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Audio Interview

Effects of Exercise Training on Depressive Symptoms in Patients With Chronic Heart Failure

The HF-ACTION Randomized Trial

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AN ESTIMATED 5 MILLION PEOPLE in the United States have heart failure, and more than 500 000 new cases are diagnosed annually.¹ Heart failure is associated with increased morbidity and mortality and compromised quality of life. Indeed, clinical depression is a common comorbidity, affecting as many as 40% of patients with heart failure,² with up to 75% of patients reporting elevated depressive symptoms.³ Depression also is associated with worse clinical outcomes in a variety of cardiac patient populations, including those with myocardial infarction, unstable angina, and coronary bypass surgery.⁴⁻⁶ Recent reports from our group and others also have reported an association between depression and increased risk of adverse events in patients with heart failure.⁷⁻¹⁰

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Context Depression is common in patients with cardiac disease, especially in patients with heart failure, and is associated with increased risk of adverse health outcomes. Some evidence suggests that aerobic exercise may reduce depressive symptoms, but to our knowledge the effects of exercise on depression in patients with heart failure have not been evaluated.

Objective To determine whether exercise training will result in greater improvements in depressive symptoms compared with usual care among patients with heart failure.

Design, Setting, and Participants Multicenter, randomized controlled trial involving 2322 stable patients treated for heart failure at 82 medical clinical centers in the United States, Canada, and France. Patients who had a left ventricular ejection fraction of 35% or lower, had New York Heart Association class I to IV heart failure, and had completed the Beck Depression Inventory II (BDI-II) score were randomized (1:1) between April 2003 and February 2007. Depressive scores ranged from 0 to 59; scores of 14 or higher are considered clinically significant.

Interventions Participants were randomized either to supervised aerobic exercise (goal of 90 min/wk for months 1-3 followed by home exercise with a goal of ≥ 120 min/wk for months 4-12) or to education and usual guideline-based heart failure care.

Main Outcome Measures Composite of death or hospitalization due to any cause and scores on the BDI-II at months 3 and 12.

Results Over a median follow-up period of 30 months, 789 patients (68%) died or were hospitalized in the usual care group compared with 759 (66%) in the aerobic exercise group (hazard ratio [HR], 0.89; 95% CI, 0.81 to 0.99; $P = .03$). The median BDI-II score at study entry was 8, with 28% of the sample having BDI-II scores of 14 or higher. Compared with usual care, aerobic exercise resulted in lower mean BDI-II scores at 3 months (aerobic exercise, 8.95; 95% CI, 8.61 to 9.29 vs usual care, 9.70; 95% CI, 9.34 to 10.06; difference, -0.76 ; 95% CI, -1.22 to -0.29 ; $P = .002$) and at 12 months (aerobic exercise, 8.86; 95% CI, 8.67 to 9.24 vs usual care, 9.54; 95% CI, 9.15 to 9.92; difference, -0.68 ; 95% CI, -1.20 to -0.16 ; $P = .01$).

Conclusions Compared with guideline-based usual care, exercise training resulted in a modest reduction in depressive symptoms, although the clinical significance of this improvement is unknown.

Trial Registration clinicaltrials.gov Identifier: NCT00047437

JAMA. 2012;308(5):465-474

www.jama.com

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Despite this increased risk, however, there have been few randomized trials to treat depression in patients with heart failure. In the Sertraline Against Depression and Heart Disease-Heart Failure (SADHART-CHF) trial, reductions in depressive symptoms were not greater in patients receiving sertraline than in placebo controls and there was no effect of treating depression on clinical outcomes.¹¹

Aerobic exercise has been proposed as a potential treatment for depression¹² and may be comparable with established pharmacologic therapies.^{13,14} The Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study reported that exercise training, when added to evidence-based, usual care, produced modest reductions in all-cause mortality and all-cause hospitalization.¹⁵ This HF-ACTION ancillary study was designed to assess the effects of exercise on depressive symptoms and to determine whether reduced depressive symptoms were associated with improved clinical outcomes.

METHODS

Eligibility and Trial Overview

A description of the methods and primary results of the HF-ACTION trial have been published previously.^{15,16} Briefly, HF-ACTION was a multicenter, randomized clinical trial of exercise training vs usual care in patients with left ventricular ejection fraction of 35% or lower and New York Heart Association class II to IV symptoms despite optimal heart failure therapy for at least 6 weeks. Patients were recruited from 82 centers within the United States, Canada, and France. Race and ethnicity were documented by self-report (ie, white, Hispanic, black/African American, Native American, Asian, Hawaiian/Pacific Islander) per National Institutes of Health reporting guidelines.

The protocol was approved by the respective institutional review boards or ethics committees for each of the clinical sites and the coordinating center. All patients voluntarily provided written in-

formed consent. The study was conducted between April 2003 and February 2007.

After an initial baseline assessment, patients were randomized 1:1 to either aerobic exercise training or usual care. A permuted block randomization scheme stratified by clinical center and by heart failure etiology (ie, ischemic vs nonischemic) was used. Ischemic etiology was defined as the presence of at least 1 of the 4 following criteria: (1) angiographic evidence of 75% or greater lesion in 1 or more of the 3 major epicardial vessels; (2) history of myocardial infarction; (3) history of revascularization procedure; or (4) evidence of significant perfusion defect in the setting of ischemic symptoms.

