95% CI =0.997-1.002; p =0.582).

Cardiovascular Hospitalizations

Compared with 51% of SHF patients who were hospitalized due to cardiovascular causes during a median follow up of 63 months, 46% of DHF patients were hospitalized from cardiovascular causes during a median follow up of 75 months (HR =0.84; 95% CI =0.73-0.96). Kaplan-Meier plots for time to first hospitalization due to cardiovascular causes are displayed in Figure 3b. The association between DHF and all-cause hospitalization remained essentially unchanged after multivariable covariate adjustment (Table 3). In the pre-match cohort of 7617 patients, unadjusted, PS adjusted and multivariable adjusted HR (95% CI) for cardiovascular hospitalization, when DHF was compared with SHF, were respectively 0.82 (0.74-0.91; p <0.0001), 0.89 (0.80-0.99; p =0.026) and 0.93 (0.84-1.04; p =0.201).

Heart Failure Hospitalizations

Compared with 27% of SHF patients who were hospitalized due to worsening HF during a median follow up of 86 months, 18% of DHF patients were hospitalized due to worsening HF during a median follow up of 90 months (matched pairs HR = 0.63; 95% CI = 0.52 - 0.77). Kaplan-Meier plots for time to first HF hospitalization are displayed in Figure 3c. The association between DHF and all-cause hospitalization remained essentially unchanged after multivariable covariate adjustment (Table 3). In the pre-match cohort of 7617 patients, unadjusted, PS adjusted and multivariable adjusted HR (95% CI) for HF hospitalization, when DHF was compared with SHF, were respectively 0.55 (0.47-0.64; p <0.0001), 0.65 (0.56-0.77; p =0.026) and 0.69 (0.59-0.81; p <0.0001).

Subgroup Analysis

Associations between DHF and reduced all-cause mortality were observed in various subgroups of patients (Figure 4). DHF patients had better prognosis, regardless of age, sex, race, HF etiology, NYHA functional class, diabetes, or therapy with ACE inhibitors, diuretics or digoxin. There were no significant interactions between DHF and any of these subgroups, except for female sex (p =0.045).

DISCUSSION

The key findings of our study are that in a PS-matched cohort of ambulatory chronic HF patients, compared with SHF patients, DHF patients had reduced risk of mortality, and cardiovascular and HF hospitalizations, but similar all-cause hospitalizations. These findings

are important, as with the aging of the US population, the prevalence of HF in general, and that of DHF in particular, is expected to increase in the coming decades, with significant implications for health care utilization and costs.

Potential Mechanistic Explanation

DHF patients also share similar clinical and pathophysiologic characteristics with SHF patients, including reduction in exercise capacity, neurohormonal activation, and impairment of quality of life.[3, 24, 34 35, 36] Despite these similarities, DHF was associated with reduced mortality and cardiovascular morbidity. Even though, diastolic function was not specifically measured, most HF patients with normal or near normal have abnormal DHF.[37] Recent evidence that a significant proportion of DHF patients eventually develop SHF suggests that DHF may represent an earlier stage in the natural history of HF and thus better prognosis.[38, 39] However, do not know why overall hospitalization was similar for both SHF and DHF patients. It is possible that due to the advanced nature of the SHF patients, they had more competing cardiovascular causes for hospitalization than those with DHF.

Comparison with Prior Studies

The most commonly studied outcome in community-based comparisons of DHF patients (versus SHF) is all-cause mortality, which has yielded varying results.[1, 2, 7] In the Framingham Heart Study, 51% of the 73 patients had DHF (LVEF >50%).[1] During a median follow-up of 6.2 years, DHF patients had an unadjusted annual mortality of 8.7% (versus 18.9% in SHF). This mortality difference lost significance after adjustment for age and sex.[1] In the Cardiovascular Health Study, 4.9% of the 5532 persons ≥65 years had HF [2]. Of these, 78% had DHF (LVEF ≥45%) and 22% had SHF (LVEF <45%), who had annual mortality of about 10% and 15%, respectively. Compared with healthy controls, LVEF >55%, 45-55% and <45% were associated with respectively 48%, 140% and 88% higher risk of death.[2]

In the Olmstead County study, LVEF was known in137 of the 216 incident HF patients and 43% had DHF (LVEF ≥50%).[5] In that study, the 4 year unadjusted mortality rate was about 50% for both DHF and SHF patients. After adjustment for age, sex, NYHA class, and coronary artery disease, DHF patients had a non-significant 20% lower risk of death (adjusted relative risk =0.80; p =0.369). Curtis et al. have also reported an overall inverse association between LVEF and mortality among participants in the DIG trial.[40] However, propensity analysis and inclusion of hospitalizations as outcomes distinguish our study from theirs.

Clinical Implications

We noted that the overall hospitalization rates of patients with DHF and SHF patients were similar, suggesting that DHF patients may suffer excess morbidity from non-cardiovascular causes relative to the SHF patients. This is likely to negatively impact health care resource utilization, especially as the prevalence of HF increases with the aging of the US population. Many of these non-cardiac conditions are chronic and studies need to determine if a chronic disease management model would be effective in reducing hospitalization due to those non-cardiac causes. In addition, we also noted a non-significant increased incidence of supraventricular arrhythmias, unstable angina, and coronary revascularization in HF patients with PSF. This might be due to a higher prevalence of subclinical ischemic heart disease and presence of viable myocardium in DHF than commonly believed.[41] Future studies should investigate these associations in DHF.

