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Fatigue as a Predictor of Outcome in Patients With Heart Failure

Analysis of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)

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Objectives The purpose of this study was to examine the relationship between fatigue and clinical outcomes, using dyspnea as a comparator, in patients with left ventricular ejection fraction (LVEF) ≤35% enrolled in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study.

Background Although fatigue is a common symptom in heart failure (HF), little is known about its association with prognosis.

Methods At baseline in CORONA, fatigue "during the past few days" was measured using a 5-point exertion scale (0 = none, 1 = heavy exertion, 2 = moderate exertion, 3 = slight exertion, 4 = rest); a 4-point scale was used for dyspnea (1 to 4 as for fatigue). Patients were grouped into 3 categories: a fatigue score 0 to 1 (n = 535), fatigue score 2 (n = 1,632), and fatigue score 3 to 4 (n = 1,663); and a dyspnea score of 1 (n = 292), dyspnea score of 2 (n = 1,695), and dyspnea score of 3 to 4 (n = 1,843). The association between fatigue and dyspnea and the composite outcome of cardiovascular (CV) death or HF hospital stay and each component separately was examined using Kaplan-Meier analysis and Cox proportional-hazard models. We also examined all-cause mortality.

Results In univariate analyses, symptom severity was associated with a higher risk of CV death or HF hospital stay (fatigue: group 3, 49% [n = 810], vs. group 1, 30% [n = 160]; dyspnea: group 3, 50% [n = 918], vs. group 1, 28% [n = 82]) and all-cause mortality (fatigue: group 3, 38% [n = 623], vs. group 1, 24% [n = 130]; dyspnea: group 3, 38% [n = 697], vs. group 1, 23% [n = 66], log-rank $p < 0.0001$ for all). After adjusting for other prognostic variables, including LVEF, New York Heart Association class, and N-terminal pro-B-type natriuretic peptide level, worse fatigue remained associated with higher risk of HF hospital stay but not mortality (worse dyspnea remained associated with a higher risk of both). An increase in fatigue (or dyspnea) between baseline and 6 months was also associated with worse outcomes.

Conclusions In HF, greater fatigue is associated with worse clinical outcomes. Closer attention should be paid to this symptom in clinical practice, with more done to standardize its measurement and understand its origins, with a view to improving treatment. (J Am Coll Cardiol HF 2014;2:187–97) © 2014 by the American College of Cardiology Foundation

Although dyspnea is the best recognized symptomatic manifestation of heart failure (HF), fatigue is also a prototypical symptom, limiting exercise in this condition (1,2). For example, in 1 community-based survey, more than half (59%) of 540 patients with chronic HF reported being moderately to extremely troubled by fatigue, and few (9%)

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Abbreviations and Acronyms

CV = cardiovascular

HF = heart failure

HF-REF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

had not experienced this symptom at all. Of those reporting fatigue, 53% experienced the symptom at least once a day (3). Similar findings have been reported in other studies (4,5). Despite the prevalence of fatigue in HF, the cause of this symptom is uncertain and contentious (6–10). It has even been argued that both fatigue and the other cardinal symptom of HF, dyspnea, have a common origin (7,10). Even less is known about the prognostic importance of fatigue (and change in fatigue) in patients with chronic HF, and these questions were the focus of this study (11).

We examined the prevalence and severity of fatigue (and dyspnea for comparison) at baseline in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study and whether these symptoms were predictors of outcome (12). We also examined the relationship between change in fatigue (and dyspnea) from baseline to outcomes.

Methods

A total of 5,011 patients age ≥60 years with symptomatic (New York Heart Association [NYHA] class II to IV), systolic (left ventricular ejection fraction [LVEF] ≤40% but no more than 35% in patients with NYHA class II) HF of ischemic origins were enrolled in CORONA. Patients were randomized to receive 10 mg of rosuvastatin or matching placebo once daily (12,13). The ethics committee at each of the participating hospitals approved the trial, and patients provided written informed consent. The primary composite outcome was death from cardiovascular (CV) causes, nonfatal myocardial infarction, or nonfatal stroke. The median follow-up was 32.8 months. Compared with placebo, rosuvastatin did not reduce the primary outcome or death from any cause.

Fatigue "during the past few days" was measured using a 5-point exertion scale (0 = none, 1 = heavy exertion, 2 = moderate exertion, 3 = slight exertion, 4 = rest) recorded by the investigator. Dyspnea "during the past few days" was measured using a 4-point exertion scale (1 = heavy exertion, 2 = moderate exertion, 3 = slight exertion, 4 = rest); a 4- rather than 5-point scale was used for dyspnea because the presence of dyspnea at baseline was an inclusion criterion for CORONA. These symptoms were measured at baseline and at 6 and 12 weeks after randomization and every 3 months thereafter.

Only patients with LVEF ≤35% (n = 3,830) were included in the current analyses because patients with LVEF >35% (and ≤40%) had to be in NYHA class III or IV; we wished to examine the predictive value of fatigue and dyspnea in addition to NYHA functional class.

Patients were grouped into 3 categories at baseline in order to provide sufficient numbers for analysis in each category (see Results): fatigue score 0 to 1 and 2 and 3 to 4; dyspnea score 1 and 2 and 3 to 4. We also examined change in fatigue from baseline to the 6-month visit, classifying patients as showing a decrease (reduction in score), an increase (an increase in score), or no change (unchanged score) in symptoms.

Statistical analyses. Baseline characteristics are presented as mean ± SD symptom group at baseline for continuous variables and percent for categorical variables. Baseline characteristics were compared across groups, using one-way analysis of variance for continuous variables and the chi-square test for categorical variables.

We tested the prognostic value of each symptom relative to the composite outcome of CV death or hospital stay due to worsening HF, using Cox proportional hazard regression models. CV death or hospital stay due to worsening HF rather than the prespecified primary outcome of CORONA was used in the present analysis as it better reflects disease-specific morbidity and mortality related to HF (and the primary endpoint of CORONA was recommended by regulatory authorities to reflect the treatment intervention used, e.g., a statin) (14,15). Other outcomes analyzed were the components of the composite (CV death and HF hospital stay individually) and all-cause death. The covariates used were on the basis of previously reported predictive models (age, sex, NYHA class, LVEF, body mass index [kg/m^2], systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implantable cardioverter-defibrillator, apolipoprotein A-1, apolipoprotein B, creatinine, alanine aminotransferase, creatine kinase, triglycerides, C-reactive protein, high-density lipoprotein, low-density lipoprotein, estimated glomerular filtration rate, and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) (16). A logarithmic transformation of NT-proBNP was performed. Linearity and proportional hazard assumptions were assessed for all model covariates.