The primary medical end point was all-cause mortality, hospitalization, or both, whereas the primary psychological end point was depressive symptoms assessed after 3 months of supervised exercise. Secondary medical end points included cardiovascular (CV) mortality and hospitalization and heart failure mortality and hospitalization. The secondary psychological end point was depressive symptoms assessed at 12 months.

Assessment Procedures

Exercise Testing. All patients underwent baseline exercise stress testing under continuous electrocardiographic monitoring with direct measurement of oxygen consumption to document aerobic fitness. Tests were reviewed by investigators to identify significant arrhythmias or ischemia that would prevent safe exercise training and to establish appropriate training heart rate ranges.

Assessment of Depression. Depression was assessed using the Beck Depression Inventory II (BDI-II).¹⁷ The BDI-II is a 21-item, self-report measure of depressive symptoms using a 0-to-3 scale (range, 0-63). Each item asks about a particular symptom of depression, as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.¹⁸ The BDI-II has been widely studied in car-

diac patients and has excellent psychometric properties including a test-retest reliability coefficient of 0.93. A score of 14 or greater is considered to reflect clinically significant depressive symptoms.¹⁷ A previous report suggested that an approximate 50% reduction in clinical symptoms is generally considered to be clinically meaningful in trials of patients with major depression,¹⁹ but a clinically significant difference in BDI-II scores between 2 treatment groups has not been established.

Interventions

Aerobic Exercise. Patients randomized to aerobic exercise participated in 3 supervised exercise sessions per week for 3 months. Patients exercised using a treadmill or stationary cycle ergometer as their primary training mode. Patients were encouraged to begin home-based exercise after 18 supervised sessions and to fully transition to home exercise after 36 supervised sessions. Patients were provided home exercise equipment of their choice (cycle or treadmill by ICON) and heart rate monitors (Polar USA). The primary index of adherence was weekly volume of self-reported exercise (in minutes). Full adherence was defined a priori as at least 90 min/wk of supervised exercise during months 1 through 3 and at least 120 min/wk of home-based exercise during months 4 through 12.

Usual Care. Patients randomized to usual care were not provided with a formal exercise prescription. All patients, regardless of treatment group, received detailed self-management educational materials at the time of enrollment, including information on medications, fluid management, symptom exacerbation, sodium intake, and activity recommendations of 30 minutes of moderate-intensity activity on most days of the week, consistent with the American College of Cardiology/American Heart Association guidelines.²⁰

Follow-up. Patients were asked to return for clinic visits every 3 months for the first 2 years of participation and yearly thereafter up to 4 years. Depression was assessed by repeat adminis-

tration of the BDI-II at 3-month intervals for the first year. To provide comparable levels of attention from study personnel in the aerobic exercise and usual care groups, patients were called every 2 weeks for the first 9 months, monthly until 24 months of follow-up, and quarterly thereafter. During these calls, patients in the aerobic exercise group were asked if they were performing the exercise training regimen as prescribed. Antidepressant medication use was recorded at baseline and 12 months. Patients in the usual care group were asked if they were exercising, but because of concern that inquiring about exercise could unintentionally promote exercise, no quantification of exercise was obtained.

Patients made their final visit at the end of the study follow-up period or at 4 years, whichever came first. Follow-up was completed on March 15, 2008. For patients lost to follow-up, searches of the Social Security Death Index and the National Death Index were performed to assess whether any of these patients had died.

Primary and Secondary Outcomes. The primary medical end point was a composite of all-cause mortality or all-cause hospitalization; cardiovascular (CV) mortality and hospitalization and heart failure mortality and hospitalization served as combined secondary medical end points. The primary psychological end point was the BDI-II score at 3 months (ie, at the completion of the supervised exercise phase of the study); BDI-II scores at 12 months served as a secondary end point. We also explored the relationship between exercise adherence and BDI-II scores. Patients and investigators were blinded with respect to their BDI-II scores.

Deaths and hospitalizations were adjudicated by a clinical end point committee, blinded to treatment assignment and BDI-II scores. Once the patient had an adjudicated heart failure hospitalization, no further hospitalizations for the patient were reviewed. Event times were calculated as the time elapsed from randomization to the first event or to censoring (time to last contact).

Statistical Analysis

Sample characteristics were described as median and interquartile range (IQR) for continuous variables and frequency and percent for categorical variables. To examine the effect of exercise on BDI-II scores at months 3 and 12, we used 2 separate general linear models, in which treatment group assignment predicted posttreatment BDI-II scores. We selected, a priori, age, sex, race/ethnicity, smoking, mitral valve regurgitation grade, Weber class (ie, aerobic capacity), New York Heart Association class, diabetes, use of antidepressant medication, and pretreatment BDI-II score as adjustment covariates. We supplemented this analysis by exploring the same model with the sample restricted to participants with clinically significant levels of depressive symptoms (BDI-II ≥ 14) at baseline. These analyses adhered to the intent-to-treat principle, using SAS PROC MI to impute missing data.

