Heart Failure and Midrange Ejection Fraction
Implications of Recovered Ejection Fraction for Exercise Tolerance and Outcomes

Wilson Nadruz, Jr, MD, PhD; Erin West, MSc; Mário Santos, MD; Hicham Skali, MD, MSc; John D. Groarke, MBBCh, MPH; Daniel E. Forman, MD; Amil M. Shah, MD, MPH

Background—Evidence-based therapies for heart failure (HF) differ significantly according to left ventricular ejection fraction (LVEF). However, few data are available on the phenotype and prognosis of patients with HF with midrange LVEF of 40% to 55%, and the impact of recovered systolic function on the clinical features, functional capacity, and outcomes of this population is not known.

Methods and Results—We studied 944 patients with HF who underwent clinically indicated cardiopulmonary exercise testing. The study population was categorized according to LVEF as follows: HF with reduced LVEF (HFrEF; LVEF<40%; n=620); HF with midrange ejection fraction and no recovered ejection fraction (LVEF was consistent between 40% and 55%; n=107); HF with recovered midrange ejection fraction (LVEF, 40%–55% but previous LVEF<40%; n=170); and HF with preserved LVEF (HFpEF; LVEF>55%; n=47). HF with midrange ejection fraction and no recovered ejection fraction and HF with recovered midrange ejection fraction had similar clinical characteristics, which were intermediate between those of HFrEF and HFpEF, and comparable values of predicted peak oxygen consumption and minute-ventilation/carbon dioxide production slope, which were better than HFrEF and similar to HFpEF. After a median of 4.4 (2.9–5.7) years, there were 253 composite events (death, left ventricular assist device implantation, or transplantation). In multivariable Cox-regression analysis, HF with recovered midrange ejection fraction had lower risk of composite events than HFrEF (hazard ratio, 0.25; 95% confidence interval, 0.13–0.47) and HF with midrange ejection fraction and no recovered ejection fraction (hazard ratio, 0.31; 95% confidence interval, 0.15–0.67), and similar prognosis when compared with HFpEF. In contrast, HF with midrange ejection fraction and no recovered ejection fraction tended to show intermediate risk of outcomes in comparison with HFpEF and HFrEF, albeit not reaching statistical significance in fully adjusted analyses.

Conclusions—Patients with HF with midrange LVEF demonstrate a distinct clinical profile from HFpEF and HFrEF patients, with objective measures of functional capacity similar to HFpEF. Within the midrange LVEF HF population, recovered systolic function is a marker of more favorable prognosis. (Circ Heart Fail. 2016;9:e002826. DOI: 10.1161/CIRCHEARTFAILURE.115.002826.)

Key Words: heart failure ■ oxygen consumption ■ ventricular ejection fraction ■ ventricular function, left

Heart failure (HF) is routinely classified according to left ventricular ejection fraction (LVEF) as HF with reduced LVEF (HFrEF) or HF with preserved LVEF (HFpEF), a distinction driven by the important differences in the evidence base for therapies for HF. Studies of HFrEF have been restricted to patients with LVEF<40%, whereas diagnostic guidelines for HFpEF typically include patients with LVEF >50% to 55%. As a consequence, few data are available on the phenotype, natural history, and prognosis of patients with HF with midrange LVEF of 40% to 55%. Results from previous reports have suggested that patients with HF with midrange LVEF have clinical features and mortality rates that are intermediate between those of HFrEF and HFpEF. However, substantial heterogeneity may exist within patients with HF with midrange LVEF. In particular, this group may include both patients with de novo HF and patients with HF with previously reduced LVEF who have recovered their systolic function. This fact is clinically relevant because subjects with recovered LVEF have been reported to have more favorable prognosis among patients with HF. However,
whether midrange LVEF patients with recovered LVEF have distinct phenotypic and prognostic features compared with those without a previous frankly reduced LVEF is not known. The aim of this study was to compare the clinical features, cardiopulmonary response to exercise, and long-term clinical outcomes in patients with HF with midrange LVEF either without previously frankly reduced LVEF (HF with midrange ejection fraction and no recovered ejection fraction [HFmEF]) or with recovery from previously frankly reduced LVEF (HF with recovered midrange ejection fraction [HFm-recEF]) in relation to each other and to HFrEF and HFP EF patients.

Methods

Study Population

This study included 974 patients with a diagnosis of HF who were referred for cardiopulmonary exercise testing (CPET) at the Brigham and Women’s Hospital between July 2007 and June 2013. We excluded participants with missing baseline LVEF data (n=4), who performed arm ergometer exercise testing (n=1), developed tachyarrhythmias during the CPET (n=2), or had ventricular-paced rhythm with decreased or similar peak heart rate when compared with resting heart rate at CPET (n=9), resulting in 958 participants for the analysis. The Partners Human Research Committee approved this study and waived the requirement for informed consent.

Classification of Patients With HF

LVEF was assessed clinically at the Brigham and Women’s Hospital by quantitative echocardiography. Baseline LVEF values were obtained from echocardiography exams that were most contemporaneous to the CPET dates (median time difference [25th, 75th percentiles]=0 [0, 9] days). The study population was categorized based on LVEF as follows (Figure 1): (1) HFrEF if the LVEF was <40% (n=620); (2) HF with midrange LVEF if the LVEF was between 40% and 55% (n=277); and (3) HFP EF if the LVEF was >55% (n=61). Among patients with midrange LVEF, those who had previously documented LVEF<40% (n=100) or a history of recent onset (<3 months) of HF (n=27) were considered to have HFmEF and 4 subjects had recent onset (<3 months) of HF. The subjects had previous echocardiography documentation of no recovered midrange LVEF and 4 subjects had recent onset (<3 months) of HF. The distribution of LVEF according to the studied groups is shown in Figure I in the Data Supplement.

Clinical Variables Definition

Information on patients’ demographics, current medications, pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy, body mass index, blood pressure, heart rate, and gas-exchange variables were collected at the time of CPET. Additional clinical characteristics and laboratory values most contemporaneous to CPET dates were obtained from chart review. In HFP EF and HFm-recEF subjects, LVEF data from the latest echocardiogram examination performed after the CPET test were also collected, except if there was an interval event (myocardial infarction, LV assistant device [LVAD] implantation, and heart transplantation) between baseline and follow-up echocardiogram.

Symptomatic HF was defined if patients were New York Heart Association Classification functional class II or greater as determined by the referring physician, or if the patient had a previous history of hospitalization for decompensated HF. Antiarrhythmic medications included amiodarone or digoxin. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were coded into a single variable (ACEI/ARB). Cardiac resynchronization therapy and implantable cardioverter defibrillator were coded as a single variable.