Kaplan-Meier cumulative event curves are presented by symptom category and compared with log-rank tests. Similar analyses were carried out that examined the relationship between change in symptoms (baseline to 6 months) and subsequent clinical outcomes (from 6 months to the end of the study). All p values reported are two-sided and a value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 12 (Stata Corp, College Station, Texas).

Results

Of the 5,011 patients randomized, 3,830 (76%) had a baseline LVEF ≤35%; all of them had a baseline measure for dyspnea and fatigue. Figure 1 shows the distribution of fatigue and dyspnea at baseline. Patients were grouped into 3 categories: those with fatigue scores 0 to 1 (n = 535 [14%]),

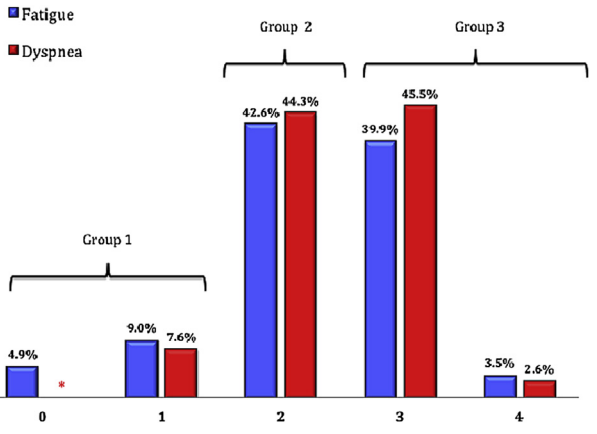

Figure 1 **Baseline Distribution of Symptoms**

Symptoms of fatigue **(blue) and dyspnea (red)** are shown.

2 (n = 1,632 [43%]) and 3 to 4 (n = 1,663 [43%]); and with dyspnea scores of 1 (n = 292 [8%]), 2 (n = 1,695 [44%]), and 3 to 4 (n = 1,843 [48%]).

Baseline characteristics, including comorbidities and concomitant drug treatments, are summarized in Table 1. Patients with higher levels of fatigue (i.e., fatigue on slight exertion or at rest) were more likely to be older, female, and have lower systolic blood pressure than patients with lower levels of fatigue. They also had higher heart rates and were more likely to be in NYHA functional class III or IV. Patients with greater fatigue more frequently had a history of myocardial infarction, hypertension, diabetes, atrial fibrillation or stroke, lower lipid levels, and estimated glomerular filtration rate, and higher levels of NT-proBNP and high-sensitivity CRP. They were less likely to smoke.

Patients with higher levels of dyspnea (i.e., dyspnea at rest or slight exertion) presented a generally similar pattern, although there was no association between level of dyspnea and history of stroke. The patients with both higher levels of fatigue and dyspnea were more likely to be in atrial fibrillation/flutter at baseline and were more likely to be treated with diuretic agents and digitalis. A cross-tabulation of numbers with symptoms at baseline and between numbers with a change in symptom severity at 6 months are presented in Tables 2 and 3 respectively.

Clinical outcomes according to symptom severity at baseline. UNADJUSTED OUTCOMES. Patients with higher symptom severity were significantly more likely to die from any cause (fatigue group 3, n = 623 [38%], vs. group 1, n = 130 [24%]; dyspnea group 3, n = 697 [38%], vs. group 1, n = 66 [23%]) and from CV causes (fatigue group 3, n = 501 [30%], vs. group 1, n = 104 [19%]; dyspnea group 3, n = 569 [31%], vs. group 1, n = 52 [18%]). Those with greater symptom severity were also more likely to be hospitalized for worsening HF (fatigue group 3, n = 559 [34%], vs. group 1, n = 90 [17%]; dyspnea group 3, n = 637 [35%], vs. group 1, n = 42 [14%]; log rank p < 0.0001 for all outcomes) (Tables 4, 5, and 6, Figs. 2 and 3).

ADJUSTED OUTCOMES. Adjustment for the other variables associated with worse clinical outcomes listed in Methods (excluding NT-proBNP) weakened the relationship between symptom severity and death (group 3 vs group 1): fatigue, CV death hazard ratio (HR) 1.18 (95% confidence interval [CI]: 0.92 to 1.52), p = 0.20 and HF hospital stay HR 1.54 (95% CI: 1.19 to 2.00), p = 0.001 (Table 5); dyspnea, CV death HR 1.46 (95% CI: 1.04 to 2.07), p = 0.03, and HF hospital stay HR 1.85 (95% CI: 1.28 to 2.68), p = 0.001 (Table 6). Fatigue and dyspnea continued to be predictive of the primary outcome even when NT-proBNP level was considered (Figs. 4A and 4B). However, adding NT-proBNP to the multivariable models slightly weakened the association between severity of fatigue and death but not between fatigue and HF hospital stay. Dyspnea at rest or slight exertion continued to predict death as well as HF hospital stay even after NT-proBNP was added to the multivariable analyses.

Clinical outcomes according to change in symptom severity between baseline and 6 months. UNADJUSTED OUTCOMES. Of the 3,830 patients in this analysis, 3,548 (90.3%) had both a baseline and 6-month measure of fatigue and dyspnea. Of these 3,548 patients, 712 (20.1%) reported a decrease, 481 (13.6%) an increase, and 2,355 (66.4%) no change in fatigue over that period. Those reporting an increase in fatigue were significantly more likely to die from any cause and from a CV cause (Table 7). Patients reporting an increase in fatigue were also less likely to be hospitalized for worsening HF (Pearson chi-square test, p < 0.01 for all outcomes) (Table 7). Of the 3,548 patients with both a baseline and 6-month measure of dyspnea, 761 (21.5%) reported a decrease, 367 (10.3%) an increase, and 2,420 (60.2%) no change in this symptom over that period. The associations between change in dyspnea and outcomes were similar to those observed for fatigue (Table 7).