Strengths and Limitations

The strengths of our study are (1) use of PS matching; (2) a relatively large number of DHF patients (n=697) compared with Framingham Heart Study (n=37),[1] Cardiovascular Health

Study (n=170),[2] and Rochester Epidemiology Project (n=83)[5]; (3) validation of HF diagnosis by cardiologist DIG investigators; (4) exclusion of patients with atrial fibrillation and valvular heart disease; and (5) examination of multiple outcomes including hospitalizations not reported before.

Our study has several limitations. First, women and elderly HF patients were underrepresented, which is reflected in the lower overall mortality rates in our analysis. Second, HF patients with atrial fibrillation and valvular heart disease were excluded. Although this was useful to avoid misclassification of DHF patients, it limits generalizability. Third, we combined LVEF >55% and 45-55% as DHF. However, overall mortality for these patients are similar (23% each).[40] Fourth, confounding due to unmeasured covariates is possible. However, an unmeasured confounder must be unrelated to all the measured covariates and also be correlated with DHF and outcomes. Finally, exclusion of patients during matching compromises generalizability. However, only patients at the extremes of PS were excluded, leaving patients with similar PS to be matched. This increased the internal validity of our study. This is important as only strong and internally valid associations should precede studies of external validity.[42]

Conclusions

In conclusion, compared with SHF, ambulatory chronic DHF patients have lower mortality, and cardiovascular and HF hospitalization, but similar overall hospitalizations, suggesting disproportionately higher non-cardiovascular comorbidity and hospitalizations in these patients. LVEF should be measured in all HF patients, for risk stratification and to guide therapy, with special attention to the assessment and management of non-cardiovascular comorbidities in those with DHF. SHF patients should be treated with an ACE inhibitor (or an angiotensin receptor blocker if intolerant to an ACE inhibitor), approved beta-blockers, and digoxin.[19, 43, 44] Diuretics should be used with caution for symptomatic patients with fluid overload.[20] Evidence-based therapy for DHF is limited. However, recent data suggest that digoxin and candesartan may be beneficial in reducing HF hospitalizations in such patients.[45, 46] Future studies needs to focus on reduction in non-cardiovascular and non-HF hospitalizations in DHF patients.

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Appendix

Addendum

Two recent reports by Bhatia et al and Owan et al, bothbased on hospitalized HF patients, published after this manuscript was accepted, reported variable outcomes in DHF, compared with SHF patients.[47,48] Using data from the Mayo Clinical hospitals in Olmstead County, MO, Owan et al reported that DHF was associated with somewhat better survival (adjusted HR 0.96; 95%CI 0.92-1.00).[48] Using data from 103 hospitals in Ontario, Canada, Bhatia et al reported similar 1-year survival for DHF compared to SHF patients (adjusted HR 1.13; 95% CI 0.96-1.36, when SHF compared with DHF).[47] Neither of these hospital-based studies,

however, used PS matching to reduce imbalances in baseline covariates between DHF and SHF groups.[48]