We used general linear models to examine the association between self-reported minutes of exercise and BDI-II scores at months 3 and 12. Because self-reported minutes of exercise were not recorded in the usual care group, the analysis was limited to only participants in the aerobic exercise group. In this model, we included the following baseline variables selected a priori: BDI-II, sex, age, race/ethnicity, smoking status, blood urea nitrogen, left ventricular ejection fraction, New York Heart Association class, hypertension, diabetes, 6-minute walk distance, Weber score, Kansas City Cardiomyopathy Questionnaire score,²¹ site, β -blocker dose, and mitral valve regurgitation, ventricular conduction status, and use of any antidepressant medication. We also estimated a Cox regression model²² to investigate the association between self-reported minutes of exercise and the primary and secondary clinical end points. These latter models included the same covariates described above in the analysis of minutes of exercise and BDI-II scores.

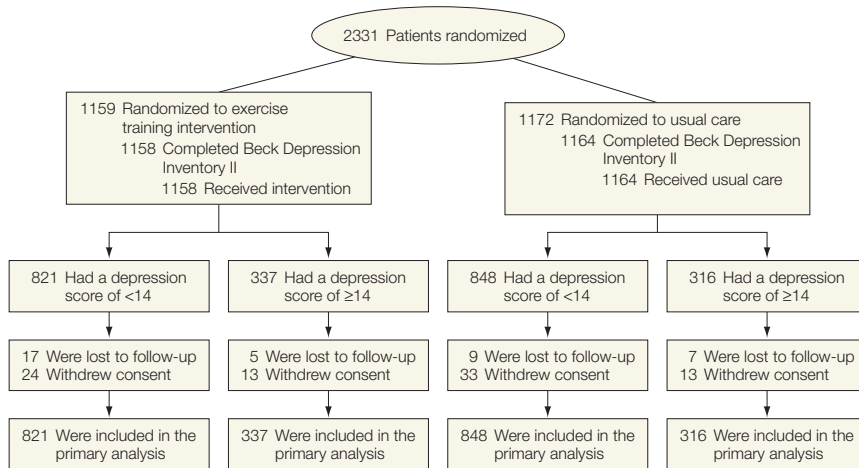
In addition, we estimated 2 sets of Cox regression models that examined

the association between the baseline BDI-II scores and the primary clinical end point and the change in BDI-II scores from baseline to month 3 with the clinical end points. In the latter model, we limited our analysis to clinical events that occurred after the end of the 3-month treatment period. The models included the same covariates described above in the analysis of exercise minutes and BDI-II scores. With the exception of the general linear models for the 3- and 12-month depression outcomes, adjustment covariates with missing data were imputed using the median of the variable. For key predictor variables that were measured as continuous variables (minutes of exercise, BDI-II scores), we tested for potential nonlinearity using restricted cubic splines with 3 knots.²³

The sample size for the main trial was calculated for the primary medical end point such that there was 90% power to detect an 11% reduction associated with treatment in 2-year all-cause mortality or all-cause hospitalization. In a post hoc calculation, we estimated the detectable effect size for treatment on the BDI-II scores, given the known available sample size. With a sample size of 2322, assuming a standard deviation of 10 on the BDI-II and a 2-sided significance level of .05, we estimated that we would have 80% power to detect a treatment group difference of about 1 point on the BDI-II. All analyses used a 2-sided test for significance at an α of .05. Analyses were carried out using SAS (SAS Institute Inc) and the rms package in R (<http://www.r-project.org>).

RESULTS

The sample comprised 2322 participants (99% of the original sample of 2331 patients) who completed the BDI-II at baseline (pretreatment). FIGURE 1 displays the patient flow through the study. TABLE 1 displays the background demographic and clinical characteristics of the sample for each treatment group, stratified by baseline depressive symptom severity. The median age of the participants was 59 years (IQR, 51-68; range, 19-91). The major-

Figure 1. Flow of Participants Through Trial

The total number of patients screened and the reasons for their exclusion are not known.

ity of participants were white, men, and married and had achieved at least a high school education. The median BDI-II score at study entry was 8 (IQR, 4-15; range, 0-59); BDI-II scores of 14 or higher are considered to reflect clinically significant depressive symptoms,¹⁷ which was noted in 28% of the sample.

The aerobic exercise and usual care groups were generally comparable with respect to baseline demographic and clinical characteristics. A slightly higher proportion of aerobic exercise participants had a greater than high school education compared with usual care participants (62% vs 58%) and had achieved a shorter distance on the 6-minute walk test (366 vs 373 meters). Participants with more severe depressive symptoms at baseline were more likely to be taking an antidepressant medication and also were more likely to have more severe heart failure, although these differences were comparable across treatment groups. (eTable available at <http://www.jama.com>.)