ADJUSTED OUTCOMES. Adjustment for other variables (including NT-proBNP level) weakened the relationship between change in symptom severity and death (Table 8). However, compared with those patients who exhibited no change in symptoms, those with an increase in either symptom had a higher HR for all outcomes (and the adjusted HR for these outcomes was lower in patients reporting a decrease in either fatigue or dyspnea) (Table 8). Patients with an increase in fatigue had a significantly higher risk of the composite outcome of CV death or HF hospital stay (HR: 1.35 [95% CI: 1.11 to 1.65]) and HF hospital stay (HR: 1.55 [95% CI: 1.24 to 1.94]). The corresponding findings for increase in dyspnea were: CV death or HF hospital stay HR of 1.56 (95% CI: 1.26 to 1.92) and HF hospital stay HR of 1.88 (95% CI: 1.50 to 2.37).

Table 1 Baseline Characteristics

	All patients	Fatigue 1 (n = 535)	Fatigue 2 (n = 1632)	Fatigue 3 (n = 1663)	p Value	Dyspnea 1 (n = 292)	Dyspnea 2 (n = 1695)	Dyspnea 3 (n = 1843)	p Value
Age (yrs)	73.0 ± 7.1	72.7 ± 6.9	72.7 ± 7.0	74.4 ± 7.3	0.02	72.1 ± 6.8	72.5 ± 7.0	73.6 ± 7.2	<0.01
Age ≥70 yrs	2,557 (66.7%)	351 (65.6%)	1,057 (64.8%)	1,149 (69.1%)	0.22	185 (63.4%)	1,091 (64.4%)	1,281 (69.5%)	<0.01
Female	810 (21.2%)	80 (15%)	306 (18.8%)	424 (25.5%)	<0.01	42 (14.4%)	320 (18.9%)	448 (24.3%)	<0.01
Race									
Caucasian	3,768 (98.4%)	529 (98.9%)	1,612 (98.8%)	1,627 (97.8%)		288 (98.6%)	1,672 (98.6%)	1,808 (98.1%)	
Black	12 (0.3%)	2 (0.4%)	4 (0.3%)	6 (0.4%)		1 (0.3%)	5 (0.3%)	6 (0.3%)	
Asian	34 (0.9%)	3 (0.6%)	5 (0.3%)	26 (1.56%)		3 (1.0%)	8 (0.5%)	23 (1.3%)	
Other	16 (0.4%)	1 (0.2%)	11 (0.7%)	4 (0.2%)	<0.01	0 (0%)	10 (0.6%)	6 (0.3%)	0.18
NYHA III/IV	2,001 (52.3%)	93 (17.4%)	529 (32.4%)	1,379 (82.9%)	<0.01	17 (5.8%)	400 (23.6%)	1,584 (86.0%)	<0.01
LVEF (%)	28.6 ± 5.7	28.5 ± 5.8	28.8 ± 5.5	28.3 ± 5.8	0.06	28.7 ± 5.7	28.8 ± 5.6	28.3 ± 5.8	0.04
Systolic BP, mm Hg	128.5 ± 16.9	129.8 ± 17.7	129.6 ± 16.6	127.1 ± 16.7	<0.01	129.5 ± 16.8	129.8 ± 17.0	127.3 ± 16.6	<0.01
Heart rate, beats/min	71.8 ± 11.3	69.3 ± 10.5	70.9 ± 11.4	73.4 ± 11.3	<0.01	68.3 ± 10	70.6 ± 11.3	73.4 ± 11.3	<0.01
BMI, kg/m^2	26.9 ± 4.4	26.5 ± 4	27.1 ± 4.4	26.9 ± 4.4	0.01	26.5 ± 4	27.0 ± 4.4	27.0 ± 4.5	0.29
BMI > median (26.4 kg/m^2)	1,900 (49.6%)	250 (46.7%)	839 (51.4%)	811 (51.4%)	0.05	132 (45.2%)	850 (50.1%)	918 (49.8%)	0.43
Current smoker	349 (9.1%)	67 (12.5%)	140 (8.6%)	142 (8.5%)	0.01	33 (11.3%)	161 (9.5%)	155 (8.4%)	0.21
Medical history									
MI	2,311 (60.3%)	289 (54.0%)	987 (59.9%)	1,044 (62.8%)	<0.01	149 (51.0%)	1,009 (59.5%)	1,153 (62.6%)	<0.01
Angina pectoris	2,728 (71.2%)	313 (58.5%)	1,167 (71.5%)	1,248 (75.1%)	<0.01	162 (55.5%)	1,176 (69.4%)	1,390 (75.4%)	<0.01
CABG	694 (20.0%)	94 (19.8%)	323 (22.0%)	277 (18.1%)	0.03	50 (18.9%)	331 (21.8%)	313 (18.5%)	0.06
PCI/PTCA	1,052 (27.5%)	72 (13.5%)	221 (13.5%)	187 (11.2%)	0.11	37 (12.7%)	227 (13.4%)	216 (11.7%)	0.32
Hypertension	2,308 (60.3%)	261 (48.8%)	976 (59.8%)	1,071 (64.4%)	<0.01	142 (48.6%)	1,008 (59.5%)	1,158 (62.8%)	<0.01
Diabetes mellitus	1,109 (29.0%)	120 (22.4%)	452 (27.7%)	537 (32.3%)	<0.01	60 (20.6%)	448 (26.4%)	601 (32.6%)	<0.01
Baseline AF/F	895 (23.4%)	89 (16.6%)	345 (21.1%)	461 (27.7%)	<0.01	39 (13.4%)	350 (20.7%)	506 (27.5%)	<0.01
Stroke	478 (12.5%)	50 (9.4%)	175 (10.7%)	253 (15.2%)	<0.01	26 (8.9%)	197 (11.6%)	255 (13.8%)	0.02
Pacemaker	454 (11.9%)	60 (11.2%)	188 (11.5%)	206 (12.4%)	0.66	22 (7.5%)	182 (10.7%)	250 (13.6%)	<0.01
ICD	122 (3.2%)	24 (4.5%)	50 (3.1%)	48 (2.9%)	0.17	6 (2.1%)	59 (3.5%)	57 (3.1%)	0.42
Laboratory measurements									
Cholesterol, mmol/l	5.3 ± 1.1	5.4 ± 1.0	5.4 ± 1.0	5.3 ± 1.1	0.01	5.4 ± 1.0	5.4 ± 1.0	5.3 ± 1.1	<0.01
ApoB:ApoA-1 ratio	0.87 ± 0.25	0.87 ± 0.23	0.86 ± 0.24	0.88 ± 0.26	0.06	0.86 ± 0.23	0.87 ± 0.24	0.88 ± 0.26	0.53
ApoB	1.27 ± 0.30	1.28 ± 0.29	1.27 ± 0.29	1.26 ± 0.31	0.50	1.26 ± 0.27	1.28 ± 0.29	1.26 ± 0.31	0.05
ApoA-1	1.50 ± 0.28	1.51 ± 0.28	1.51 ± 0.28	1.47 ± 0.28	<0.01	1.51 ± 0.26	1.51 ± 0.27	1.48 ± 0.29	0.01
Triglycerides, mmol/l	2.0 ± 1.3	2.0 ± 1.2	2.0 ± 1.3	2.0 ± 1.3	0.97	1.9 ± 1.0	2.0 ± 1.3	2.0 ± 1.4	0.22
Serum creatinine, μmol/l	116.8 ± 28.3	115.4 ± 27.0	116.0 ± 27.9	118.0 ± 29.1	0.05	114.6 ± 26.0	115.5 ± 28.0	118.3 ± 29.0	<0.01
Estimated GFR, ml/min/1.73 m^2*	55.8 ± 15.4	57.2 ± 15.2	56.6 ± 15.2	54.7 ± 15.5	<0.01	57.5 ± 14.5	57.0 ± 15.4	54.5 ± 15.4	<0.01
NT-proBNP, pmol/l (median)	193.8	140.5	178.3	232.2	<0.01	135.6	168.0	234.6	<0.01
hs-CRP, mg/l (median)	3.5	2.9	3.3	3.9	0.02	2.4	3.3	3.9	<0.01