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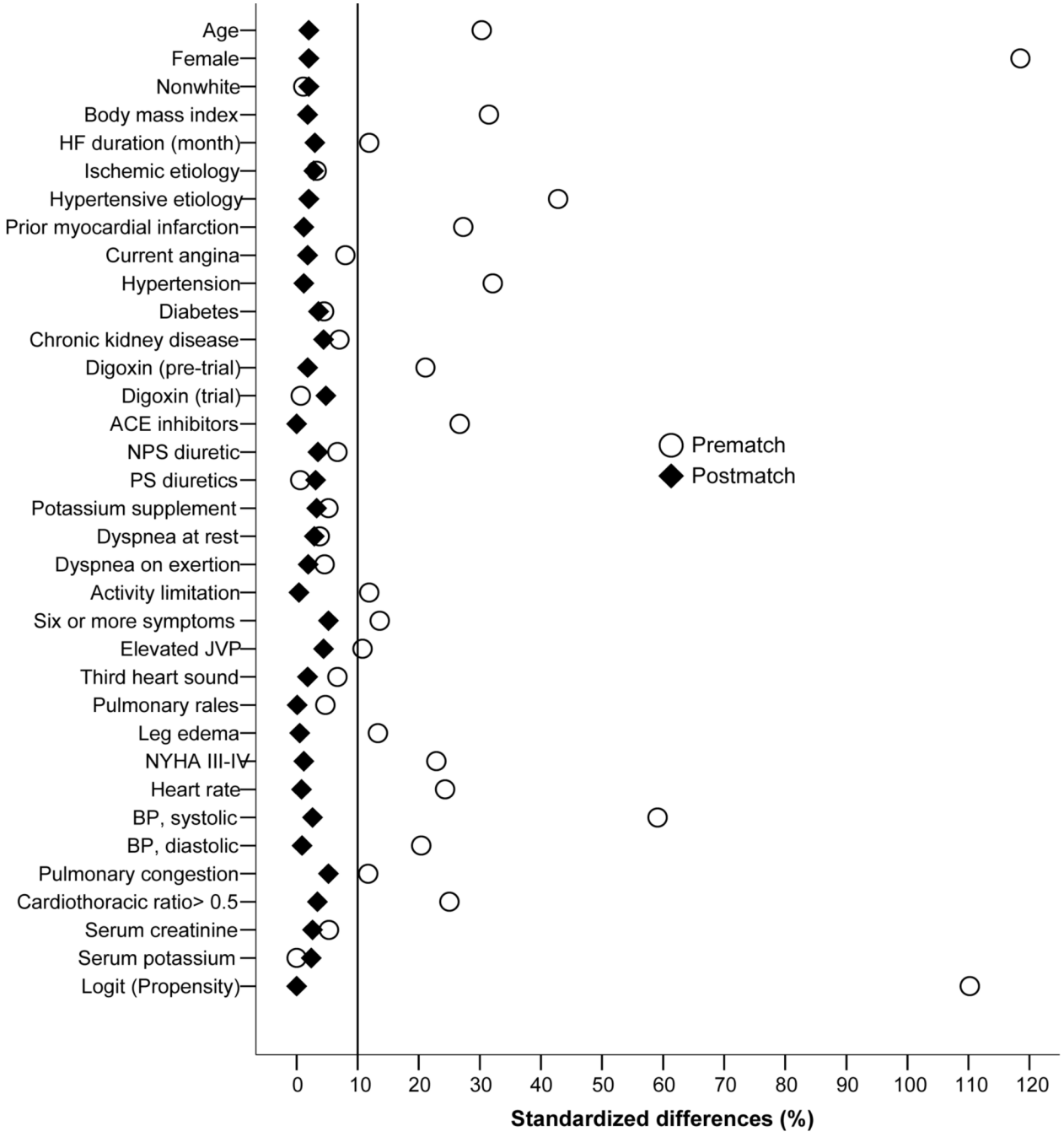
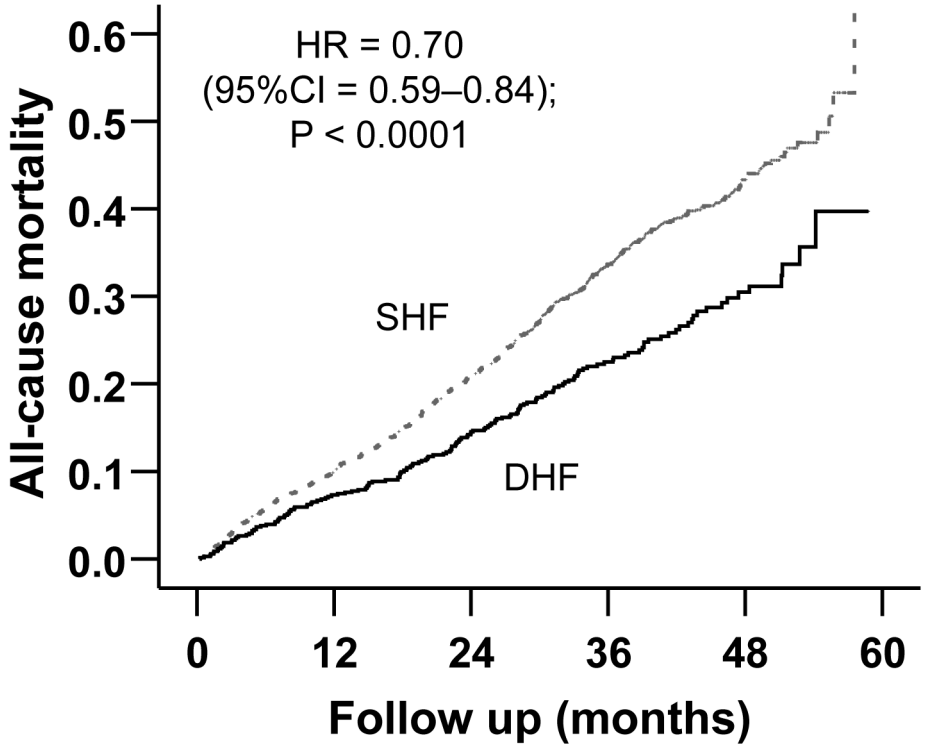


Figure 1.
Absolute standardized differences in covariates between heart failure patients with left ventricular ejection fraction ≤45% and >45%, before and after propensity score matching

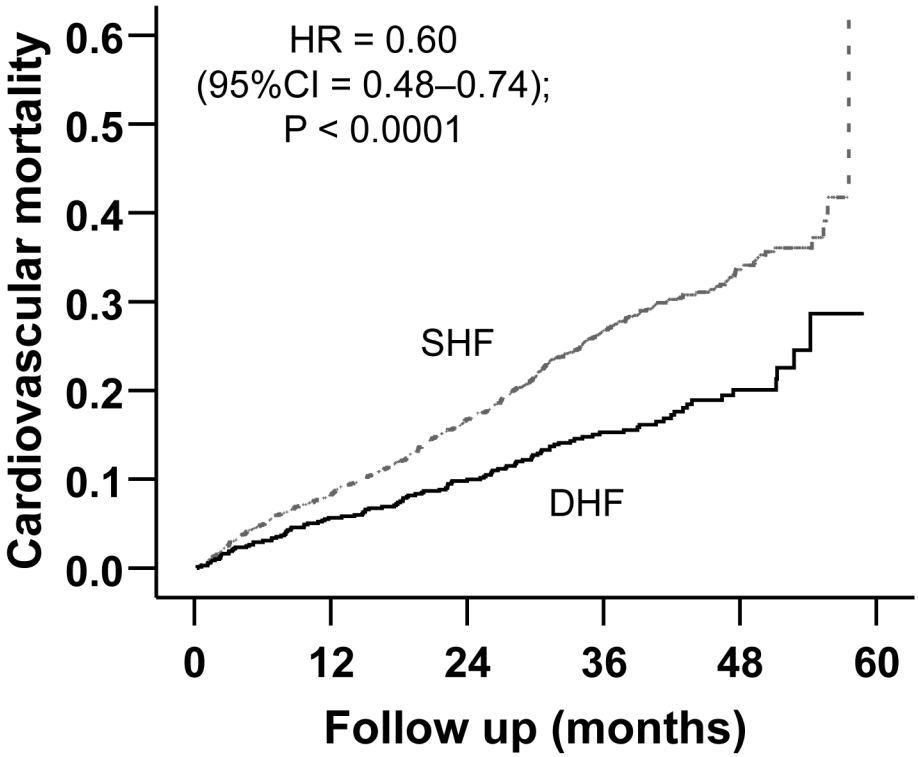
(a)