Adherence to Exercise Protocol

As reported in the primary article,¹⁵ patients in the aerobic exercise group exercised for a median of 76 min/wk during the first 3 months of supervised exercise, increased to a median of 95 min/wk during months 4 through 6,

and then decreased to 74 min/wk at months 10 through 12. During the supervised phase (ie, months 0-3), 41% of the sample achieved full adherence (defined as ≥ 90 min/wk), whereas full adherence (defined as >120 min/wk) during the home-based phase was achieved in 42% of the sample in months 4 through 6, 41% of the sample achieved full adherence in months 7 through 9, and 38% of the sample achieved full adherence in months 10 through 12.

Cardiopulmonary Changes With Treatment

After 3 months, participants in the aerobic exercise group increased their peak oxygen consumption by 0.6 mL/min/kg compared with 0.2 mL/min/kg in the usual care group ($P < .001$); aerobic exercise participants further increased it by 0.7 mL/min/kg from baseline to 12 months compared with 0.1 mL/min/kg for those in the usual care group ($P < .001$).

Effects of Exercise on Depressive Symptoms

Depression scores were available for 2322 participants at baseline, 2019 at month 3 and 1738 at month 12. The adjusted 3-month BDI-II mean score was 8.95 (95% CI, 8.61 to 9.29) for the aerobic exercise group and 9.70 (95% CI,

9.34 to 10.06) for usual care, for a difference of -0.76 (95% CI, -1.22 to -0.29 ; $P = .002$). The adjusted BDI-II score at month 12 was 8.86 (95% CI, 8.67 to 9.24) for the aerobic exercise group and 9.54 (95% CI, 9.15 to 9.92) for usual care, for a difference of -0.68 (95% CI -1.20 to -0.16 ; $P = .01$).

We also examined the treatment effects within the subset of patients with clinically significant depressive symptoms (baseline BDI-II scores ≥ 14). In this case, the BDI-II scores at 3 months were lower for patients in the aerobic exercise group (mean, 16.66; 95% CI, 15.78 to 17.53) than for patients in usual care group (mean, 17.98; 95% CI, 17.04 to 18.91; $P = .04$), for a difference of -1.31 (95% CI, -2.54 to -0.09), and also lower after month 12 for depressed patients in the aerobic exercise group (mean, 15.85; 95% CI, 14.90 to 16.78) than for depressed patients in usual care group (mean, 17.34; 95% CI, 16.34 to 18.34; $P = .02$), for a difference of -1.56 (95% CI, -2.84 to -0.27).

We also explored the association between self-reported minutes of exercise per week and BDI-II scores at months 3 and 12. Because detailed exercise information was available for only the participants in the aerobic exercise group, participants in the usual care group were excluded from these analyses, leaving 814 participants with complete data for the 3-month analysis and 629 for the 12-month analysis.

Volume of exercise (in minutes) at month 3 was inversely related to depressive symptoms. Compared with a participant reporting no exercise, a participant reporting 90 minutes of exercise per week could be expected to have a 1.55-point lower BDI-II score at 3 months (95% CI, -2.88 to -0.33 ; $P = .001$) and a 1.67-point lower BDI-II score at 12 months (95% CI, -2.62 to -0.73 , $P = .001$). Self-reported exercise at 12 months was associated with BDI-II scores at 12 months in a nonlinear fashion ($P = .003$; FIGURE 2). The nonlinear effect was such that exercise time beyond 90 minutes of exercise per week appeared to provide little added benefit.

Relation of Exercise and Subsequent Clinical Events

TABLE 2 displays the frequency for the primary end point and 2 secondary end points for each treatment group stratified by BDI-II severity at baseline. Among the 2322 cases available for the analysis of the primary clinical end point (all-cause death or first all-cause hospitalization), we observed 1548 events (386 deaths and 1162 hospitalizations) over a median follow-up time of 30 months (IQR, 5.3-

27; range, 0-49). FIGURE 3 displays Kaplan-Meier curves for event-free survival for the primary end point, stratified by treatment group and BDI-II severity categories (BDI-II <14 vs BDI-II ≥14). The Cox regression model revealed that aerobic exercise was associated with a lower risk for an event than usual care (HR, 0.89; 95% CI, 0.81-0.99, $P=.03$). Aerobic exercise also was associated with lower risk for the secondary end point of heart failure hospitalizations and death (HR, 0.85; 95%

CI, 0.73-0.98; $P=.03$) than usual care and was associated with a statistically nonsignificant lower risk of CV hospitalization and death (HR, 0.91; 95% CI, 0.81-1.01; $P=.09$).

