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Clinical Characteristics, Response to Exercise Training and Outcomes in Heart Failure Patients with Chronic Obstructive Pulmonary Disease: Findings from HF-ACTION

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Abstract

Background—To investigate the clinical characteristics, exercise training response, beta-blocker selectivity and outcomes in heart failure (HF) patients with chronic obstructive pulmonary disease (COPD).

Methods—We performed an analysis of HF-ACTION, which randomized 2,331 HF patients with ejection fraction $\geq 35\%$ to usual care with or without aerobic exercise training. We examined clinical characteristics and outcomes [mortality/hospitalization, mortality, cardiovascular (CV) mortality/CV hospitalization, and CV mortality/HF hospitalization] by physician-reported COPD status using adjusted Cox models and explored an interaction with exercise training. The interaction between beta-blocker cardioselectivity and outcomes was investigated.

Results—Of patients with COPD status documented (N=2311), 11% (N=249) had COPD. COPD patients were older, had more comorbidities, and lower use of beta-blockers compared to those without COPD. At baseline, COPD patients had lower peak $\dot{V}O_2$ and higher $\dot{V}E/\dot{V}CO_2$ slope. During a median follow-up of 2.5 years, COPD was associated with increased mortality/hospitalization, mortality, and CV mortality/HF hospitalization. After multivariable adjustment, the risk of CV mortality/HF hospitalization remained increased (Hazard Ratio [HR] 1.46, 95% Confidence Interval [CI]: 1.14–1.87), while mortality/hospitalization (HR 1.15, 95% CI: 0.96–

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1.37) and mortality (HR 1.33, 95% CI: 0.99–1.76) were not significantly increased. There was no interaction between COPD and exercise training on outcomes or between COPD and beta-blocker selectivity on mortality/hospitalization (all $P>0.1$).

Conclusions—COPD in HF patients was associated with older age, more comorbidities, reduced exercise capacity, and increased CV mortality/HF hospitalization, but not a differential response to exercise training. Beta-blocker selectivity was not associated with differences in outcome for patients with versus without COPD.

Keywords

heart failure; COPD; exercise training

Chronic obstructive pulmonary disease (COPD) is a common comorbidity seen in ~30% of patients with heart failure (HF)¹, yet its impact on clinical outcomes is unclear. Until recently, few studies have focused on the prognosis of HF patients with COPD. HF predictive models have been inconsistent regarding the impact of COPD on mortality. Several studies support worse outcomes in HF patients with COPD^{4–6}, while others have been neutral. The primary effect of COPD in HF patients may be increased non-cardiovascular (CV) mortality in the acute HF setting⁹ with similar outcomes following hospital discharge¹⁰.

In COPD patients with concomitant HF, clinicians underuse evidence-based HF therapies. Concerns exist about beta-blockers, particularly non-cardioselective beta-blockers, precipitating bronchospasm or attenuating the benefit of inhaled beta-2 agonists in such patients¹¹. However, the impact of beta-blocker selectivity in patients with concomitant HF and COPD is not well-characterized. Similarly, while data suggest a positive effect of pulmonary rehabilitation on patients' symptoms and outcomes in the general COPD population¹⁴, limited data exist on the impact of exercise training in COPD patients with HF.

We aimed to describe the baseline clinical characteristics and long-term outcomes of HF patients with COPD in a cohort of ambulatory HF patients enrolled in the HF-ACTION study (Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing). We were interested in the baseline quality of life and exercise capacity of HF patients with and without COPD. Our secondary aims were to explore interactions with exercise training and beta-blocker selectivity on outcomes and health status. We hypothesized that COPD would be associated with increased hospitalization, but not increased mortality or a differential exercise training response. We also hypothesized that non-cardioselective beta-blockers would not be associated with worse outcomes compared with cardioselective beta-blockers in HF patients with COPD.