Number of patients at risk

SHF	2091	1888	1682	1148	428
DHF	697	735	683	449	165

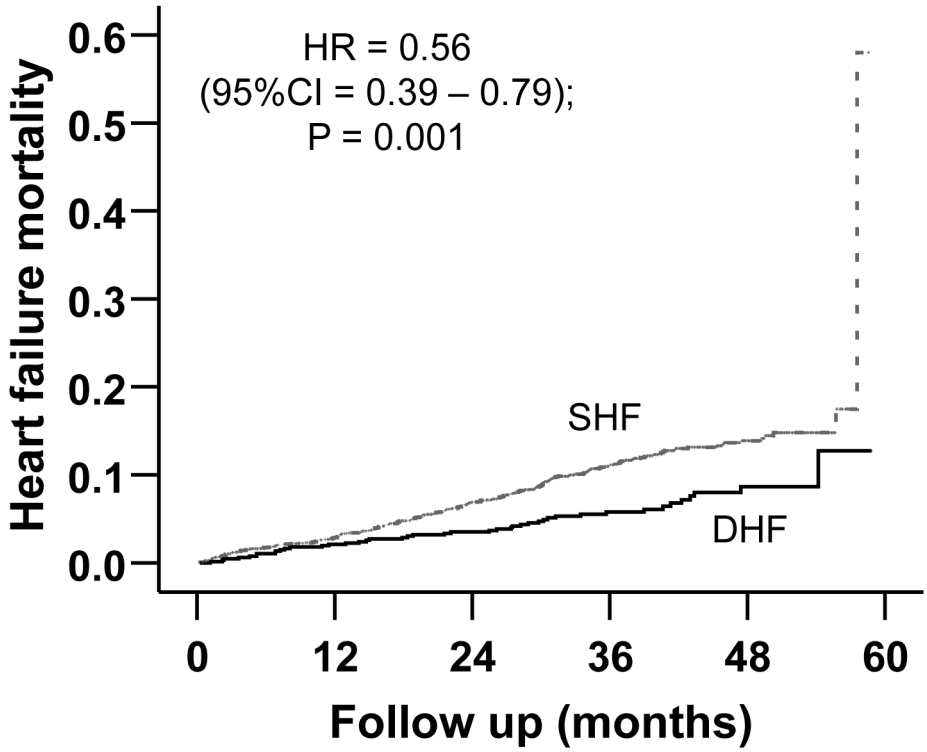
(b)



Number of patients at risk

SHF	2091	1888	1682	1148	428
DHF	697	735	683	449	165

(c)