Relation of Depressive Symptoms and Subsequent Clinical Events

Higher baseline BDI-II was associated with increased event risk. Because BDI-II scores were modeled as a continuous variable, in post hoc analysis we elected to scale the BDI-II scores in the Cox

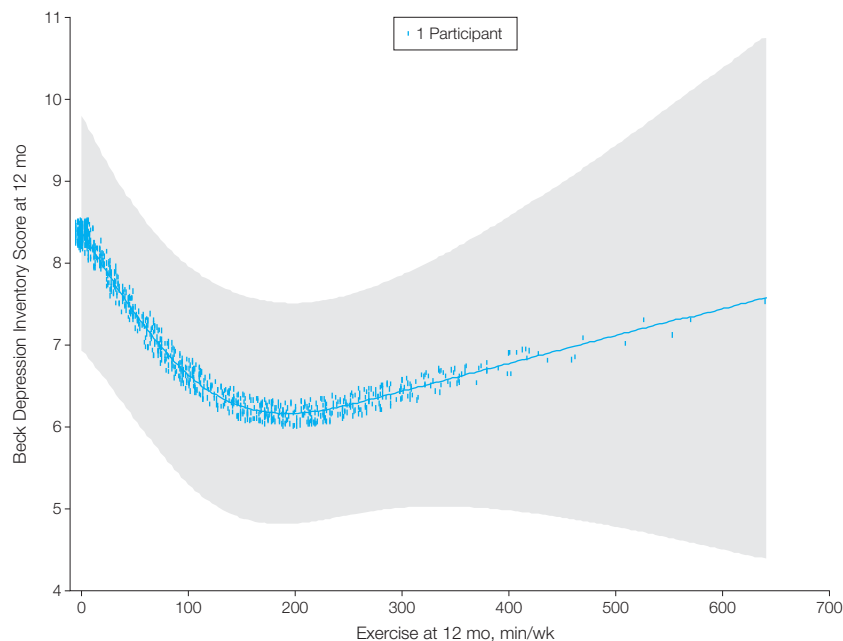
Table 1. Baseline Demographic and Clinical Characteristics of Sample

	No. of Participants With Nonmissing Data	No. (%) of Participants					
		Exercise (n = 1158)			Usual Care (n = 1164)		
		BDI-II Score		All Exercise Participants	BDI-II Score		All Usual Care Participants
		<14 (n = 821)	≥14 (n = 337)		<14 (n = 848)	≥14 (n = 316)	
Age, median (IQR), y	2322	61 (52-69)	56 (50-64)	59 (51-68)	61 (53-69)	56 (47-63)	59 (51-68)
Race/ethnicity							
Black	2288	262 (32)	115 (35)	377 (33)	254 (30)	116 (37)	377 (33)
White		503 (62)	194 (59)	697 (61)	539 (64)	184 (59)	697 (61)
Other		43 (5)	22 (7)	65 (6)	45 (5)	11 (4)	65 (6)
Women	2322	31 (252)	28 (94)	30 (346)	26 (220)	28 (90)	30 (346)
United States	2322	723 (88)	303 (90)	1026 (89)	744 (88)	292 (92)	1026 (89)
Married	2315	481 (59)	178 (53)	659 (57)	513 (61)	165 (52)	678 (58)
>High school	2271	505 (63)	189 (57)	694 (62)	500 (61)	161 (51)	661 (58)
>\$25 000 annual income	2067	460 (62)	156 (52)	616 (59)	459 (62)	144 (50)	603 (59)
BDI-II score	2322	6 (4-9)	20 (16-25)	8 (5-15)	6 (3-9)	20 (17-25)	8 (4-15)
Peak oxygen consumption, median (IQR), mL/min/kg	2268	15 (12-18)	14 (11-17)	14 (11-18)	15 (12-18)	14 (11-17)	14 (12-18)
BMI, median (IQR)	2316	30 (26-34)	31 (27-36)	30 (26-35)	29 (26-34)	32 (27-37)	30 (26-35)
Diabetes	2322	261 (32)	117 (35)	378 (33)	255 (30)	115 (36)	370 (32)
Hypertension	2309	504 (62)	207 (61)	711 (62)	483 (57)	190 (61)	673 (58)
Current smoking	2311	116 (14)	68 (20)	184 (16)	133 (16)	66 (21)	199 (17)
NYHA class							
III or IV	2322	258 (31)	177 (53)	435 (38)	269 (32)	147 (47)	416 (36)
Angina class							
None	2319	694 (85)	261 (78)	955 (83)	735 (87)	252 (80)	987 (85)
CHF etiology							
Nonischemic	2322	399 (49)	162 (48)	561 (48)	396 (47)	173 (55)	569 (49)
LVEF, median (IQR), %	2318	25 (20-30)	25 (20-30)	25 (20-30)	25 (20-30)	25 (20-30)	25 (20-30)
6-Minute walk, median (IQR), m	2271	377 (300-442)	351 (279-420)	366 (296-436)	380 (310-440)	354 (266-420)	373 (300-432)
Mitral valve regurgitation							
High	2129	81 (11)	42 (14)	123 (12)	88 (11)	44 (15)	132 (12)
Ventricular conduction							
Normal	2263	352 (44)	137 (42)	489 (43)	360 (44)	127 (41)	487 (43)
KCCQ score, median (IQR) ^a	2322	75 (61-86)	48 (37-62)	68 (50-82)	76 (61-88)	48 (36-58)	69 (52-84)
Weber score, median (IQR) ^b	2268	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)
Blood urea nitrogen, median (IQR), mg/dL	2020	21 (16-28)	18 (15-28)	20 (15-28)	19 (15-28)	21 (15-29)	21 (15-28)
β-Blocker dose, median (IQR), mg/d	2302	25 (13-50)	50 (13-50)	38 (13-50)	28 (13-50)	25 (13-50)	25 (13-50)
Loop diuretic dose, median (IQR), mg/d	2289	40 (1-80)	40 (20-80)	40 (20-80)	40 (20-80)	40 (20-80)	40 (20-80)
Any antidepressant, median (IQR)	2322	131 (16)	117 (35)	248 (21)	149 (17)	129 (40)	278 (23)

Abbreviations: BDI-II, Beck Depression Inventory II; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CHF, congestive heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

^aKansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item survey to assess quality of life in patients with heart failure. The range of scores is 0-100; higher scores reflect better quality of life.