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Table 1 Continued

	All patients	Fatigue 1 (n = 535)	Fatigue 2 (n = 1632)	Fatigue 3 (n = 1663)	p Value	Dyspnea 1 (n = 292)	Dyspnea 2 (n = 1695)	Dyspnea 3 (n = 1843)	p Value
Medication									
Loop diuretic agent	2,944 (76.9%)	356 (66.5%)	1,206 (73.9%)	1,382 (83.1%)	<0.01	196 (67.1%)	1,220 (72.0%)	1,528 (82.9%)	<0.01
Loop or thiazide diuretic agent	3,364 (87.8%)	427 (79.8%)	1,412 (86.5%)	1,525 (91.7%)	<0.01	225 (77.1%)	1,448 (85.4%)	1,691 (91.8%)	<0.01
ACE inhibitor	3,051 (79.7%)	427 (79.8%)	1,290 (79.0%)	1,334 (80.2%)	0.70	234 (80.1%)	1,340 (79.1%)	1,477 (80.1%)	0.71
ACE inhibitor or ARB	3,548 (92.6%)	505 (94.4%)	1,515 (92.8%)	1,528 (91.9%)	0.14	272 (93.2%)	1,579 (93.2%)	1,697 (92.1%)	0.44
Beta-blocker	2,847 (74.3%)	396 (74.0%)	1,235 (75.7%)	1,216 (73.1%)	0.24	221 (75.7%)	1,284 (75.8%)	1,342 (72.8%)	0.12
Digitalis glycoside	1,305 (34.1%)	125 (23.4%)	522 (32.0%)	658 (39.6%)	<0.01	64 (21.9%)	519 (30.6%)	722 (39.2%)	<0.01
Antiarrhythmic therapy	479 (12.5%)	68 (12.7%)	184 (11.27%)	227 (13.7%)	0.12	39 (13.4%)	201 (11.9%)	239 (13.0%)	0.55
Antiplatelet therapy	2,209 (57.7%)	315 (58.9%)	949 (58.2%)	945 (56.8%)	0.62	176 (60.3%)	993 (58.6%)	1,040 (56.4%)	0.28
Anticoagulant therapy	1,433 (37.4%)	203 (37.9%)	609 (37.3%)	621 (37.3%)	0.96	111 (38.0%)	627 (37.0%)	695 (37.7%)	0.89
Antiplatelet or anticoagulant therapy	3,465 (90.5%)	493 (92.2%)	1,476 (90.4%)	1,496 (90.0%)	0.32	275 (94.2%)	1,531 (90.3%)	1,659 (90.0%)	0.08

Values are mean ± SD or n (%). *To convert to ng/l multiply by 8.457.
ACE = angiotensin converting enzyme; AF/F = atrial fibrillation/flutter; ICD = implanted cardioverter-defibrillator; ApoA = apolipoprotein A; ApoB = apolipoprotein B; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; hs-CRP = high sensitive C-reactive protein; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; PCI/PTCA = percutaneous coronary intervention/percutaneous transluminal coronary angioplasty.

Table 2 Cross-Tabulation Between Symptoms at Baseline

	Dyspnea			
Fatigue	1	2	3/4	Total
0/1	219	238	78	535
2	57	1,245	330	1,632
3/4	16	212	1,435	1,663
Total	292	1,695	1,843	3,830

Various sensitivity analyses were performed (Online Tables). Inclusion of all patients (i.e., those with LVEF between 36% and 40%) and those receiving randomized treatment (i.e., placebo or rosuvastatin) in the adjusted models and use of a more parsimonious adjusted model (top 10 predictive variables ranked by chi-square test) did not materially change the results. When both fatigue and dyspnea were entered in the predictive models together, the predictive value of each symptom was diminished, moderately, for the primary composite outcome. However, the strongest association of fatigue, which was with HF hospital stay, was maintained qualitatively: level 3 versus 1 fatigue alone had an HR of 1.57 (95% CI: 1.15 to 2.14; p = 0.01), and the fatigue plus dyspnea HR was 1.37 (95% CI: 0.97 to 1.94; p = 0.07). The association between dyspnea and all-cause death was also maintained: level 3 versus 1 dyspnea alone had an HR of 1.60 (95% CI: 91.08 to 2.37; p = 0.02), and dyspnea plus fatigue HR was 1.61 (95% CI: 1.04 to 2.49; p = 0.03).