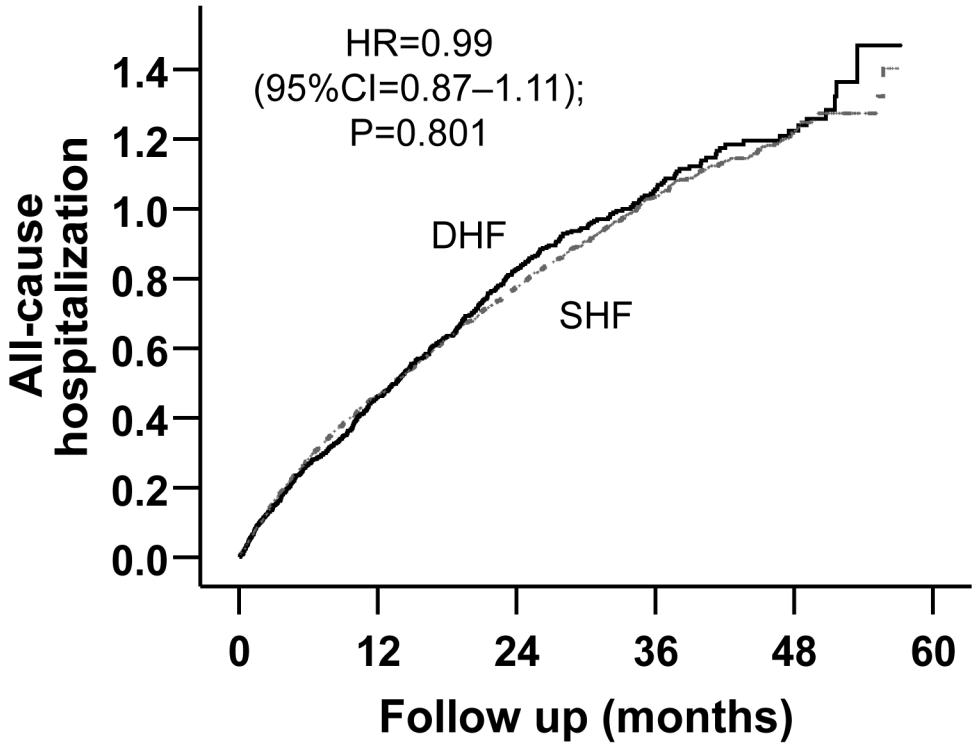
Number of patients at risk

SHF	2091	1888	1682	1148	428
DHF	697	735	683	449	165

Figure 2.

Kaplan-Meier plots demonstrating cumulative risk of mortality due to (a) all causes, (b) cardiovascular causes, and (c) heart failure, in ambulatory patients with systolic heart failure (SHF) and diastolic heart failure (DHF)

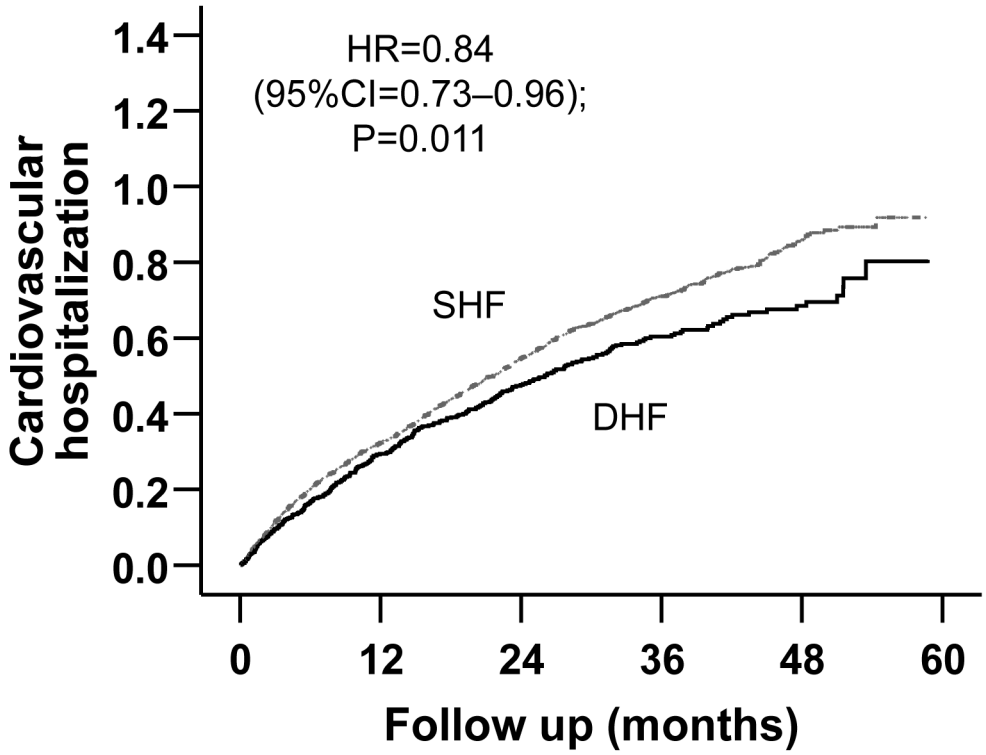
(a)



Number of patients at risk

SHF	2091	1241	877	495	174
DHF	697	431	290	165	64

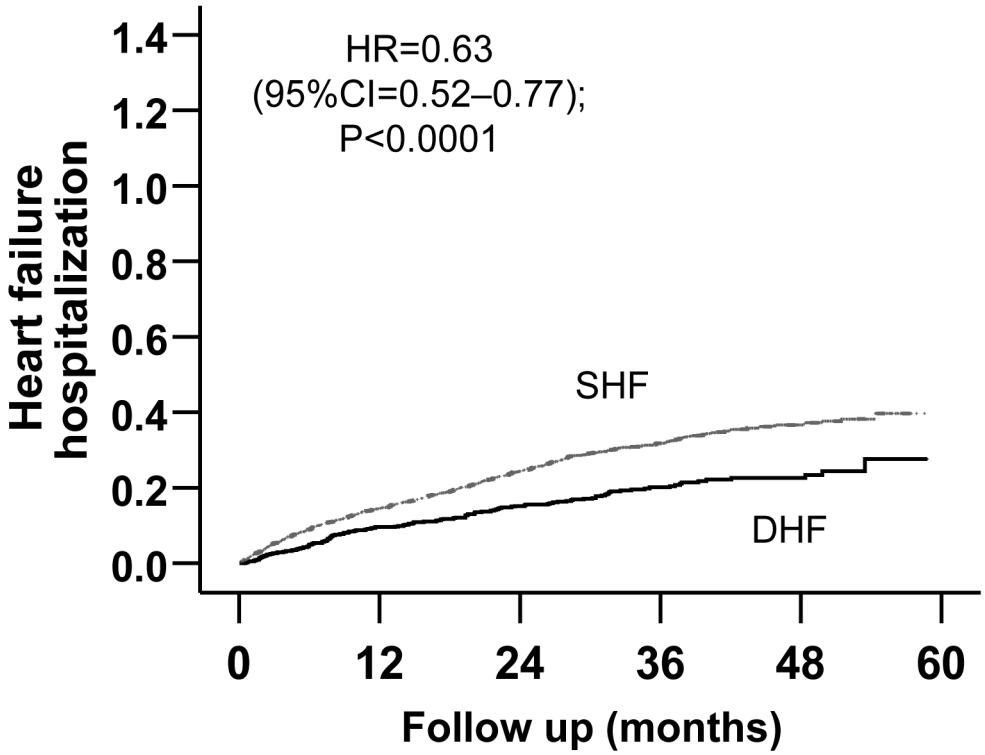
(b)