Exercise Protocol

All exercise tests were performed in the Brigham and Women’s Hospital cardiopulmonary exercise laboratory using an upright cycle ergometer (Lode, Groningen, The Netherlands; 98% of tests) or a treadmill (General Electric Healthcare, Waukesha, WI; 2% of tests) with the subject breathing room-air. Symptom-limited CPET was performed on all subjects. All pharmacological therapy was continued.

Figure 1. Study design. *Used arm ergometer (n=1), developed tachyarrhythmias (n=2), and had ventricular-paced rhythm with decreased or similar peak heart rate when compared with resting (n=9) during CPET. CPET indicates cardiopulmonary exercise testing; HF, heart failure; HFrEF, HF with midrange and without recovered LVEF; HFP EF, HF with midrange and recovered LVEF; HFP EF, heart failure with preserved LVEF; HFP EF, HF with reduced LVEF; LVAD, left ventricular assistance device; and LVEF, left ventricular ejection fraction.
before and through exercise testing. The equipment was calibrated daily in standard fashion using reference gases. Minute ventilation (VE), oxygen consumption (VO2), and carbon dioxide production (VCO2) were acquired breath-by-breath and averaged over a 10-second interval, using a ventilatory expired gas analysis system (MGC Diagnostics, St. Paul, MN). Peak VO2 was defined as the highest 10-second averaged VO2 during the last stage of the symptom-limited exercise test. Percentage of predicted peak VO2 was determined based on the Wasserman formula:12,13 VE/VCO2 slope was taken from rest to the gas exchange at peak exercise. Rhythm was monitored with a continuous 12-lead ECG. Blood pressure was measured using a standard cuff sphygmomanometer. Resting and peak heart rate were obtained from the ECG. Age-predicted maximal heart rate was estimated by Astrand formula13: 220–age (years). Chronotropic index was calculated as follows: (peak heart rate–resting heart rate)/age-predicted maximal heart rate–resting heart rate.14

Outcomes
All-cause death was determined using the National Death Index with complete follow-up through December 31, 2014. The composite end point was defined as the composite outcome of LVAD implantation, heart transplantation, or all-cause mortality.

Statistical Analysis
Continuous variables are expressed as mean±SD for normally distributed data or median [25th, 75th percentiles] for non-normally distributed data. Categorical variables are expressed as numbers of subjects and proportion. Comparisons of baseline features among the studied groups were performed using 1-way ANOVA followed by Bonferroni correction among the studied groups. HFmEF and HFm-recEF had comparable ventilatory responses to exercise, with a higher peak VO2 (both absolute and percent of predicted) and lower VE/VCO2 slope than HFrEF. HFpEF tended to show lower absolute levels of peak VO2 than HFmEF and HFm-recEF, although the percent of predicted peak VO2 values—which accounts for between group differences in age—were similar between HFpEF and the midrange LVEF groups. HFmEF and HFm-recEF had similar clinical features when compared with both HFpEF and HFrEF. The prevalence of aldosterone antagonist use and of pacemakers or cardiac resynchronization therapy and implantable cardioverter defibrillator in HFm-recEF and HFmEF tended to be intermediate between HFpEF and HFrEF. Both HFm-recEF and HFmEF had a lower prevalence of diuretic use than HFpEF and HFrEF.

Cardiopulmonary Exercise Performance
CPET variables according to LVEF categories are shown in Table 2. Mean peak respiratory exchange ratio, a measure of exercise effort, was >1.1 in all patient groups. HFmEF and HFm-recEF had comparable ventilatory responses to exercise, with a higher peak VO2 (both absolute and percent of predicted) and lower VE/VCO2 slope than HFrEF. HFpEF tended to show lower absolute levels of peak VO2 than HFmEF and HFm-recEF, although the percent of predicted peak VO2 values—which accounts for between group differences in age—were similar between HFpEF and the midrange LVEF groups. HFmEF and HFm-recEF had similar VE/VCO2 slope when compared with HFpEF. Resting heart rate of HFmEF and HFm-recEF was similar to HFpEF but lower than HFrEF patients. Furthermore, HFm-recEF and HFmEF showed intermediate values of resting systolic blood pressure in comparison with those of HFpEF and HFrEF, but had peak systolic blood pressure values that were similar to HFpEF and higher than HFrEF. Finally, age-adjusted CPET findings among LVEF categories were concordant to the results obtained in unadjusted analyses (Table III in the Data Supplement).