Methods

The design, rationale, and primary results of the HF-ACTION study have been published. Briefly, HF-ACTION was a randomized trial evaluating the effect of exercise training and usual care versus usual care alone on outcomes in patients with chronic HF (New York Heart Association [NYHA] class II–IV, left ventricular ejection fraction [LVEF] $\geq 35\%$). The primary endpoint was mortality/hospitalization over a median follow-up of 2.5 years. An independent clinical events committee adjudicated CV hospitalizations; if a HF hospitalization for a patient was confirmed by the committee, no future hospitalizations were adjudicated for that patient. COPD status was prospectively recorded on study enrollment by the clinician-investigator based on clinical evidence and knowledge by past medical history

of COPD. HF-ACTION was approved by local institutional review boards, and all enrolled patients provided written informed consent.

Statistical Methods

Baseline characteristics were described by COPD status. Continuous variables were summarized with the median and 25th and 75th percentiles and compared using the Wilcoxon rank-sum statistic. Categorical variables are presented as percentages and compared with a Pearson chi-squared statistic or exact test when appropriate. The change in exercise capacity (indexed by 6-minute walk distance, and the cardiopulmonary exercise testing [CPX] parameters of peak oxygen consumption [VO₂] and exercise duration) and health status (as reported on the Kansas City Cardiomyopathy Questionnaire [KCCQ]), from baseline to 3 months was examined in the usual care and exercise training study arms. Emphasis was given to the 3-month time point due to the greater amount of missing data at later time points.

The primary outcome was hospitalization/mortality. We also evaluated the secondary outcomes of time to cardiovascular (CV) death/CV hospitalization, CV death/HF hospitalization, and mortality. We analyzed the relationship between COPD and outcomes using Cox proportional hazards models, including adjustment for a comprehensive set of predictors¹⁷. We explored the interaction between COPD and treatment assignment for the primary and secondary outcomes using adjusted Cox models.

Linear regression modeling adjusted for baseline covariates was used to explore an interaction between COPD and treatment as a predictor of the change in exercise parameters and health status variables from baseline to 3 months. Baseline adjustment covariates were determined via stepwise selection from a list of candidate covariates. To account for increased missing data at 3 months, possibly correlated with treatment or COPD status, subjects in the linear regression model were inversely weighted by their probability of having a missing response.

We examined the interaction between COPD and beta-blocker cardioselectivity as a predictor of mortality/hospitalization using adjusted Cox models. A two-tailed *P* value <0.05 was considered statistically significant for all analyses, bearing in mind the exploratory nature of this study. All statistical analyses were performed by the Duke Clinical Research Institute using SAS (Cary, NC) system version 9.2. No extramural funding was used. The authors are solely responsible for the study analyses, the drafting and editing of the paper and its final contents.

Results

Of patients with baseline determination of COPD status (N=2311), 11% (N=249) had COPD. Table 1 presents the baseline characteristics by COPD status. COPD patients were significantly older, with more ischemic etiology, compared to those without COPD. COPD patients more often had hypertension, atrial fibrillation/flutter and prior myocardial infarction. The COPD group had a similar LVEF to those without COPD. Blood pressure and heart rate were similar between those with and without COPD as were basic laboratory values. Over 90% of patients with and without COPD were receiving ACE-inhibitors (ACE-Is)/angiotensin II receptor blockers (ARBs) at baseline, with approximately half as many receiving aldosterone antagonists. There were no significant between-group differences in the use of ACE-Is/ARBs or aldosterone antagonists, but COPD patients were less likely to receive beta-blockers. Patients with COPD were more likely to receive cardioselective than non-cardioselective beta-blockers (54% vs. 38% of patients on a beta-blocker). COPD

patients received lower doses of both cardioselective and non-cardioselective beta-blockers compared to non-COPD patients.

Table 2 presents the baseline health status and exercise parameters in patients with and without COPD. Compared with non-COPD patients, those with COPD had worse quality of life. COPD patients also had worse baseline exercise capacity as evidenced by shorter CPX duration and 6-minute walk distance compared to those without COPD. Those patients with COPD had lower peak VO_2 and higher VE/VCO_2 slope and were significantly less likely to achieve a respiratory exchange ratio (RER) >1.10 , a value suggestive of near-maximal effort¹⁸.