Discussion

We found the symptom of fatigue to be almost ubiquitous in our trial, which enrolled only patients with symptoms (i.e., those in NYHA functional class II or greater and with dyspnea at baseline) and a reduced LVEF. Overall, only 5% of patients reported no fatigue, and 9% reported fatigue only on severe exertion. For most patients, fatigue was present on slight (43%) or moderate (43%) exertion. The only other large trial we know of which recorded fatigue was COMET (Carvedilol Or Metoprolol European Trial), which used a 5-point scale, although that scale was labeled differently (1 = asymptomatic; 2 = walking up stairs at normal pace; 3 = walking at normal pace on a flat surface; 4 = walking slowly on a flat surface or during washing or dressing; and 5 = at rest). Few patients

Table 3 Cross-Tabulation Between Change in Symptoms at 6 Months

	Dyspnea			
Fatigue	Decrease	Increase	Unchanged	Total
Decrease	478	22	212	712
Increase	42	222	217	481
Unchanged	241	123	1,991	2,355
Total	761	367	2,420	3,548

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Table 4 Clinical Outcomes According to Baseline Symptom Severity

	No. of Patients With Fatigue (%)			No. of Patients With Dyspnea (%)		
Outcome	1 (n = 535)	2 (n = 1,632)	3 (n = 1,663)	1 (n = 292)	2 (n = 1695)	3 (n = 1,843)
CV death or HF hospital stay	160 (29.9)	598 (36.6)	810 (48.7)	82 (28.1)	568 (33.5)	918 (49.8)
CV death	104 (19.4)	356 (21.8)	501 (30.1)	52 (17.8)	340 (20.1)	569 (30.9)
HF hospital stay	90 (16.8)	391 (24.0)	559 (33.6)	42 (14.4)	361 (21.3)	637 (34.6)
All-cause death	130 (24.3)	452 (27.7)	623 (37.5)	66 (22.6)	442 (26.1)	697 (37.8)

CV = cardiovascular; HF = heart failure.

(<8%) were given the lowest or highest score on this scale, although there was a more even distribution across the middle 3 scores in COMET than in CORONA, presumably reflecting the different scale labeling, different patient characteristics, or both. For example, patients in CORONA were on average 10 years older than those in COMET and more likely to have a history of myocardial infarction, hypertension, or diabetes, and to be treated with beta-blockers at baseline; they were less likely to be treated with angiotensin-converting enzyme (ACE) inhibitors or diuretics.

We found that the baseline level of fatigue (as well as dyspnea) was related to the primary composite endpoint examined in the present analysis (CV death or HF hospital stay), although this was driven by the HF hospital stay component. This association was maintained after adjustment for other known prognostic variables, including NYHA class, LVEF, and NT-proBNP but was of borderline significance. Indeed, after adjustment, there was no longer a statistically significant association between fatigue and CV mortality alone (or all-cause mortality), although the association with HF hospital stay persisted. Interestingly, and in contrast, the significant relationship between dyspnea and fatal outcomes persisted after adjustment, perhaps questioning the view that these 2 symptoms are different expressions of the same underlying disease mechanism or mechanisms (7,17). If this were the case, it might be expected that both symptoms would predict outcomes in the same manner and proportion.

Again, we know of only 1 other study testing whether fatigue is an independent predictor of outcomes in HF. That study was COMET (discussed earlier), and, in agreement with our findings in CORONA, fatigue in COMET was a predictor of death in unadjusted but not adjusted analyses. Fatigue did, however, remain a predictor of HF hospital stay after adjustment, as we also observed in CORONA, although the model used in COMET contained fewer variables and did not include NT-proBNP level. Curiously, in COMET, dyspnea remained a predictor of death after adjustment (as we found in CORONA) but not of HF hospital stay (of which it remained strongly predictive of in CORONA). The reason for this discrepancy is uncertain.

We also found that worsening of fatigue between baseline and 6 months was predictive of worse outcomes, although, once more, after adjustment, this association was most clear cut for HF hospitalization. A similar relationship was seen for worsening dyspnea. We do not believe that these findings have been reported before.

Why fatigue is predictive of clinical outcomes in HF is unknown. It is easy to surmise that fatigue reflects muscle hypoperfusion and is therefore a measure of diminished cardiac output. However, this notion is probably too simplistic. A skeletal myopathy may occur in HF and this, in turn, may arise as a result of disturbed anabolic-catabolic imbalance (10). Activation of metabolic or ergoreceptors in muscle may also lead to sympathetic nervous system activation, which is known to be detrimental in HF. Severity

Table 5 Hazard Ratio for Fatigue Severity and Clinical Outcomes: Fatigue

	Unadjusted				Adjusted*			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
Fatigue	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
CV death or HF hospital stay	1.29 (1.08–1.53)	0.005	1.96 (1.65–2.32)	<0.001	1.12 (0.89–1.41)	0.34	1.28 (1.00–1.64)	0.05
CV death	1.14 (0.92–1.42)	0.23	1.71 (1.39–2.12)	<0.001	1.02 (0.76–1.36)	0.92	1.13 (0.82–1.54)	0.46
HF hospital stay	1.49 (1.19–1.88)	0.001	2.39 (1.91–2.98)	<0.001	1.29 (0.96–1.74)	0.10	1.57 (1.15–2.14)	0.01
All-cause death	1.16 (0.95–1.41)	0.14	1.71 (1.41–2.06)	<0.001	1.06 (0.82–1.38)	0.45	1.17 (0.89–1.55)	0.26

*Adjusted for age, sex, New York Heart Association class, left ventricular ejection fraction, body mass index, kg/m^2, systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implant, cardioverter-defibrillator, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, triglycerides, C-reactive protein, high-density lipoprotein, low-density lipoprotein, estimated glomerular filtration rate, and NT-proBNP.

CV = cardiovascular; HF = heart failure.