Number of patients at risk

SHF	2091	1412	1068	657	229
DHF	697	502	402	245	99

(c)



Number of patients at risk

SHF	2091	1665	1404	937	346
DHF	697	601	538	344	128

Figure 3.

Kaplan-Meier plots demonstrating cumulative risk of first hospitalizations due to (a) all causes, (b) cardiovascular causes, and (c) worsening heart failure, in ambulatory patients with systolic heart failure (SHF) and diastolic heart failure (DHF)

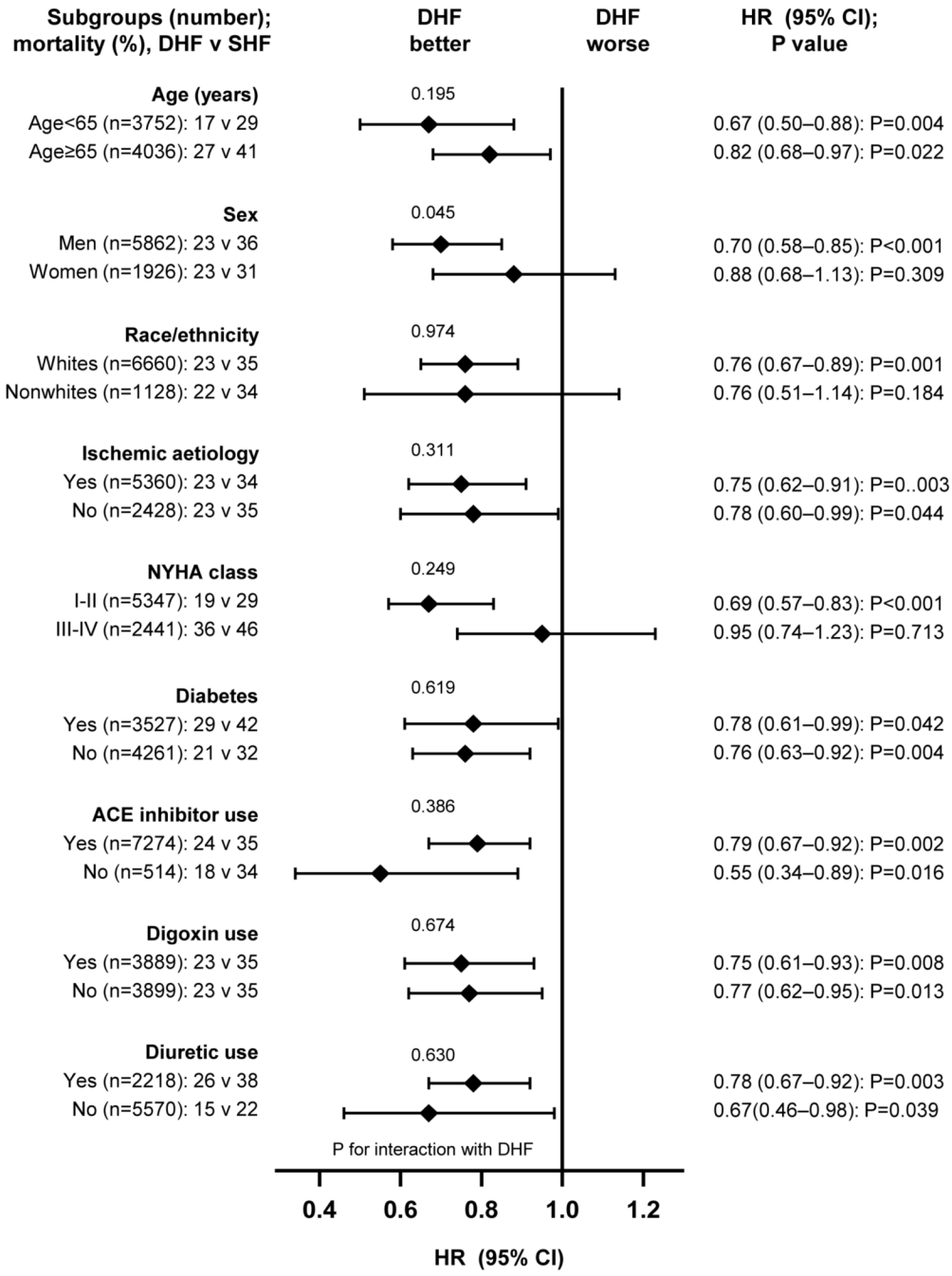


Figure 4.