Exercise training adherence as measured by total exercise minutes per week for months 1–3 (excluding the initial three weeks) was similar in those with and without COPD [median of 77 minutes (40, 118) versus 77 (29, 109), respectively]. The absolute change in exercise capacity and health status outcomes from baseline to 3 months in those with and without COPD is presented in Table 3. After adjusting for baseline characteristics, there was insufficient evidence to suggest an interaction between COPD status and exercise training for each of the exercise and health status variables (all $P>0.1$) (Table 3).

COPD was associated with increased mortality/hospitalization, mortality, and CV mortality/HF hospitalization on unadjusted analysis, but not with increased CV mortality/CV hospitalization (Table 4). After multivariable adjustment, the increased risk of CV mortality/HF hospitalization remained statistically significant (Hazard Ratio [HR] 1.46, 95% Confidence Interval [CI]: 1.14–1.87), while mortality/hospitalization (HR 1.15, 95% CI: 0.96–1.37) and mortality (HR 1.33, 95% CI: 0.99–1.76) were not significantly increased. There was no evidence to suggest an interaction between exercise training and COPD status for any of the clinical endpoints (all $P>0.15$).

For the overall cohort, there was no significant difference in mortality/hospitalization by beta-blocker type (65% vs. 68%, non-cardioselective vs. cardioselective beta-blockers, $P=0.09$; adjusted HR 0.97; 95% CI, 0.86–1.10). Figure 1 presents the Kaplan-Meier survival estimates for mortality/hospitalization by beta-blocker selectivity and COPD status. The adjusted HR for mortality/hospitalization in the COPD cohort with cardioselective beta-blockers vs. noncardioselective beta-blockers was 0.91; 95% CI, 0.64–1.29; $P=0.58$). There was insufficient evidence to suggest an interaction between COPD status and beta-blocker selectivity associated with mortality/hospitalization following risk adjustment ($P=0.72$).

Discussion

The prognosis for patients with COPD and HF have been conflicting and limited data exist with respect to the impact of exercise training and beta-blocker selectivity on outcomes in this population. In HF-ACTION, the largest randomized trial of exercise training in chronic, stable HF patients with reduced EF¹⁶, we demonstrated that COPD was associated with older age, an increased burden of comorbidities, worse baseline clinical status, and reduced exercise capacity. In the adjusted analysis, COPD was associated with a 46% increased risk for CV mortality/HF hospitalization, but not with the other clinical endpoints, nor did it confer a differential response to exercise training. In addition, beta-blocker selectivity was not associated with differences in outcome for HF patients with COPD versus those without.

HF patients with COPD had an increased burden of comorbidities, including hypertension, atrial fibrillation/flutter and coronary disease compared to those without COPD. The underlying pathophysiology may be due, in part, to the shared risk factor of smoking with low-grade systemic inflammation accelerating the progression of atherosclerosis, ischemic heart disease and COPD¹⁹. The diagnosis and management of comorbidities should be

targeted to this high-risk population, since the risk for adverse outcomes for HF patients substantially increases with the number of chronic conditions⁵.

In contrast to previous studies, HF-ACTION patients with and without COPD had similar baseline vital signs, laboratory values, and ACE-inhibitor/aldosterone antagonist use. In EVEREST and OPTIMIZE-HF, COPD patients tended to have lower blood pressure, higher serum creatinine and underuse of ACE-inhibitors/aldosterone antagonists. Our findings may be due, in part, to the relatively stable chronic HF population in HF-ACTION. Therefore, while HF patients with COPD may demonstrate different clinical profiles compared to those without COPD in the acute setting, the between-group differences may be less marked following HF stabilization. These findings suggest greater attention to the initiation and uptitration of HF therapies in the COPD population following HF stabilization. Nevertheless, we found that COPD patients with HF were significantly less likely to receive beta-blockers than those without COPD. Guidelines recommend beta-blocker therapy in patients with coexistent COPD and HF with reduced EF. Notably, the usage of beta-blockers in COPD patients in HF-ACTION (88%) was greater than in previous studies (e.g. ~65%). This finding was likely related to the HF-ACTION protocol which encouraged the use of an optimal guideline-based HF regimen for 6 weeks before enrollment.