^bWeber scores indicate levels of aerobic capacity with a range of 1 to 4 with lower scores representing higher fitness levels by peak oxygen consumption: 1 (> 20 mL/min/kg); 2 (> 16 and < 20 mL/min/kg); 3 (> 10 and < 16 mL/min/kg); and 4 (< 10 mL/min/kg).

Figure 2. Nonlinear Association Between Self-Reported Weekly Minutes of Exercise (From Months 9-12) and BDI-II Scores at 12 Months

Adjusted for sex, age, race, smoking status, blood urea nitrogen, left ventricular ejection fraction, New York Heart Association class, hypertension, diabetes, 6-minute walk distance, Weber score, Kansas City Cardiomyopathy Questionnaire score,²¹ site, β -blocker dose, mitral valve regurgitation, ventricular conduction status, use of any antidepressant medication, and baseline and 3-month Beck Depression Inventory II (BDI-II) scores. The weekly minutes term in the model was fitted using a 3-knot restricted cubic spline. The analysis is limited to participants in the aerobic exercise group who had complete BDI-II data at 12 months ($n=629$). The fitted line is for a typical participant (median of continuous covariates, most prevalent class for categorical variables). Shaded area represents 95% confidence intervals. Data markers display data density with respect to minutes of exercise, are drawn at actual minutes of exercise values for each patient along the fitted regression line, and are scattered vertically along fitted line to display case density; some data markers may extend beyond the x-axis range in order to display case density more clearly. Comparing a participant who reported 90 minutes of exercise per week to a participant who reported 0 minutes per week revealed a regression coefficient of -1.67 (95% CI, -2.62 to -0.73).

model such that the HR compared a nondepressed participant, a score of 4 (the value at the 25th percentile) with a participant with mild clinical depression, a score 14 or higher. The HR for this BDI-II scaling was 1.16 (95% CI, 1.05-1.29, $P=.01$). Participants with higher levels of depression also were at increased risk for heart failure death and heart failure hospitalizations. Comparing a participant with a BDI-II score of 14 with a participant with score of 4 resulted in a HR of 1.20 (95% CI, 1.03-1.40; $P=.02$). Similarly, for the combined secondary CVD end point, comparing a typical participant with a BDI-II score of 14 at baseline to a participant with a score of 4, the HR was 1.17 (95% CI, 1.04-1.31; $P=.003$).

We also examined the association of change in BDI-II score from baseline to 3 months and the time to all-cause death or first hospitalization by adding the raw change in score, from baseline to 3 months, to the primary model, maintaining the baseline score in the model. After excluding persons who had no BDI-II data at 3 months, 2009 patients were available for analysis, 1289 of whom experienced an event during the subsequent follow-up period. The treatment group by BDI-II change interaction was not significant ($P=.73$), suggesting that the relationship between change in depressive symptoms and the primary end point was similar for both treatment groups. After adjusting for covariates (includ-

ing baseline BDI-II scores and antidepressant medication use), we observed a significant association between BDI-II change score and risk of all cause death or hospitalization ($P=.02$; eFigure available at <http://www.jama.com>). Also, we examined 2 HRs and 95% CIs using predicted values from the Cox model; 1 HR reflecting a comparison of a participant whose BDI-II score improved vs no change (-10 point change vs 0 change), and a second comparing a participant whose score worsened vs no change ($+10$ points vs 0 change). The HR for improvement in BDI-II score was 0.92 (95% CI, 0.79 to 1.06), whereas the HR for BDI-II worsening was 1.21 (95% CI, 1.03-1.43). A similar pattern was seen for BDI-II change and the 2 secondary end points, combined CV death and hospitalization ($P=.003$) and heart failure death and hospitalization ($P=.001$). For the combined CV end points, the HR for improvement was 0.87 (95% CI, 0.74-1.02), whereas the HR for worsening was 1.27 (95% CI, 1.06-1.51). For the combined heart failure end points, the HR for improvement was 0.88 (95% CI, 0.72-1.09), whereas the HR for worsening was 1.43 (95% CI, 1.15-1.78).

COMMENT

The results of this HF-ACTION ancillary study confirm and extend previous research by demonstrating that exercise training may be effective in reducing depressive symptoms and by further documenting the prognostic significance of depression in patients with heart failure. Although previous studies have reported that exercise is associated with reduced symptoms of depression in patients with clinical depression,^{12,24} to our knowledge, this is the first randomized trial to show that exercise resulted in a small but statistically significant reduction in depressive symptoms in patients with heart failure.