Table 6 Hazard Ratio for Fatigue Severity and Clinical Outcomes: Dyspnea

	Unadjusted				Adjusted*			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
Dyspnea	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
CV death or HF hospital stay	1.23 (0.98–1.55)	0.08	2.15 (1.72–2.70)	<0.001	1.14 (0.84–1.55)	0.41	1.49 (1.07–2.08)	0.02
CV death	1.13 (0.84–1.51)	0.42	1.91 (1.44–2.54)	<0.001	1.32 (0.87–2.02)	0.19	1.80 (1.15–2.81)	0.01
HF hospital stay	1.53 (1.11–2.11)	0.01	2.90 (2.12–3.97)	<0.001	1.22 (0.82–1.82)	0.32	1.72 (1.12–2.62)	0.01
All-cause death	1.15 (0.89–1.49)	0.28	1.85 (1.44–2.38)	<0.001	1.37 (0.96–1.97)	0.09	1.60 (1.08–2.37)	0.02

*Adjusted for age, sex, New York Heart Association class, left ventricular ejection fraction, body mass index kg/m^2, systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implanted cardioverter-defibrillator, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, triglycerides, C-reactive protein, high-density lipoprotein, low-density lipoprotein, estimated glomerular filtration rate, NT-proBNP.

CV = cardiovascular; HF = heart failure.

of fatigue is also related to depressive symptoms (3,18,19), and depression is also an adverse prognostic finding in HF. Whether there is a mechanistic link between fatigue, muscle dysfunction, and depression (e.g., autonomic dysfunction) is unknown. Fatigue in HF is also associated with anemia, another adverse prognostic finding (20).

What are the clinical implications of our findings? Although fatigue is regarded as a cardinal symptom of HF, its severity does not seem to be routinely recorded judging by the lack of published reports from clinical trials and other large datasets. Despite this, smaller studies show it to be a distressing and disabling as well as common symptom

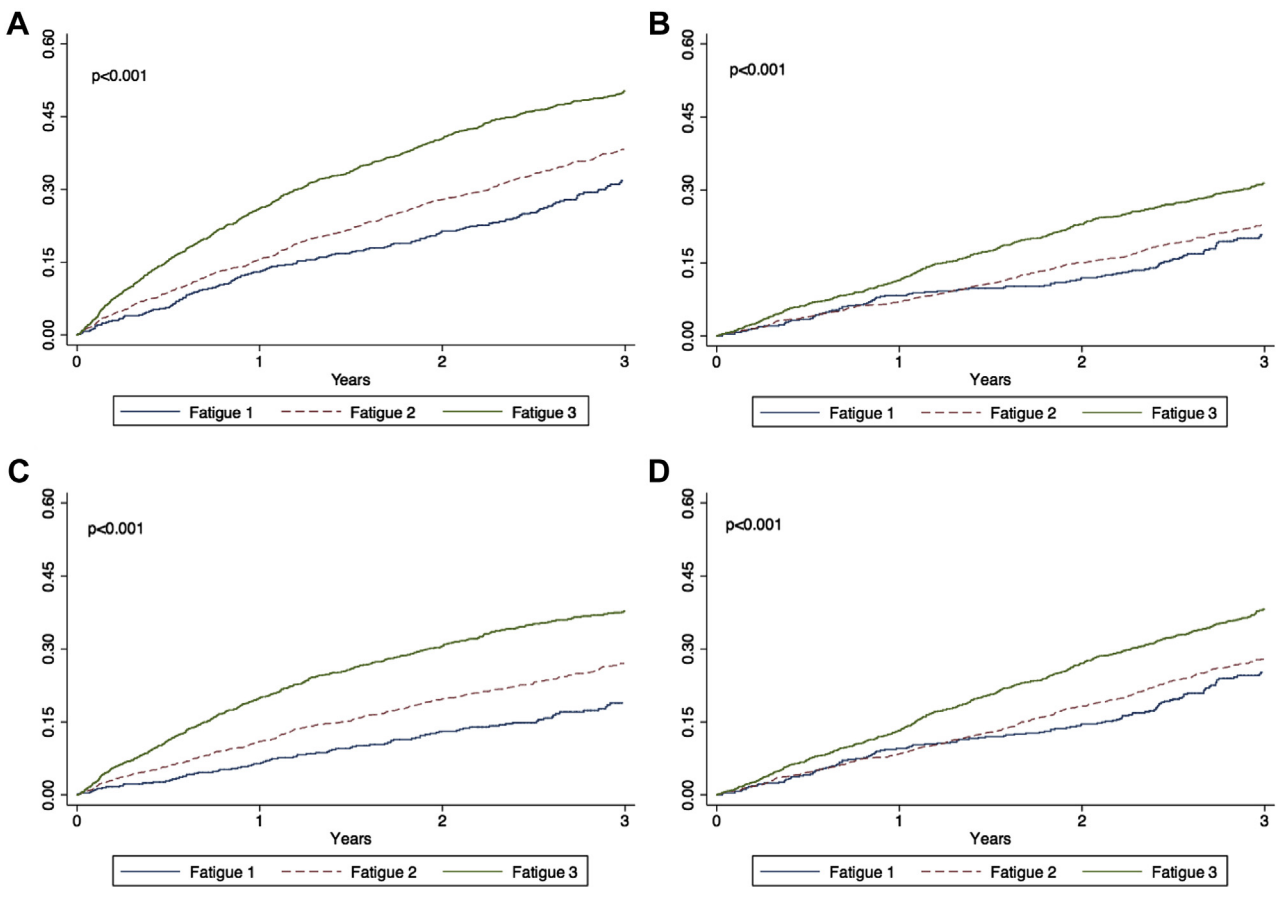

Figure 2 Outcomes According to Symptom Severity

Fatigue 1, none or occurs upon heavy exertion; fatigue 2 occurs upon moderate exertion; fatigue 3 occurs while at rest or upon slight exertion. On the composite outcome, CV death or HF hospital stay **(A)**, CV death **(B)**, HF hospital stay **(C)** and all-cause death **(D)**.