It has been suggested that improved utilization of beta-blockers in HF patients with COPD should involve cardioselective beta-blockers pending additional data. We found that COPD patients more often received cardioselective beta-blockers compared to non-COPD patients, but those with COPD still tended to receive lower doses of cardioselective beta-blockers. Careful uptitration of beta-blocker dosage is warranted in HF patients²² including in those with concomitant COPD. Despite concerns about beta-blocker therapy in HF patients with COPD, there was no evidence that beta-blocker selectivity was associated with differences in clinical outcomes for the overall cohort or for those with COPD. Similar findings have been demonstrated in OPTIMIZE-HF²³.

Functional limitation as quantified by 6-minute walk distance and CPX testing has been associated with poor quality of life and worse outcomes in both COPD patients and HF patients²⁴⁻³¹. However, baseline functional capacity and the impact of exercise training in patients with concomitant COPD and HF have not been well characterized. We demonstrated that, compared with non-COPD patients, HF patients with COPD had a significant reduction in functional capacity at baseline, both during CPX testing and the 6-minute walk test. COPD patients were also significantly less likely to achieve a peak RER >1.10, a value generally considered to indicate near-maximal effort¹⁸. However, a RER <1.10 may also be seen in those with a pulmonary limitation to exercise¹⁸. There was insufficient evidence to suggest an interaction between COPD status and the exercise training effect on health status and CPX variables after adjusting for baseline characteristics. Nonetheless, the differences in exercise variables observed between those with and without COPD should be taken into account when interpreting functional evaluations for clinical risk stratification and in the design and analysis of trials in HF and COPD populations.

Our finding of no association between COPD and the primary outcome of mortality/hospitalization has several possible explanations. First, it may be that COPD is not associated with increased mortality/hospitalization. Other factors such as neurohormonal activation, renal dysfunction and metabolic status may play a more prominent role than COPD in determining outcomes. Second, the difficulty of diagnosing COPD in patients with HF may have limited the ability to detect between-group differences in outcome. Alternatively, our neutral findings may be related to selecting a lower risk COPD cohort in the setting of an exercise training clinical trial.

There was a significant 46% increased risk for CV mortality/HF hospitalization associated with COPD. COPD may worsen HF due to mechanisms including low-grade inflammation, underuse of beta-blockers and adverse CV effects of bronchodilators⁹. The increased risk for hospitalization in HF patients with COPD may also be related to the reduction in HF-related mortality with contemporary therapies. With the improved survival of HF patients with COPD, there is a larger population at risk for hospitalization.

Our study should be interpreted in the context of several limitations. This was a retrospective analysis. Outside the context of a prospective, controlled trial, definitive cause-and-effect relationships are difficult to determine. The study population had strict inclusion and exclusion criteria for a trial of exercise training in HF, such that these findings may not apply to those with different baseline characteristics; the percentage of patients with COPD in this study (11%) was substantially lower than in the general HF community (~30%). COPD was defined by the clinician-investigator at patient enrollment based on clinical evidence or knowledge by past medical history. While objective criteria such as pulmonary function tests (PFTs) were not explicitly used, our stratification is strengthened by the fact that clinicians prospectively collected the data in the controlled setting of a clinical trial. Since the majority of HF patients have not had PFTs,³³ which may be confounded by abnormal respiratory physiology due to HF, the classification of COPD in the present analysis represents the method frequently used in clinical practice. Given the exclusion of individuals on supplemental oxygen and lack of information on forced expiratory volume in 1 second and bronchodilator therapy, future prospective studies are warranted⁹. Since patients with COPD are commonly excluded from HF clinical trials (and vice-versa), this analysis provides background for future trials that incorporate PFT criteria and document bronchodilator and steroid use (inhaled and oral). Despite covariate adjustment, other measured and unmeasured factors may have influenced these findings. Given the potential for type II error, future prospective studies with longer follow-up duration will need to externally validate these associations.