Outcomes
During a median follow-up of 4.4 [2.9–5.7] years, there were 184 (19%) deaths, 62 (7%) LVAD implantations, 56 (6%) transplants, and 253 (27%) composite events. Kaplan–Meier analysis showed that HFmEF had the highest event rates among the studied groups, HFm-recEF had the lowest rate,
Mid-EF Heart Failure and HFmEF had event rates intermediate between HFrEF and HFpEF (unadjusted log-rank P < 0.001 for the overall difference; Figure 2). Results of univariate and multivariable Cox-regression analysis are shown in Table 3. In fully adjusted analysis, HFm-recEF was associated with lower risk of death (hazard ratio, 0.42; 95% confidence interval, 0.21–0.82; Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HFrEF, n=620 (66%)</th>
<th>HFm-recEF, n=170 (18%)</th>
<th>HFmEF, n=107 (11%)</th>
<th>HFpEF, n=47 (5%)</th>
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<td></td>
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<td>Age, y</td>
<td>55.4±13.2</td>
<td>52.2±13.0*</td>
<td>54.4±15.2</td>
<td>63.3±15.5*,†,‡</td>
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<td>Male, n (%)</td>
<td>452 (73)</td>
<td>104 (61)*</td>
<td>59 (55)*</td>
<td>23 (49)*</td>
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<td>White, n (%)</td>
<td>507 (82)</td>
<td>145 (85)</td>
<td>98 (92)*</td>
<td>40 (85)</td>
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<td>Body mass index, kg/m²</td>
<td>28.3±5.7</td>
<td>28.7±6.1</td>
<td>29.4±6.6</td>
<td>31.5±8.9*</td>
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<td>Ischemic cardiomyopathy, n (%)</td>
<td>188 (30)</td>
<td>18 (11)*</td>
<td>12 (12)*</td>
<td>3 (6)*</td>
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<td>Postchemotherapy, n (%)</td>
<td>38 (6)</td>
<td>20 (12)</td>
<td>17 (16)*</td>
<td>2 (4)</td>
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<td>NYHA, n (%)</td>
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<tr>
<td>I</td>
<td>147 (24)</td>
<td>81 (47)*</td>
<td>40 (37)</td>
<td>16 (34)</td>
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<tr>
<td>II</td>
<td>214 (34)</td>
<td>61 (36)</td>
<td>35 (33)</td>
<td>14 (30)</td>
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<tr>
<td>III</td>
<td>210 (34)</td>
<td>27 (16)*</td>
<td>30 (28)</td>
<td>16 (34)†</td>
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<tr>
<td>IV</td>
<td>49 (8)</td>
<td>1 (1)*</td>
<td>2 (2)</td>
<td>1 (2)</td>
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<td>Previous HF hospitalization, n (%)</td>
<td>486 (78)</td>
<td>96 (57)*</td>
<td>64 (60)*</td>
<td>41 (87)†,‡</td>
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<td>Symptomatic HF, n (%)</td>
<td>560 (90)</td>
<td>128 (75)*</td>
<td>77 (72)*</td>
<td>41 (87)</td>
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<td>Hypertension, n (%)</td>
<td>365 (59)</td>
<td>87 (51)</td>
<td>62 (58)</td>
<td>36 (77)†</td>
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<td>Diabetes mellitus, n (%)</td>
<td>182 (29)</td>
<td>27 (16)*</td>
<td>22 (21)</td>
<td>15 (32)</td>
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<td>Coronary artery disease, n (%)</td>
<td>255 (41)</td>
<td>36 (21)*</td>
<td>28 (26)*</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>215 (35)</td>
<td>46 (27)</td>
<td>30 (28)</td>
<td>18 (38)</td>
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<tr>
<td>COPD, n (%)</td>
<td>61 (10)</td>
<td>16 (10)</td>
<td>9 (8)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>72±26</td>
<td>82±24*</td>
<td>75±26</td>
<td>67±26†</td>
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<td>Hemoglobin, g/dL</td>
<td>13.6±1.7</td>
<td>13.5±1.7</td>
<td>13.0±2.0*</td>
<td>12.8±2.0†,*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25 [19, 30]</td>
<td>45 [40, 50]*</td>
<td>50 [45, 55]*†</td>
<td>60 [60, 65]*‡,†</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRT/ICD, n (%)</td>
<td>335 (54)</td>
<td>44 (26)*</td>
<td>15 (14)*†</td>
<td>1 (2)*†</td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>340 (55)</td>
<td>47 (28)*</td>
<td>23 (22)*</td>
<td>6 (13)*</td>
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<tr>
<td>β-blockers, n (%)</td>
<td>555 (90)</td>
<td>145 (85)</td>
<td>73 (68)*†</td>
<td>29 (62)*†</td>
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<tr>
<td>ACE/ARB, n (%)</td>
<td>510 (82)</td>
<td>146 (86)</td>
<td>58 (54)*†</td>
<td>30 (64)*†</td>
</tr>
<tr>
<td>Aldosterone antagonists, n (%)</td>
<td>220 (36)</td>
<td>38 (22)*</td>
<td>15 (14)*</td>
<td>2 (4)*†</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>468 (76)</td>
<td>80 (47)*</td>
<td>48 (45)*</td>
<td>34 (72)†,‡</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>24 (4)</td>
<td>13 (8)*</td>
<td>27 (25)*†</td>
<td>11 (23)*†</td>
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<tr>
<td>Anticoagulation, n (%)</td>
<td>244 (39)</td>
<td>43 (25)*</td>
<td>23 (22)*</td>
<td>15 (32)</td>
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<tr>
<td>Antiplatelets, n (%)</td>
<td>350 (57)</td>
<td>68 (40)*</td>
<td>44 (40)*</td>
<td>22 (47)</td>
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<tr>
<td>Antiarrhythmics, n (%)</td>
<td>254 (41)</td>
<td>38 (22)*</td>
<td>6 (6)*†</td>
<td>4 (9)*†</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>322 (52)</td>
<td>72 (43)</td>
<td>41 (38)</td>
<td>21 (45)</td>
</tr>
</tbody>
</table>

All P values are Bonferroni-adjusted. Data are presented as mean±SD for normally distributed variables and median [25th, 75th percentile] for non-normally distributed continuous variables. ACEI/ARB indicates angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; CRT/ICD, cardiac resynchronization therapy and/or implantable cardioverter defibrillator; GFR, glomerular filtration rate; HF, heart failure; HFmEF, HF with midrange and without recovered LVEF; HFm-recEF, HF with midrange and recovered LVEF; HFpEF, heart failure with preserved LVEF; HFrEF, HF with reduced LVEF; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association Classification.

*P<0.05 compared with HFrEF.
†P<0.05 compared with HFm-recEF.
‡P<0.05 compared with HFmEF.
P = 0.011) and composite end point (hazard ratio, 0.25; 95% confidence interval, 0.13–0.47; P < 0.001) than HFrEF, but had similar risk of death and composite end point when compared with HFpEF. HFmEF tended to show intermediate risk of outcomes in comparison with HFpEF and HFrEF, albeit not reaching statistical significance in fully adjusted analyses. Compared with HFmEF, HFm-recEF showed a lower risk of composite end point (hazard ratio, 0.31; 95% confidence interval, 0.15–0.67; P = 0.003) and a trend toward lower risk of death (hazard ratio, 0.48; 95% confidence interval, 0.22–1.05; P = 0.067) in analyses adjusted for all potential confounders.

### Temporal Change in LVEF Among HFmEF and HFm-recEF

To further evaluate the natural history of HFmEF and HFm-recEF, we investigated the temporal change in LVEF in these groups. Follow-up LVEF data were available in 73% (n=78) of HFmEF patients and in 72% (n=123) of HFm-recEF patients. The median time between baseline and follow-up echocardiograms was 2.7 [1.8, 3.7] years. Median values of LVEF showed modest increase in HFmEF (from 50% [44%, 55%] to 52% [45%, 55%]; P=0.03), but did not change in HFm-recEF (from 48% [40%, 55%] to 50% [44%, 55%]; P=0.42) at follow-up. Conversely, there was no difference in the proportion of patients who decreased (16% in HFm-recEF and 12% in HFmEF; P=0.77) or increased (20% in HFm-recEF and 27% in HFmEF; P=0.24) LVEF at follow-up in both groups. Older age, higher prevalence of hypertension and lower glomerular filtration rate were associated with reductions in LVEF in patients with HFm-recEF, whereas no studied variable was associated with changes in LVEF in HFmEF (Tables IV and V in the Data Supplement). Among HFm-recEF patients, 71% remained with LVEF between 40% and 55%, whereas 14% and 15% developed frankly reduced LVEF (values <25%) and normal LVEF (values >55%), respectively, at follow-up. Among HFmEF patients, 66% remained with LVEF between 40% and 55%, whereas 13% and 21% of HFmEF developed frankly reduced and normal LVEF values at follow-up, respectively.