After 3 months of supervised exercise, patients in the aerobic exercise group achieved a 1.75-point reduction in BDI-II scores compared with 0.98 points in the usual care control group;

Table 2. Primary and Secondary Event Rates by Treatment Assignment and Depressive Symptom Severity

	Treatment Assignment, No. (%)					
	Exercise			Usual Care		
	BDI-II Score		All Exercise (n = 1158)	BDI-II Score		All Usual Care (n = 1164)
	<14 (n = 821)	≥14 (n = 337)		<14 (n = 848)	≥14 (n = 316)	
All-cause						
Deaths	123 (15.0)	66 (19.6)	189 (16.3)	134 (15.8)	63 (19.9)	197 (16.9)
Hospitalizations	393 (47.9)	177 (52.5)	570 (49.2)	423 (49.9)	169 (53.5)	592 (50.9)
Total	516 (62.9)	243 (72.1)	759 (49.0)	557 (65.7)	232 (73.4)	789 (51.0)
Heart failure-related ^a						
Deaths	8 (1.0)	5 (1.5)	13 (1.1)	13 (1.5)	7 (2.2)	20 (1.7)
Hospitalizations	174 (21.8)	105 (32.2)	284 (24.5)	214 (25.2)	99 (31.3)	313 (26.9)
Total	182 (22.2)	110 (32.6)	297 (25.7)	227 (26.8)	106 (33.5)	333 (28.6)
Cardiovascular-related ^a						
Deaths	40 (4.9)	9 (2.7)	49 (4.2)	38 (4.5)	15 (4.8)	53 (4.6)
Hospitalizations	382 (46.5)	202 (60.0)	584 (50.4)	433 (51.1)	181 (57.3)	619 (53.2)
Total	422 (51.4)	211 (62.6)	633 (54.7)	471 (55.5)	196 (62.0)	672 (57.7)

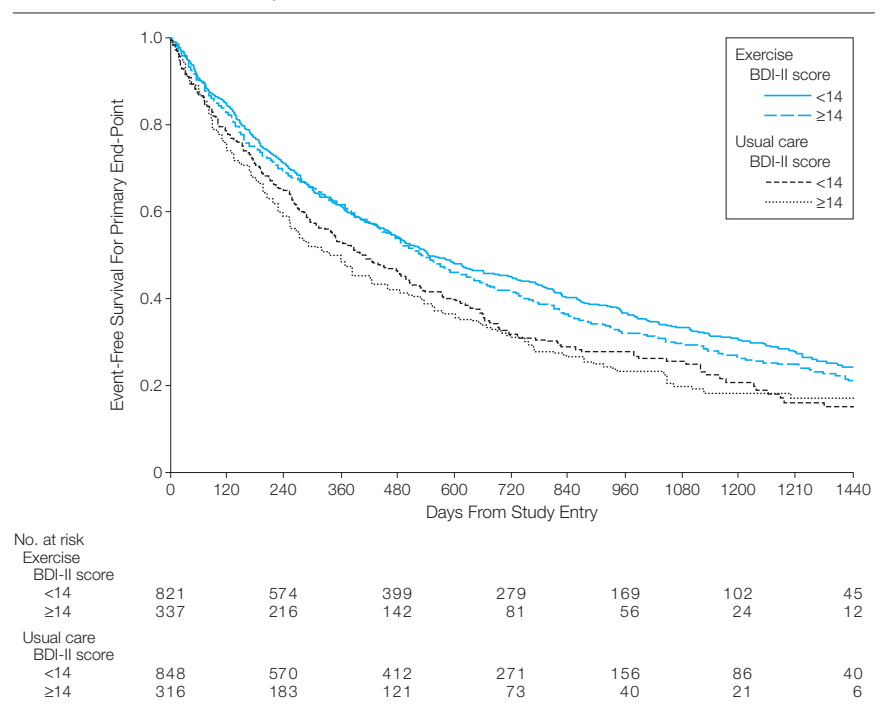
Abbreviation: BDI-II, Beck Depression Inventory II.

^aHeart failure-related and cardiovascular-related deaths include deaths of undetermined cause.

differences were even larger for patients with BDI-II scores of 14 or higher. Patients in the aerobic exercise group continued to exhibit greater reductions in depressive symptoms in months 4 through 12, during which they engaged in home-based exercise, showing a 2.2-point reduction from baseline compared with 1.3-points in the usual care group.

The difference between exercise and control is modest and the clinical significance of this small improvement is not known. However, because the difference was consistent over 12 months suggests that the difference is robust and does not simply reflect daily fluctuations in symptoms but is likely to be associated with better social functioning and higher quality of life. Among patients with BDI-II scores of 14 or higher at baseline, the difference at 3 months between aerobic exercise and usual care was 1.3 and was 1.6 points at 12 months, which is comparable with placebo-control trials involving patients with a major depressive disorder.