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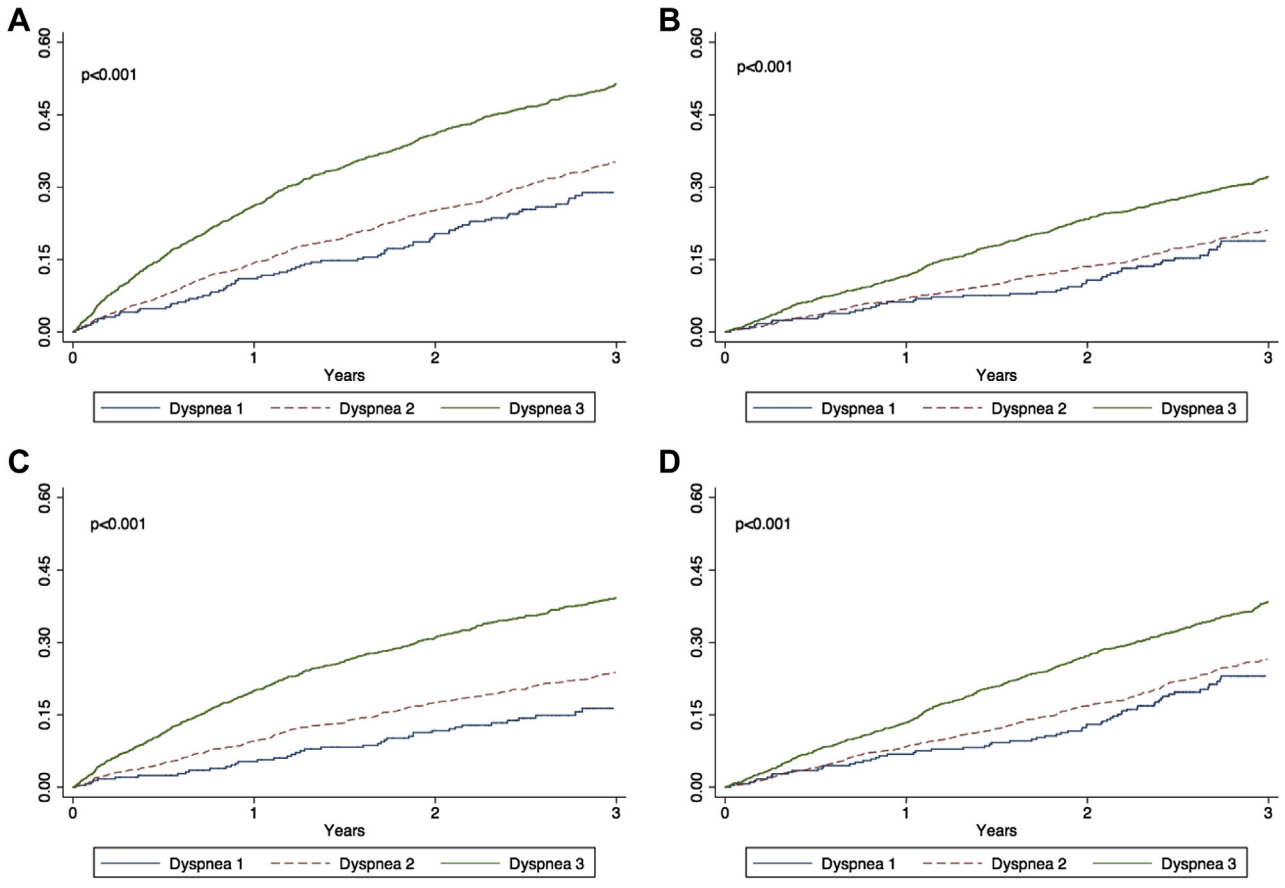

Figure 3 **Outcomes According to Symptom Severity**

Dyspnea 1 occurs upon heavy exertion; dyspnea 2 occurs upon moderate exertion; dyspnea 3 occurs when at rest or upon slight exertion. On the composite outcome, CV death or HF hospital stay **(A)**, CV death **(B)**, HF hospital stay **(C)**, and all-cause death **(D)**.

(21–23). Not only that, COMET and CORONA clearly show that fatigue is an independent predictor of HF hospital stay, even after adjusting for NYHA class and other powerful prognostic variables, including NT-proBNP level (in CORONA). Moreover, CORONA also shows that worsening fatigue is an adverse prognostic development. These findings suggest that closer attention should be paid to this symptom in clinical practice, that more should be done to standardize its measurement, and that effort to understand its origins be intensified and better treatment strategies developed. Clearly, there is the possibility that early detection and treatment of worsening fatigue might improve outcomes, although this is a hypothesis that needs to be tested prospectively.

Study limitations. Our study has several limitations. It was not a prespecified analysis of the CORONA trial. The patients enrolled were older subjects with systolic HF of ischemic origins. A total of 1,181 patients (23.6%) were excluded from the analyses because patients with an LVEF >35% (and ≤40%) had to be in NYHA class III or IV, and we wished to examine the predictive value of fatigue and dyspnea in addition to NYHA functional class. However, additional analyses that included these patients gave similar results. Although our findings are consistent with those of COMET and therefore probably can be generalized to most patients with HF and reduced ejection fraction, we do not know about the prevalence or prognostic importance of fatigue in patients with HF and preserved ejection fraction. Fatigue was not measured using a validated score, although we do not know of any instrument that has been fully validated in HF and is suitable for use in a large multinational trial. Because dyspnea was an inclusion criterion in CORONA, the dyspnea scale had only 4 possible points as opposed to 5 for fatigue. Subjects were asked about symptoms over "the past few days," and these responses were recorded by investigators. Depression, which is predictive of adverse events in patients with CV disease, was not measured in CORONA (24).