Hazard ratios (HR) and 95% confidence interval (CI) for all-cause mortality in subgroups of patients with diastolic heart failure (DHF) compared with systolic heart failure (SHF) (ACE=angiotensin-converting enzyme; NYHA=New York Heart Association)

Table 1

Baseline patient characteristics in patients with left ventricular ejection fraction (LVEF) ≤45% and >45%, before and after propensity score matching

	Pre-match			Post-match		
	SHF	DHF	P	SHF	DHF	P
	N = 6701 (88.0%)	N = 916 (12.0%)		N = 2091 (75.0%)	N = 697 (25.0%)	
Age (years), mean (±SD)	63.4 (±10.9)	66.6 (±10.2)	<0.0001	65.7 (±10.1)	65.9 (±10.2)	0.667
Female	1490 (22.2%)	367 (40.1%)	<0.0001	670 (32.0%)	217 (31.1%)	0.673
Non-white	978 (14.6%)	130 (14.2%)	0.803	265 (12.7%)	94 (13.5%)	0.601
Body mass index, kilogram per square meter, mean (±SD)	27.1 (±5.2)	28.9 (±6.2)	<0.0001	28.1 (±5.6)	28.0 (±5.0)	0.717
Duration of HF (months), median	30.2 (±36.8)	26.1 (±32.2)	0.007	26.6 (±33.2)	27.2 (±33.9)	0.569
Primary cause of HF						
Ischemic	4803 (71.7%)	557 (60.8%)		1446 (69.2%)	473 (67.9%)	
Hypertensive	583 (8.7%)	222 (24.2%)		306 (14.6%)	107 (15.4%)	
Idiopathic	1007 (15.0%)	104 (11.4%)	<0.0001	270 (12.9%)	92 (13.2%)	0.946
Alcoholic	222 (3.3%)	13 (1.4%)		29 (1.4%)	12 (1.7%)	
Others	86 (1.3%)	20 (2.2%)		40 (1.9%)	13 (1.9%)	
Comorbid conditions						
Prior myocardial infarction	4402 (65.7%)	480 (52.4%)	<0.0001	1278 (61.1%)	422 (60.5%)	0.788
Current angina pectoris	1805 (26.9%)	280 (30.6%)	0.022	665 (31.8%)	216 (31.0%)	0.707
Hypertension	3043 (45.4%)	561 (61.2%)	<0.0001	1136 (54.3%)	383 (54.9%)	0.792
Diabetes mellitus	1917 (28.6%)	281 (30.7%)	0.200	643 (30.8%)	203 (29.1%)	0.447
Chronic kidney disease	2993 (44.7%)	441 (48.1%)	0.048	1009 (48.3%)	321 (46.1%)	0.335
Medications						
Pre-trial digoxin use	2968 (44.3%)	312 (34.1%)	<0.0001	768 (36.7%)	262 (37.6%)	0.684
Digoxin by randomization	3349 (50.0%)	461 (50.3%)	0.860	1052 (50.3%)	334 (47.9%)	0.294
ACE inhibitors	6332 (94.5%)	795 (86.8%)	<0.0001	1896 (90.7%)	632 (90.7%)	>0.999
Nitrate and hydralazine	103 (1.5%)	8 (0.9%)	0.140	20 (1.0%)	7 (1.0%)	>0.999
Non-potassium sparing diuretics	5243 (78.2%)	691 (75.4%)	0.056	1600 (76.5%)	523 (75.0%)	0.442
Potassium sparing diuretics	509 (7.6%)	71 (7.8%)	0.842	145 (6.9%)	54 (7.7%)	0.497
Potassium supplement	1897 (28.3%)	238 (26.0%)	0.147	564 (27.0%)	178 (25.5%)	0.488
Symptoms and signs of heart failure (past or present)						
Dyspnea at rest	4704 (70.2%)	627 (68.4%)	0.282	1418 (67.8%)	482 (69.2%)	0.491
Dyspnea on exertion	6382 (95.26%)	881 (96.2%)	0.241	2002 (95.7%)	670 (96.1%)	0.542
Activity limitation	5128 (76.5%)	653 (71.3%)	0.001	1529 (73.1%)	511 (73.3%)	0.961
Jugular venous distension	3498 (52.2%)	429 (46.8%)	0.002	1021 (48.8%)	325 (46.6%)	0.336
Third heart sound	3361 (50.2%)	299 (32.6%)	<0.0001	759 (36.3%)	259 (37.2%)	0.683
Pulmonary râles	4768 (71.2%)	671 (73.3%)	0.198	1499 (71.7%)	500 (71.7%)	>0.999
Lower extremity edema	3471 (51.8%)	535 (58.4%)	<0.0001	1129 (54.0%)	378 (54.2%)	0.930
NYHA functional class						
I	891 (13.3%)	179 (19.5%)		371 (17.7%)	122 (17.5%)	
II	3629 (54.2%)	532 (58.1%)	<0.0001	1224 (58.5%)	406 (58.2%)	0.994
III	2043 (30.5%)	194 (21.2%)		464 (22.2%)	158 (22.7%)	
IV	138 (2.1%)	11 (1.2%)		32 (1.5%)	11 (1.6%)	
Heart rate (/minute), mean (±SD)	78.7 (±12.7)	75.7 (±12.0)	<0.0001	76.1 (±12.2)	76.0 (±12.2)	0.684
Blood pressure (mm Hg), mean (±SD)						
Systolic	125.8 (±20.0)	138.0 (±21.3)	<0.0001	133.5 (±20.1)	134.0 (±19.2)	0.864
Diastolic	74.9 (±11.3)	77.2 (±11.2)	<0.0001	76.3 (±11.0)	76.4 (±10.9)	0.753
Chest radiograph findings						
Pulmonary congestion	4509 (67.3%)	565 (61.7%)	0.001	1360 (65.0%)	436 (62.6%)	0.235
Cardiothoracic ratio >0.5	4118 (61.5%)	450 (49.1%)	<0.0001	1115 (53.3%)	360 (51.6%)	0.457
Laboratory data, mean (±SD)						
Serum creatinine (mg/dL),	1.28 (±0.37)	1.26 (±0.39)	0.002	1.27 (±0.37)	1.26 (±0.39)	0.530