### Discussion

This study of patients with HF with midrange LVEF had 3 major novel findings. First, among patients with HF and midrange LVEF, HFm-recEF had similar clinical characteristics and measures of exercise tolerance, but better prognosis compared with HFmEF. Second, although their clinical characteristics were distinct from HFpEF and HFrEF, HFmEF and HFm-recEF had ventilatory responses to exercise that were better than HFrEF and similar to HFpEF. Third, HFm-recEF had event rates that were lower than HFrEF and similar to HFpEF, whereas HFmEF had an intermediate risk of outcomes in comparison with HFpEF and HFrEF. These findings suggest that, among patients with HF with midrange LVEF, recovered systolic function is a marker of more favorable prognosis despite similar clinical characteristics and cardiopulmonary response to exercise.

In the present study, HFm-recEF had lower risk of death, LVAD implantation, and heart transplantation in comparison with HFmEF and HFrEF. These findings provide further support to the idea that patients with HF with recovered LVEF have better prognosis when compared with patients with lower LVEF but also to patients with similar LVEF levels but...
Mortality and morbidity program, those with midrange LVEF had mortality rates more similar to HFpEF. In the light of our findings, it can be speculated that midrange LVEF HF population was intermediate between HFpEF and HFrEF, whereas those with lower prevalence of recovered systolic function would tend to have prognosis more similar to HFpEF; whereas those with lower prevalence of recovered systolic function would tend to have an intermediate risk of outcomes in comparison with HFpEF and HFrEF. However, further studies are needed to confirm this hypothesis.

Consistent with previous studies in HF, our midrange LVEF groups had intermediate clinical characteristics (Tables VI and VII in the Data Supplement)1,5–7,17–19 and tended to have less clinical manifestations of HF when compared with HFrEF and HFpEF.6,8 HFmEF and HFm-recEF were also more likely to have a history of prior exposure to chemotherapy, pointing toward chemotherapy cardiotoxicity as a potential risk factor for the development of midrange LVEF. Furthermore, our finding that most of HFmEF and HFm-recEF patients remained with LVEF between 40% and 55% after a median of 2.8 years of follow-up indicates that HF with midrange LVEF is not necessarily a transition step of the progression from normal LVEF to HFrEF or vice versa. It was noteworthy that a high proportion (61%) of our midrange LVEF sample had recovered LVEF. Likewise, high rates of improved systolic function were also reported among HF populations with LVEF>40% or LVEF>50%.9,20 which implies that the prevalence of recovered LVEF among HF with midrange LVEF is substantial.

The reasons for the difference in prognosis between HFmEF and HFm-recEF are not clear. Exercise performance measures with validated prognostic value, such as peak VO2, percent of predicted peak VO2, and VE/VCO2 slope,11,22 had comparable values in both midrange LVEF groups, making differences in cardiopulmonary capacity unlikely as a cause. Additionally, the fact that HFm-recEF had lower baseline LVEF levels than HFmEF suggests that the more favorable prognosis in HFm-recEF is not explained by superior LV systolic performance of this group. HFm-recEF patients were more likely to use β-blockers, ACEI/ARB, and cardiac resynchronization therapy and implantable cardioverter defibrillator than HFmEF patients. Although we were unable to estimate changes in medical therapy over time, these findings suggest that differences in treatment regimens may partially account for the differences in outcomes. However, further studies are necessary to understand the precise mechanisms by which HFmEF and HFm-recEF had different outcomes.

Several limitations of this study should be acknowledged. This is an observational study and therefore unmeasured confounding factors may influence the observed associations. As noted above, HFm-recEF patients were more likely to use β-blockers and ACEI/ARB than HFmEF patients, which may be related to differences in tolerability of these medications and may have influenced differences in outcomes. Furthermore, we were unable to evaluate the influence of changes in medical therapy over time on measured outcomes. Skeletal muscle function and CPET performance can be influenced by duration of HF and the presence of cachexia, but these data were not available in our study. Similarly, biomarkers such as N-terminal of the prohormone brain natriuretic peptide are prognostically relevant in HF but were not uniformly assessed or available in our study population. Our sample included patients referred for CPET from a tertiary medical center and therefore might not be representative of the overall HF population, potentially limiting the generalizability of our findings. Because physicians who ordered CPET did not follow any standardized protocol, it is possible that our findings were influenced by indication without previously reduced systolic function.9 In contrast, HFm-recEF showed similar prognosis as HFpEF, indicating that HF with midrange LVEF and recovered systolic function still carries a significant risk of adverse outcomes. These latter findings are clinically relevant because they provide additional basis for maintaining subjects with recovered LVEF on background medical and device therapy, as previously recommended.8,9,16 The differences in prognosis between HFmEF and HFm-recEF may also help explain some reported discrepancies in prognosis in the midrange LVEF HF population. In the Cardiovascular Health Study, survival of midrange LVEF was intermediate between HFpEF and HFrEF,3 whereas in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity program, those with midrange LVEF had mortality rates more similar to HFpEF.6 In the light of our findings, it can be speculated that midrange LVEF HF populations with higher prevalence of recovered LVEF would have prognosis more similar to HFpEF; whereas those with lower prevalence of recovered systolic function would tend to have
bias. However, we tried to overcome this potential limitation by adjusting our Cox-regression models for important clinical characteristics. LVAD and heart transplantation were only obtained by clinical charts of Brigham and Women’s Hospital, which might have led to underestimation of these outcomes. Nevertheless, the frequency that patients with HF get these treatments at a referral institution different from where they are being longitudinally followed is usually low.

**Conclusion**

Patients with HF with midrange LVEF demonstrate a distinct clinical profile from HFpEF and HFrEF patients, with objective measures of functional capacity similar to HFpEF. Within the midrange LVEF HF population, recovered systolic function is a marker of more favorable prognosis, suggesting that identification of recovered LVEF status is important in prognostication and should be systematically assessed.

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**References**

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11. Few data are available on the phenotype, natural history, and prognosis of patients with heart failure with midrange ejection fraction (left ventricular ejection fraction [LVEF]) of 40% to 55%. Our study provides novel evidence that, among patients with heart failure with midrange LVEF, recovered systolic function is associated with more favorable prognosis than mid-range without prior reduced LVEF, despite similar clinical characteristics and cardiopulmonary response to exercise. Furthermore, our data suggest that patients with heart failure with midrange LVEF and recovered systolic function have similar prognosis as compared with patients with preserved LVEF, indicating that heart failure with midrange LVEF and recovered systolic function still carries a significant risk of adverse outcomes.