Conclusion

COPD in patients with HF due to systolic dysfunction was associated with older age, more comorbidities, worse clinical status, lower beta-blocker use, reduced exercise capacity, and increased CV mortality/HF hospitalization, but not with the primary endpoint of mortality/hospitalization. We did not observe a differential response to aerobic exercise training in those with and without COPD. Beta-blocker selectivity was not associated with differences in long-term outcome. However, given baseline differences in these patient groups, COPD status should be taken into account in the design and analysis of trials of exercise training in HF patients.

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Figure 1.
Kaplan-Meier Survival Estimates for All-Cause Mortality/Hospitalization by Beta-blocker Selectivity and COPD Status.

Table 1

Baseline Characteristics by COPD Status.

Variable	No COPD (n=2062, 89%)	COPD (n=249, 11%)
Age, years *	59 (51, 68)	64 (56, 71)
Female Sex	29	25
Race		
Black or African American	33	24
White	60	70
Other	5	6
New York Heart Association Class III-IV *	35	50
Ischemic Etiology *	50	62
Left Ventricular Ejection Fraction, %	25 (20, 30)	25 (20, 30)
Diabetes Mellitus	32	34
Previous Myocardial Infarction *	41	53
Hypertension *	59	66
Atrial Fibrillation/Flutter *	20	27
Systolic Blood Pressure, mmHg	110 (100, 126)	112 (104, 124)
Heart Rate, bpm	70 (63, 77)	72 (64, 79)
Sodium, mmol/L	139 (137, 141)	139 (137, 141)
Blood Urea Nitrogen, mg/dL	20 (15, 28)	21 (16, 31)
Serum Creatinine, mg/dL	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)
ACE-Inhibitor/Angiotensin II Receptor Blocker	95	92
Beta-blocker *	95	88
Cardioselective *	38	54
Cardioselective dose †, mg/day *	50 (25, 75)	25 (13, 50)
Non-Cardioselective *	62	46
Non-Cardioselective dose †, mg/day	38 (19, 50)	25 (13, 50)
Aldosterone Antagonist	45	44
Loop Diuretic	77	82
Digoxin	44	49
Implantable Cardioverter Defibrillator	40	41
Biventricular Pacemaker	18	20

Expressed as median (IQR) or percentage

* P-value<0.05

† Carvedilol dose equivalent

Table 2

Baseline Health Status and Exercise Parameters by COPD Status.

Variable	No COPD (n=2062, 89%)	COPD (n=249, 11%)	P-value
Beck Depression Inventory II Score	8 (4, 15)	9 (5, 16)	0.023
Kansas City Cardiomyopathy Questionnaire Score	69 (52, 84)	61 (49, 78)	<0.001
6-Minute Walk Distance, meters	376 (303, 439)	326 (259, 405)	<0.001
Cardiopulmonary Exercise Duration, min	10.0 (7.1, 12.2)	7.4 (5.6, 10.2)	<0.001
Peak VO ₂ , mL/kg/min	14.6 (11.6, 17.8)	13.1 (10.1, 15.9)	<0.001
VE/VCO ₂ Slope	32 (28, 38)	34 (29, 41)	0.003
% with Respiratory Exchange Ratio >1.10	44	36	0.024
Heart Rate at Peak Exercise, bpm	120 (105, 135)	114 (97, 126)	<0.001

Expressed as median (IQR) unless noted

Table 3

Change in Exercise and Health Status Outcomes from Baseline to 3 Months.