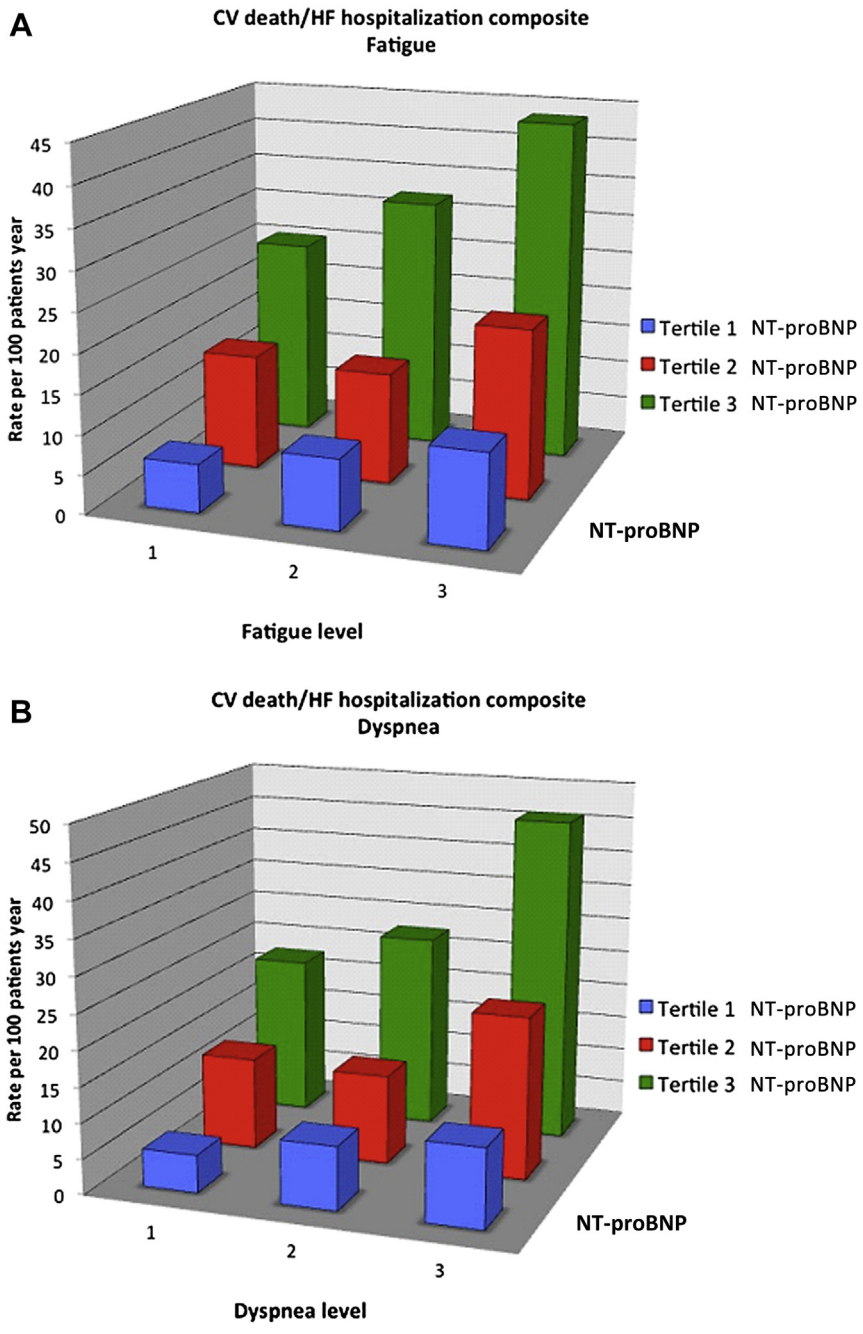

Figure 4 CV Death/HF Hospitalization Composite

(A) Outcome is shown according to fatigue level at baseline and NT-proBNP levels at baseline. **(B)** Outcome is shown according to dyspnea level at baseline and NT-proBNP levels at baseline.

Conclusions

In patients with systolic HF, greater fatigue (and an increase in fatigue) is associated with worse clinical outcomes; the same is true for dyspnea. Closer attention should be paid to the symptom of fatigue in clinical practice. More should be done to standardize its measurement and greater efforts made to understand its origins. It is possible that an early therapeutic response to worsening fatigue might reduce

Table 7 Number of Events by Change in Symptoms at 6 Months

	Fatigue				Dyspnea			
	Decrease (n = 712)	Unchanged (n = 2355)	Increase (n = 481)	p Value	Decrease (n = 761)	Unchanged (n = 2420)	Increase (n = 367)	p Value
CV death/HF hospital stay	65/173 (33.4%)	264/627 (37.8%)	50/167 (45.1%)	<0.001	76/182 (33.9%)	267/638 (37.4%)	36/147 (49.9%)	<0.001
CV death	130 (18.3%)	487 (20.7%)	130 (27.0%)	0.001	141 (18.5%)	506 (20.9%)	100 (27.3%)	0.003
HF hospital stay	173 (24.3%)	627 (26.6%)	167 (34.7%)	<0.001	182 (23.9%)	638 (26.4%)	147 (40.1%)	<0.001
All-cause death	178 (25.0%)	616 (26.2%)	158 (32.9%)	0.005	192 (25.2%)	635 (26.2%)	125 (34.1%)	0.004

CV = cardiovascular; HF = heart failure.

Table 8 Adjusted Outcomes in Relation to Change in Symptom Severity

	CV Death/HF Hospital Stay HR (95% CI)	p Value	Cardiovascular Death HR (95% CI)	p Value	HF Hospital Stay HR (95% CI)	p Value	All-Cause Death HR (95% CI)	p Value
Change in fatigue								
Decrease	0.87 (0.73–1.04)	0.14	0.85 (0.67–1.10)	0.22	0.90 (0.73–1.11)	0.34	0.89 (0.72–1.11)	0.31
Increase	1.35 (1.11–1.65)	0.003	1.26 (0.97–1.65)	0.09	1.55 (1.24–1.94)	<0.001	1.22 (0.97–1.55)	0.09
Change in dyspnea								
Decrease	0.86 (0.72–0.02)	0.08	0.91 (0.7–1.15)	0.41	0.80 (0.65–0.98)	0.04	0.95 (0.77–1.17)	0.62
Increase	1.56 (1.26–1.92)	<0.001	1.19 (0.88–1.61)	0.26	1.88 (1.50–2.37)	<0.001	1.20 (0.92–1.56)	0.17

*Adjusted for age, sex, New York Heart Association class, left ventricular ejection fraction, body mass index (kg/m^2), systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, implanted cardioverter-defibrillator, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatine kinase, triglycerides, C-reactive protein, high-density lipoproteins, low-density lipoprotein, estimated glomerular filtration rate.

CV = cardiovascular; HF = heart failure.

adverse outcomes in HF, although this hypothesis must be tested prospectively.

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Key Words: dyspnea ■ fatigue ■ heart failure ■ outcomes ■ symptoms.

APPENDIX

For supplemental tables, please see the online version of this article.