**CLINICAL PERSPECTIVE**

Few data are available on the phenotype, natural history, and prognosis of patients with heart failure with midrange ejection fraction (left ventricular ejection fraction [LVEF]) of 40% to 55%. Our study provides novel evidence that, among patients with heart failure with midrange LVEF, recovered systolic function is associated with more favorable prognosis than mid-range without prior reduced LVEF, despite similar clinical characteristics and cardiopulmonary response to exercise. Furthermore, our data suggest that patients with heart failure with midrange LVEF and recovered systolic function have similar prognosis as compared with patients with preserved LVEF, indicating that heart failure with midrange LVEF and recovered systolic function still carries a significant risk of adverse outcomes.
Heart Failure and Midrange Ejection Fraction: Implications of Recovered Ejection Fraction for Exercise Tolerance and Outcomes
Wilson Nadruz, Jr, Erin West, Mário Santos, Hicham Skali, John D. Groarke, Daniel E. Forman and Amil M. Shah

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Heart failure and mid-range ejection fraction: Implications of recovered ejection fraction for exercise tolerance and outcomes

Short title: Nadruz et al; Mid-EF Heart Failure

Wilson Nadruz Junior, MD, PhD\textsuperscript{1,2}; Erin West, MSc\textsuperscript{1}; Mário Santos, MD\textsuperscript{3}; Hicham Skali, MD, MSc\textsuperscript{1}; John D. Groarke MBBCh, MPH\textsuperscript{1}; Daniel E. Forman MD\textsuperscript{4}; Amil M. Shah, MD, MPH\textsuperscript{1}
**Supplemental Table 1.** Forward stepwise Cox regression analysis for death including all baseline clinical and treatment variables that showed significant differences among the studied groups in univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio [95% confidence interval]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate</td>
<td>0.99 [0.99-0.99]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.05 [1.44-2.94]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.84 [1.32-2.57]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1.71 [1.23-2.37]</td>
<td>0.001</td>
</tr>
<tr>
<td>Post-chemotherapy</td>
<td>2.18 [1.33-3.57]</td>
<td>0.001</td>
</tr>
<tr>
<td>Diuretics use</td>
<td>2.06 [1.29-3.29]</td>
<td>0.003</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.65 [0.45-0.93]</td>
<td>0.017</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.89 [0.81-0.97]</td>
<td>0.012</td>
</tr>
<tr>
<td>White race</td>
<td>1.79 [1.09-2.92]</td>
<td>0.021</td>
</tr>
<tr>
<td>Statins use</td>
<td>0.66 [0.46-2.92]</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Legend. Only variables that showed significant association are shown.

ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker.
**Supplemental Table 2.** Forward stepwise Cox regression analysis for the composite endpoint including all baseline clinical and treatment variables that showed significant differences among the studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio [95% confidence interval]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate</td>
<td>0.99 [0.98-0.99]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics use</td>
<td>2.32 [1.56-3.45]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonists use</td>
<td>1.61 [1.23-2.09]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI/ARB use</td>
<td>0.65 [1.56-3.45]</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.46 [1.12-1.90]</td>
<td>0.005</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>1.46 [1.12-1.89]</td>
<td>0.005</td>
</tr>
<tr>
<td>Post-chemotherapy</td>
<td>1.59 [1.03-2.46]</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Legend. Only variables that showed significant association are shown. The composite endpoint was defined as the composite outcome of left ventricular assistant device implantation, heart transplantation or all-cause mortality.

ACEI/ARB – angiotensin converting enzyme inhibitors or angiotensin receptor blockers.
**Supplemental Table 3:** Age-adjusted baseline cardiopulmonary exercise testing features of study participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HFrEF n=620 (66%)</th>
<th>HFm-recEF n=170 (18%)</th>
<th>HFmEF n=107 (11%)</th>
<th>HFpEF n=47 (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilatory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO$_2$, mL/min/Kg</td>
<td>14.4 ± 0.2</td>
<td>17.5 ± 0.4*</td>
<td>17.1 ± 0.5*</td>
<td>15.9 ± 0.8</td>
</tr>
<tr>
<td>VE/VCO$_2$ Slope</td>
<td>34.4 ± 0.3</td>
<td>29.3 ± 0.6*</td>
<td>30.7 ± 0.8*</td>
<td>30.5 ± 1.2*</td>
</tr>
<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>74.2 ± 0.6</td>
<td>68.7 ± 1.1*</td>
<td>69.4 ± 1.3*</td>
<td>71.2 ± 2.0</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>121.5 ± 1.0</td>
<td>129.2 ± 1.9*</td>
<td>123.8 ± 2.4</td>
<td>121.7 ± 3.7</td>
</tr>
<tr>
<td>Chronotropic index</td>
<td>0.52 ± 0.01</td>
<td>0.63 ± 0.02*</td>
<td>0.57 ± 0.03</td>
<td>0.53 ± 0.4†</td>
</tr>
<tr>
<td>Resting SBP, mmHg</td>
<td>114.0 ± 0.8</td>
<td>121.6 ± 1.4*</td>
<td>120.3 ± 1.8*</td>
<td>126.9 ± 2.8*†</td>
</tr>
<tr>
<td>Peak SBP, mmHg</td>
<td>134.9 ± 1.1</td>
<td>151.8 ± 2.1*</td>
<td>151.6 ± 2.7*</td>
<td>156.2 ± 4.2*</td>
</tr>
<tr>
<td>Resting DBP, mmHg</td>
<td>73.5 ± 0.5</td>
<td>75.4 ± 0.9</td>
<td>73.8 ± 1.1</td>
<td>74.5 ± 1.7</td>
</tr>
<tr>
<td>Peak DBP, mmHg</td>
<td>74.4 ± 0.5</td>
<td>77.2 ± 0.9*</td>
<td>76.0 ± 1.2</td>
<td>76.1 ± 1.9</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.19 ± 0.01</td>
<td>1.20 ± 0.01</td>
<td>1.20 ± 0.01</td>
<td>1.15 ± 0.02†</td>
</tr>
</tbody>
</table>

**Legend.** *p<0.05 compared to HFrEF; † p<0.05 compared to HFm-recEF; ‡ p<0.05 compared to HFmEF. Data are presented as mean ± standard error of the mean.

HFrEF – HF with reduced LVEF; HFm-recEF – HF with mid-range and recovered LVEF; HFmEF – HF with mid-range and without recovered LVEF; HFpEF – heart failure with preserved LVEF; LVEF- left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO$_2$ - minute ventilation-carbon dioxide production relationship; VO$_2$ – oxygen consumption.
### Supplemental Table 4. Features of heart failure with mid-range and recovered left ventricular ejection fraction (HFm-recEF) patients according to change in left ventricular ejection fraction