Test	No COPD (n=2062, 89%)	COPD (n=249, 11%)	P-value for Interaction between COPD, Treatment Assignment and Outcome*
Change in KCCQ Score			
Usual Care	2.1 (-5.2, 9.4)	3.9 (-5.2, 13.5)	0.52
Exercise	5.2 (-2.1, 13.5)	2.1 (-4.9, 13.3)	
Change in 6-Minute Walk, m			
Usual Care	5 (-28, 37)	1 (-41, 40)	0.16
Exercise	20 (-16, 55)	19 (-9, 69)	
Change in CPX Duration, min			
Usual Care	0.3 (-0.6, 1.5)	0.1 (-1.1, 1.0)	0.51
Exercise	1.5 (0.3, 3.0)	1.4 (0.2, 2.4)	
Change in Peak VO ₂ , mL/kg/min			
Usual Care	0.2 (-1.2, 1.5)	0.1 (-1.0, 1.2)	0.82
Exercise	0.7 (-0.8, 2.4)	0.2 (-0.6, 1.5)	

Expressed as median (interquartile range)

KCCQ, Kansas City Cardiomyopathy Questionnaire; CPX, cardiopulmonary exercise test

*The interaction analyses have been adjusted as follows:

Change in KCCQ score: baseline KCCQ overall summary score, age, peripheral vascular disease, biventricular pacemaker, atrial fibrillation/flutter, Beck Depression score, BUN, BMI, CCS angina class, and peak VO₂.

Change in 6-minute walk: baseline 6-minute walk distance, number of HF hospitalizations in the previous 6 months, resting heart rate, LVEF, KCCQ clinical summary score, BUN, peak respiratory exchange ratio, smoking status, CPX duration, and peak VO₂.

Change in CPX duration: baseline CPX duration, age, sex, number of HF hospitalizations in the previous 6 months, ischemic etiology, atrial fibrillation/flutter, diastolic blood pressure, KCCQ clinical summary score, BUN, BMI, peak respiratory exchange ratio, heart rate, income, and peak VO₂.

Change in peak VO₂: baseline peak VO₂, age, sex, number of HF hospitalizations in the previous 6 months, ischemic etiology, insulin use, pacemaker, LVEF, BUN, BMI, peak respiratory exchange ratio, race, and CPX duration.

Table 4

Outcome Hazard Ratios for Patients with Concomitant COPD.

Outcome	Chi-Square	p-value	Hazard Ratio (95% CI)	P-value for Interaction between COPD, Treatment Assignment and Outcome
All-Cause Mortality or Hospitalization (# events=1542)				
Unadjusted	14.0	<0.001	1.34 (1.15 – 1.56)	
Adjusted* [N = 1756]	2.4	0.13	1.15 (0.96 – 1.37)	0.62
All-Cause Mortality (# events=384)				
Unadjusted	21.7	<0.001	1.89 (1.45 – 2.48)	
Adjusted† [N = 2220]	3.8	0.051	1.33 (0.99 – 1.76)	0.17
CV Mortality or CV Hospitalization (# events=1298)				
Unadjusted	1.7	0.20	1.12 (0.94 – 1.33)	
Adjusted‡ [N = 1728]	<0.1	0.93	0.99 (0.81 – 1.21)	0.88
CV Mortality or HF Hospitalization (# events=731)				
Unadjusted	14.3	<0.001	1.51 (1.22 – 1.86)	
Adjusted§ [N = 1692]	8.9	0.003	1.46 (1.14 – 1.87)	0.30

Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure

* Adjusted for Weber class, KCCQ symptom stability score, BUN, country, LVEF, sex, beta-blocker dosage, mitral regurgitation grade, and ventricular conduction prior to baseline CPX test.

† Adjusted for exercise duration on baseline CPX, serum creatinine level, BMI, sex, loop diuretic dose, LVEF, CCS angina classification, and ventricular conduction prior to baseline CPX.

‡ Adjusted for LVEF, mitral regurgitation grade, ventricular conduction on baseline CPX, KCCQ symptom stability score, BUN, race, heart rate at peak exercise on baseline CPX, sex, nitrates at baseline, Weber class, and KCCQ total symptom score.

§ Adjusted for loop diuretic dose, LVEF, mitral regurgitation grade, ventricular conduction prior to baseline CPX, KCCQ symptom stability score, BUN, race, sex, age, Weber class, and VE/VCO₂ on baseline CPX.