	Pre-match			Post-match		
	SHF	DHF	P	SHF	DHF	P
	N = 6701 (88.0%)	N = 916 (12.0%)		N = 2091 (75.0%)	N = 697 (25.0%)	
Serum potassium (mEq/L)	4.34 (±0.44)	4.34 (±0.42)	0.870	4.34 (±0.43)	4.35 (±0.42)	0.667
LVEF (%), mean (±SD)	28.5 (±8.8)	55.1 (±7.9)	<0.0001	30.7 (±8.5)	54.1 (±7.7)	<0.0001

ACE=Angiotensin-converting enzyme, HF=heart failure, JVP=jugular venous pressure, NYHA=New York heart association

Table 2

Matched hazard ratios (HR) and 95% confidence intervals (CI) for mortality in ambulatory patients with diastolic heart failure (DHF) compared with systolic heart failure (SHF)

	% event (median follow up)		Absolute SHF-DHF risk difference	Unadjusted HR for DHF (95% CI)	Adjusted* HR for DHF (95% CI)
	SHF (n=2091)	DHF (n=697)			
All-cause mortality	32.2% (38 months)	23.2% (38 months)	-9.0%	0.70 (0.59 - 0.84); P<0.0001	0.73 (0.61 - 0.89); P=0.002
Cardiovascular mortality	25.3% (38 months)	17.1% (38 months)	-8.2%	0.60 (0.48 - 0.74); P<0.0001	0.60 (0.47 - 0.75); P<0.0001
Heart failure mortality	10.5% (38 months)	6.2% (38 months)	-4.3%	0.56 (0.39 - 0.79); P=0.001	0.58 (0.39 - 0.85); P=0.006

*Adjusted for matching, and the following covariates, which were entered forward stepwise: age, female sex, non-white race, body mass index, duration and etiology of heart failure, past myocardial infarction, current angina, hypertension, diabetes, pre-trial use of digoxin, digoxin use during trial, use of angiotensin-converting enzyme inhibitors, combined use of hydralazine and nitrates, use of non-potassium sparing diuretics, potassium-sparing diuretics, potassium supplements, dyspnea at rest, dyspnea on exertion, activity limitation, New York Heart Association class, distended jugular vein, third heart sound, pulmonary râles, lower extremity edema, presence of 6 or more symptoms or signs, heart rate, blood pressure (systolic and diastolic), serum creatinine and potassium levels, pulmonary congestion and cardiothoracic ratio >0.5 by chest x-ray, and propensity score for left ventricular ejection fraction >45%.

Table 3

Matched hazard ratios (HR) and 95% confidence intervals (CI) for hospitalizations in ambulatory patients with diastolic heart failure (DHF) compared with systolic heart failure (SHF)

	% event (median follow up)		Absolute SHF-DHF risk difference	Unadjusted HR for DHF (95% CI)	Adjusted* HR for DHF (95% CI)
	SHF (n=2091)	DHF (n=697)			
All causes	64.0% (45 months)	66.9% (48 months)	2.9	0.99 (0.87- 1.11); P=0.801	1.00 (0.88 - 1.13); P=0.976
Cardiovascular causes	50.5% (63 months)	45.9% (75 months)	-4.6	0.84 (0.73 - 0.96); P=0.011	0.85 (0.74 - 0.98); P=0.023
Worsening heart failure	26.6% (86 months)	18.2% (90 months)	-8.4%	0.63 (0.52 - 0.77): P<0.0001	0.60 (0.48 - 0.74); P<0.0001
Ventricular arrhythmias/cardiac arrest	3.7% (95 months)	1.4% (96 months)	-2.3%	0.39 (0.18 - 0.84); P=0.016	0.37** (0.17 - 0.80); P=0.011
Supra-ventricular arrhythmias	4.1% (97 months)	5.5% (95 months)	1.2%	1.28 (0.82 - 1.98); p=0.273	1.27** (0.82 - 1.97); P=0.295)
Acute myocardial infarction	6.6% (94 months)	5.9% (95 months)	-0.7%	0.87 (0.59 - 1.28); P=0.481	0.88** (0.59 - 1.29); P=0.503
Unstable angina	13.0% (80 months)	15.8% (90 months)	2.8%	1.07 (0.81 - 1.42); P=0.631	1.07** (0.81 - 1.41); P=0.644
Coronary revascularization	2.5% (94 months)	3.6% (95 months)	1.1%	1.27 (0.67 - 2.41); P=0.468	1.18** (0.61 - 2.26); P=0.625

*Adjusted for same covariates as in Table 2.

**Adjusted for matching and propensity scores only