<table>
<thead>
<tr>
<th>Variables</th>
<th>ΔLVEF  &lt; -7%</th>
<th>ΔLVEF  -7 to +7%</th>
<th>ΔLVEF  &gt; +7%</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>n=20 (16%)</td>
<td>n=78 (64%)</td>
<td>n=25 (20%)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.1 ± 15.1</td>
<td>51.5 ± 12.3</td>
<td>44.6 ± 11.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>14 (70)</td>
<td>47 (60)</td>
<td>12 (48)</td>
<td>0.13</td>
</tr>
<tr>
<td>White, n(%)</td>
<td>16 (80)</td>
<td>65 (83)</td>
<td>21 (84)</td>
<td>0.74</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.9 ± 5.5</td>
<td>28.66 ± 6.62</td>
<td>28.93 ± 6.97</td>
<td>0.67</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n(%)</td>
<td>3 (15)</td>
<td>8 (10)</td>
<td>0 (0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Post-Chemotherapy, n(%)</td>
<td>2 (10)</td>
<td>8 (10)</td>
<td>4 (16)</td>
<td>0.50</td>
</tr>
<tr>
<td>Symptomatic heart failure, n(%)</td>
<td>15 (75)</td>
<td>56 (72)</td>
<td>19 (76)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>16 (80)</td>
<td>39 (50)</td>
<td>10 (40)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>5 (25)</td>
<td>14 (18)</td>
<td>4 (16)</td>
<td>0.46</td>
</tr>
<tr>
<td>Coronary artery disease, n(%)</td>
<td>5 (25)</td>
<td>13 (17)</td>
<td>4 (16)</td>
<td>0.46</td>
</tr>
<tr>
<td>Atrial Fibrillation, n(%)</td>
<td>5 (25)</td>
<td>26 (33)</td>
<td>3 (12)</td>
<td>0.26</td>
</tr>
<tr>
<td>COPD, n(%)</td>
<td>3 (15)</td>
<td>8 (10)</td>
<td>0 (0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>60.8 ± 29.4</td>
<td>85.9 ± 20.7</td>
<td>89.7 ± 26.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.0 ± 1.6</td>
<td>13.8 ± 1.5</td>
<td>13.5 ± 1.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Baseline treatment features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT/ICD, n(%)</td>
<td>3 (15)</td>
<td>21 (27)</td>
<td>5 (20)</td>
<td>0.77</td>
</tr>
<tr>
<td>Pacemaker, n(%)</td>
<td>3 (15)</td>
<td>23 (30)</td>
<td>5 (20)</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta-blockers, n(%)</td>
<td>17 (85)</td>
<td>66 (85)</td>
<td>20 (80)</td>
<td>0.63</td>
</tr>
<tr>
<td>ACEI/ARB, n(%)</td>
<td>19 (95)</td>
<td>67 (86)</td>
<td>21 (84)</td>
<td>0.30</td>
</tr>
<tr>
<td>Aldosterone antagonists, n(%)</td>
<td>5 (25)</td>
<td>18 (23)</td>
<td>3 (12)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diuretics, n(%)</td>
<td>13 (65)</td>
<td>37 (47)</td>
<td>12 (48)</td>
<td>0.30</td>
</tr>
<tr>
<td>Calcium channel blockers, n(%)</td>
<td>4 (20)</td>
<td>7 (9)</td>
<td>1 (4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Anticoagulation, n(%)</td>
<td>5 (25)</td>
<td>21 (27)</td>
<td>3 (12)</td>
<td>0.27</td>
</tr>
<tr>
<td>Treatment</td>
<td>Baseline n (%)</td>
<td>Follow-up n (%)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Antiplatelets, n(%)</td>
<td>11 (55)</td>
<td>27 (35)</td>
<td>7 (28)</td>
<td>0.07</td>
</tr>
<tr>
<td>Antiarrhythmics, n(%)</td>
<td>3 (15)</td>
<td>22 (28)</td>
<td>3 (12)</td>
<td>0.69</td>
</tr>
<tr>
<td>Statins, n(%)</td>
<td>8 (40)</td>
<td>32 (41)</td>
<td>10 (40)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### Baseline CPET features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Baseline Mean ± SD</th>
<th>Follow-up Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO$_2$, mL/min/Kg</td>
<td>16.7 ± 5.0</td>
<td>18.7 ± 7.1</td>
<td>18.0 ± 4.8</td>
</tr>
<tr>
<td>% Predicted Peak VO$_2$</td>
<td>70.2 ± 18.0</td>
<td>72.0 ± 20.3</td>
<td>70.0 ± 18.7</td>
</tr>
<tr>
<td>VE/VCO$_2$ Slope</td>
<td>28.9 ± 5.5</td>
<td>29.2 ± 6.5</td>
<td>27.0 ± 4.4</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>68.3 ± 12.9</td>
<td>68.5 ± 13.4</td>
<td>69.1 ± 11.4</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>125.8 ± 28.2</td>
<td>132.2 ± 23.9</td>
<td>138.0 ± 24.5</td>
</tr>
<tr>
<td>Chronotropic index</td>
<td>0.61 ± 0.26</td>
<td>0.64 ± 0.23</td>
<td>0.66 ± 0.24</td>
</tr>
<tr>
<td>Resting SBP, mmHg</td>
<td>124.4 ± 17.2</td>
<td>121.0 ± 20.9</td>
<td>118.1 ± 18.5</td>
</tr>
<tr>
<td>Peak SBP, mmHg</td>
<td>154.8 ± 19.6</td>
<td>151.7 ± 29.7</td>
<td>152.5 ± 25.7</td>
</tr>
<tr>
<td>Resting DBP, mmHg</td>
<td>74.9 ± 9.5</td>
<td>75.4 ± 11.5</td>
<td>72.7 ± 13.0</td>
</tr>
<tr>
<td>Peak DBP, mmHg</td>
<td>76.4 ± 8.8</td>
<td>78.2 ± 11.8</td>
<td>78.5 ± 13.7</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.19 ± 0.12</td>
<td>1.21 ± 0.11</td>
<td>1.24 ± 0.16</td>
</tr>
</tbody>
</table>

Legend. Data are presented as mean ± standard deviation for normally distributed continuous variables and median [25th,75th percentile] for non-normally distributed continuous variables.

ΔLVEF – change in follow-up LVEF compared to baseline LVEF; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD – chronic obstructive pulmonary disease; CRT/ICD - cardiac resynchronization therapy and/or implantable cardioverter defibrillator; GFR – glomerular filtration rate; LVEF - left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO$_2$ - minute ventilation-carbon dioxide production relationship; VO$_2$ – oxygen consumption.
**Supplemental Table 5.** Features of heart failure with mid-range and without recovered left ventricular ejection fraction (HFmEF) patients according to change in left ventricular ejection fraction

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\Delta LVEF$ $&lt; -7%$ n=9 (12%)</th>
<th>$\Delta LVEF$ $-7$ to $+7%$ n=48 (61%)</th>
<th>$\Delta LVEF$ $&gt; +7%$ n=21 (27%)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEF, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50 [45, 50]</td>
<td>50 [45, 55]</td>
<td>45 [40, 55]</td>
<td>0.09</td>
</tr>
<tr>
<td>Follow-up</td>
<td>33 [30, 35]</td>
<td>50 [45, 55]</td>
<td>55 [55, 65]</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td><strong>Baseline Clinical features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>$49.4 \pm 18.3$</td>
<td>$53.4 \pm 14.8$</td>
<td>$51.5 \pm 16.0$</td>
<td>0.92</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>4 (44)</td>
<td>25 (52)</td>
<td>12 (57)</td>
<td>0.53</td>
</tr>
<tr>
<td>White, n(%)</td>
<td>7 (78)</td>
<td>46 (96)</td>
<td>19 (91)</td>
<td>0.52</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>$28.9 \pm 9.7$</td>
<td>$28.8 \pm 6.3$</td>
<td>$30.5 \pm 6.6$</td>
<td>0.41</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n(%)</td>
<td>1 (11)</td>
<td>6 (13)</td>
<td>2 (10)</td>
<td>0.82</td>
</tr>
<tr>
<td>Post-Chemotherapy, n(%)</td>
<td>0 (0)</td>
<td>11 (23)</td>
<td>4 (19)</td>
<td>0.42</td>
</tr>
<tr>
<td>Symptomatic heart failure, n(%)</td>
<td>7 (78)</td>
<td>31 (65)</td>
<td>16 (76)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>4 (44)</td>
<td>26 (54)</td>
<td>12 (57)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>3 (33)</td>
<td>11 (23)</td>
<td>2 (10)</td>
<td>0.11</td>
</tr>
<tr>
<td>Coronary artery disease, n(%)</td>
<td>2 (22)</td>
<td>12 (25)</td>
<td>6 (29)</td>
<td>0.69</td>
</tr>
<tr>
<td>Atrial Fibrillation, n(%)</td>
<td>3 (33)</td>
<td>11 (23)</td>
<td>5 (24)</td>
<td>0.69</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>1 (11)</td>
<td>5 (10)</td>
<td>1 (5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>$79.9 \pm 28.0$</td>
<td>$75.7 \pm 23.5$</td>
<td>$85.9 \pm 22.7$</td>
<td>0.30</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>$12.3 \pm 2.1$</td>
<td>$13.4 \pm 1.8$</td>
<td>$13.4 \pm 2.3$</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Baseline treatment features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRT/ICD, n(%)</td>
<td>3 (33)</td>
<td>6 (13)</td>
<td>3 (14)</td>
<td>0.34</td>
</tr>
<tr>
<td>Pacemaker, n(%)</td>
<td>3 (33)</td>
<td>6 (13)</td>
<td>5 (24)</td>
<td>0.94</td>
</tr>
<tr>
<td>Beta-blockers, n(%)</td>
<td>8 (89)</td>
<td>30 (63)</td>
<td>16 (76)</td>
<td>0.90</td>
</tr>
<tr>
<td>ACEI/ARB, n(%)</td>
<td>7 (78)</td>
<td>27 (56)</td>
<td>11 (52)</td>
<td>0.27</td>
</tr>
<tr>
<td>Aldosterone antagonists, n(%)</td>
<td>1 (11)</td>
<td>6 (13)</td>
<td>2 (10)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diuretics, n(%)</td>
<td>4 (44)</td>
<td>16 (33)</td>
<td>11 (52)</td>
<td>0.40</td>
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<tr>
<td>Calcium channel blockers, n(%)</td>
<td>2 (22)</td>
<td>11 (23)</td>
<td>3 (14)</td>
<td>0.50</td>
</tr>
<tr>
<td>Anticoagulation, n(%)</td>
<td>3 (33)</td>
<td>9 (19)</td>
<td>3 (14)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Antiplatelets, n(%)  
4 (44.4)  20 (42)  6 (29)  0.32

Antiarrhythmics, n(%)  
1 (11)  2 (4)  2 (10)  0.86

Statins, n(%)  
2 (22)  16 (33)  7 (33)  0.65

Baseline CPET features

Peak VO\textsubscript{2}, mL/min/Kg  
20.4 ± 13.0  18.6 ± 8.7  16.0 ± 8.9  0.19

% Predicted Peak VO\textsubscript{2}  
76.0 ± 25.7  75.5 ± 24.1  62.3 ± 19.8  0.06

VE/VCO\textsubscript{2} Slope  
29.4 ± 4.9  30.3 ± 6.4  29.7 ± 4.2  0.94

Resting HR, bpm  
65.4 ± 16.4  70.9 ± 14.8  68.8 ± 14.7  0.81

Peak HR, bpm  
125.8 ± 34.4  132.0 ± 31.5  121.5 ± 29.2  0.47

Chronotropic index  
0.56 ± 0.25  0.65 ± 0.31  0.51 ± 0.22  0.35

Resting SBP, mmHg  
121.1 ± 25.4  115.5 ± 17.6  127.0 ± 20.3  0.17

Peak SBP, mmHg  
148.9 ± 31.0  152.3 ± 32.3  147.3 ± 29.6  0.75

Resting DBP, mmHg  
72.5 ± 9.1  72.2 ± 12.2  76.8 ± 9.5  0.19

Peak DBP, mmHg  
71.7 ± 16.3  75.3 ± 13.0  76.7 ± 10.5  0.39

Peak RER  
1.17 ± 0.10  1.21 ± 0.12  1.18 ± 0.13  0.14

Legend. Data are presented as mean ± standard deviation for normally distributed continuous variables and median [25\textsuperscript{th},75\textsuperscript{th} percentile] for non-normally distributed continuous variables.

\(\Delta\)LVEF – change in follow-up LVEF compared to baseline LVEF; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD – chronic obstructive pulmonary disease; CRT/ICD - cardiac resynchronization therapy and/or implantable cardioverter defibrillator; GFR – glomerular filtration rate; LVEF- left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO\textsubscript{2} - minute ventilation-carbon dioxide production relationship; VO\textsubscript{2} – oxygen consumption.
**Supplemental Table 6.** Characteristics of heart failure patients from the Brigham and Women’s Hospital and from other studies that enrolled chronic heart failure patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th><strong>Cardiovascular Health Study</strong></th>
<th><strong>CHARM</strong></th>
<th><strong>He et al</strong></th>
<th><strong>Brigham and Women’s Hospital</strong></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HFrEF</td>
<td>HFmidEF</td>
<td>HFrEF</td>
<td>HFmidEF</td>
</tr>
<tr>
<td>n</td>
<td>60</td>
<td>39</td>
<td>170</td>
<td>4576</td>
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<tr>
<td>Mean age, years</td>
<td>74</td>
<td>73</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>63</td>
<td>49</td>
<td>44</td>
<td>74</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>74</td>
<td>71</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>Mean SBP, mmHg</td>
<td>127</td>
<td>136</td>
<td>138</td>
<td>127</td>
</tr>
<tr>
<td>Mean DBP, mmHg</td>
<td>66</td>
<td>68</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57</td>
<td>72</td>
<td>59</td>
<td>49</td>
</tr>
<tr>
<td>CAD/MI, %</td>
<td>78</td>
<td>69</td>
<td>58</td>
<td>65-75</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>23</td>
<td>36</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>42</td>
<td>28</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>ARB, %</td>
<td>Beta-blockers, %</td>
<td>Aldosterone ant., %</td>
<td>Diuretics, %</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------------</td>
<td>---------------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7 8 17</td>
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<td>55 57 54</td>
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<td>39</td>
<td>58</td>
<td>36</td>
<td>88 64 63</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>67</td>
<td>4</td>
<td>13 26 37</td>
</tr>
<tr>
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<td>19</td>
<td>23</td>
<td>4</td>
<td>39 54</td>
</tr>
<tr>
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<td>21</td>
<td>23</td>
<td>4</td>
<td>58 55</td>
</tr>
<tr>
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<td>14</td>
<td>23</td>
<td>4</td>
<td>62 68</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>23</td>
<td>4</td>
<td>68 68</td>
</tr>
</tbody>
</table>

**Legend.** HFrEF – heart failure (HF) with reduced left ventricular ejection fraction (LVEF); HFmidEF – HF with mid-range LVEF; HFpEF – HF with preserved LVEF; HFm-recEF – HF with mid-range LVEF and recovered LVEF; HFmEF – HF with mid-range LVEF without recovered LVEF. CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity. BMI – body mass index; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; CAD – coronary artery disease; MI – myocardial infarction; ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blockers; Aldosterone ant. – aldosterone antagonists; CCB – calcium channel blockers.

**Supplemental Table 7.** Characteristics of heart failure patients from the Brigham and Women’s Hospital and from other studies that enrolled acutely-decompensated heart failure patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPTIMIZE-HF(^1)</th>
<th>ADHERE(^2)</th>
<th>ASCEND-HF(^3)</th>
<th>Brigham and Women’s Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFrEF</td>
<td>HFmidEF</td>
<td>HFpEF</td>
<td>HFrEF</td>
</tr>
<tr>
<td>LVEF cut-off</td>
<td>&lt;40%</td>
<td>40–50%</td>
<td>&gt;50%</td>
<td>≤40%</td>
</tr>
<tr>
<td>n</td>
<td>20118</td>
<td>7321</td>
<td>10070</td>
<td>40796</td>
</tr>
<tr>
<td>Mean age, years</td>
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<td>74</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>Men, %</td>
<td>62</td>
<td>48</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>Mean BMI, kg/m(^2)</td>
<td>39</td>
<td>44</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>89</td>
<td>86</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>Mean SBP, mmHg</td>
<td>135</td>
<td>147</td>
<td>150</td>
<td>136</td>
</tr>
<tr>
<td>Mean DBP, mmHg</td>
<td>77</td>
<td>77</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66</td>
<td>74</td>
<td>77</td>
<td>68</td>
</tr>
<tr>
<td>CAD/MI, %</td>
<td>54</td>
<td>49</td>
<td>32</td>
<td>63</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>41</td>
<td>48</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>29</td>
<td>33</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.5</td>
<td>11.9</td>
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<td>12.8</td>
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<td>eGFR, mL/min/1.73m(^2)</td>
<td>69</td>
<td>54</td>
<td>51</td>
<td>69</td>
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</tbody>
</table>

\(^1\) HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmidEF: heart failure with mid-ejection fraction; HFpEF: heart failure with preserved ejection fraction.

\(^2\) ADHERE: Acute Decompensated Heart Failure Events Following Cardiovascular Therapies.

\(^3\) ASCEND-HF: Acute Care Strategies to Reduce Events in Congestive Heart Failure.
<table>
<thead>
<tr>
<th></th>
<th>45</th>
<th>38</th>
<th>34</th>
<th>66</th>
<th>57</th>
<th>51</th>
<th>60$^\dagger$</th>
<th>61$^\dagger$</th>
<th>63$^\dagger$</th>
<th>64</th>
<th>65</th>
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</thead>
<tbody>
<tr>
<td>ACE inhibitors, %</td>
<td>45</td>
<td>38</td>
<td>34</td>
<td>66</td>
<td>57</td>
<td>51</td>
<td>60$^\dagger$</td>
<td>61$^\dagger$</td>
<td>63$^\dagger$</td>
<td>64</td>
<td>65</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>ARB, %</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>15</td>
<td>16</td>
<td>19</td>
<td>21</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
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<td>54</td>
<td>50</td>
<td>67</td>
<td>62</td>
<td>55</td>
<td>59</td>
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<td>67</td>
<td>90</td>
<td>85</td>
<td>68</td>
<td>62</td>
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<tr>
<td>Aldosterone ant., %</td>
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<td>6</td>
<td>4</td>
<td>33</td>
<td>21</td>
<td>13</td>
<td>36</td>
<td>22</td>
<td>14</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td>Diuretics, %</td>
<td>63</td>
<td>59</td>
<td>57</td>
<td>95</td>
<td>97</td>
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<tr>
<td>CCB, %</td>
<td>5$^\dagger$</td>
<td>9$^\dagger$</td>
<td>11$^\dagger$</td>
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<tr>
<td>Lipid lowering, %</td>
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<td>38</td>
<td>45</td>
<td>45</td>
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<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Defibrillator, %</td>
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<td>54</td>
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</tbody>
</table>

**Legend.** HFrEF – heart failure (HF) with reduced left ventricular ejection fraction (LVEF); HFmidEF – HF with mid-range LVEF; HFP EF – HF with preserved LVEF; HFm-recEF – HF with mid-range LVEF and recovered LVEF; HFmEF – HF with mid-range LVEF without recovered LVEF. OPTIMIZE-HF - Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; ADHERE - Acute Decompensated Heart Failure Registry; ASCEND-HF – Acute Studies of Nesiritide in Decompensated Heart Failure; BMI – body mass index; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; CAD – coronary artery disease; MI – myocardial infarction; eGFR – estimated glomerular filtration rate; ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blockers; Aldosterone ant. – aldosterone antagonists; CCB – calcium channel blockers. *values are weighted measures adapted from ref. 1. $^\dagger$ amloidipine; $^\ddagger$ ACE inhibitor or ARB; $^\ddagger$ Fonarow GC, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50:768-77. $^\ddagger$ Sweitzer NK, et al. Comparison of clinical features and outcomes of patients
Supplemental Figure 1.

Legend: Left ventricular ejection fraction (LVEF) distribution of the studied sample. HFrEF – HF with reduced LVEF; HFm-recEF – HF with mid-range and recovered LVEF; HFmEF – HF with mid-range and without recovered LVEF; HFPpEF – heart failure with preserved LVEF.