In the SADHART trial, the difference between placebo and sertraline was 0.8 points on the Hamilton Depression Rating Scale,²⁵ and in the SADHART-CHF trial, the difference was 0.3 points.¹¹ In the ENRICH trial,²⁶ pa-

Figure 3. Unadjusted Kaplan-Meier Curves for Time to Composite End Point (All-Cause Death or First All-Cause Hospitalization).

Curves represent sample stratified on treatment group assignment and depressive symptom severity category. The number of participants at risk at selected time intervals for each group is displayed across the bottom of the plot.

tients receiving cognitive behavioral therapy showed a 2.7-point greater reduction in BDI scores than the usual

care controls. However, patients in the ENRICH trial were clinically depressed and received treatment (cog-

nitive behavioral therapy and antidepressant medication) to reduce their depression. Participants in the HF-ACTION trial were not diagnosed with major depressive disorder and most were not clinically depressed. Furthermore, participants in the usual care group received biweekly telephone calls from study staff, 23% of whom received antidepressant medication, and 48% indicated that they engaged in regular (up to twice per week) exercise during the trial.

Within the aerobic exercise group, patients who reported greater adherence to the exercise prescription achieved relatively larger reductions in depressive symptoms, although the absolute reduction was small. Compared with no exercise, performing 90 minutes of exercise per week, the equivalent of three 30-minute sessions, was associated with approximately a 1.5-point reduction in BDI-II scores. These differences are relatively modest but may be of some importance, particularly because relatively few patients reported elevated depressive symptoms at study baseline. However, people who did not exercise may have been more depressed, so it is not clear whether exercise resulted in less depression or if depression resulted in less exercise.

Several prior studies have shown that exercise training may be comparable with antidepressant medication in reducing depressive symptoms.^{13,14} However, to date, studies examining the benefits of antidepressant medication in cardiac patients have provided mixed results. In the SADHART study, only the subgroup of patients with more severe depression appeared to benefit from sertraline.²⁵ Results from the SADHART-CHF trial showed that sertraline performed no better than placebo after 12 weeks of treatment and did not improve clinical outcomes.¹¹ In the present study, 90 minutes of exercise per week was sufficient to produce a modest reduction in depressive symptoms; greater volumes of exercise were not necessarily associated with greater improvements in depressive symptoms.

The optimal dose of exercise to achieve benefit remains uncertain. Prior studies in patients with major depression reported that 90 minutes of exercise per week was sufficient to reduce depressive symptoms^{13,14} and maintenance of 60 min/wk of exercise reduced the risk of relapse over a 1-year follow-up period.²⁷ Data from the present study must be interpreted with caution because patients self-selected their exercise dose; however, a small study of depressed, noncardiac patients suggested that 150 min/wk of exercise was most effective in reducing depressive symptoms.²⁸ The optimal dose of exercise needed to achieve the maximal therapeutic benefit in reducing depressive symptoms in patients with cardiac disease still needs to be determined.

We also observed that elevated depressive symptoms were associated with more than a 20% increase in risk for all-cause mortality and hospitalizations and that the increased risk was independent of antidepressant use and established risk factors in patients with heart failure including age and disease severity. These data add to the evidence suggesting that elevated depressive symptoms, without necessarily meeting diagnostic criteria for major depressive disorder, are associated with increased risk for adverse clinical events.^{29,30} These findings also support the recent recommendations of the American Heart Association Scientific Advisory Board, which recommended that depression be routinely assessed in patients with cardiac disease.³¹

Examination of the relationship of changes in depressive symptoms and clinical outcomes revealed that patients whose depression worsened over time were at particularly increased risk. These findings are consistent with our prior study involving 147 patients with heart failure, which showed that patients who had an increase in BDI-I scores of 3 points or more after 1 year had more than twice the risk of adverse outcomes than patients whose BDI score remained relatively stable.³² A recent substudy from SADHART-CHF³³ found that depressed patients with heart fail-

ure whose depression was considered to be remitted after 12 weeks of treatment had fewer cardiovascular events than patients whose depression remained, independent of treatment. Although it is possible that reduced depressive symptoms were responsible for improved clinical outcomes, it is also possible that worsening of depression may identify a subset of depressed patients who may be vulnerable to adverse events. Thus, efforts not only to reduce depressive symptoms but to prevent worsening of depressive symptoms may be especially important. In addition to its cardiopulmonary benefits, exercise may be effective in reducing depressive symptoms and preventing worsening of symptoms of patients with heart failure.

Limitations

The HF-ACTION study has several limitations. First, patients enrolled in this study had to be willing and able to engage in aerobic exercise. Because patients who either were already exercising or who were unwilling to be randomized to an exercise condition were excluded from the trial, the generalizability of the results may be limited.

Second, although this was a planned secondary analysis of HF-ACTION, the design was a retrospective analysis of prospectively collected data and participants were not randomized to different prespecified exercise volumes. Thus, it is possible that patients who were healthier or more motivated to adhere to treatment, including medications, might have been better able to engage in exercise. The observed association between minutes of exercise and reduced depressive symptoms could be a result of the beneficial effects of greater volumes of exercise in reducing depressive symptoms but also could reflect that patients with more severe depressive symptoms may be less likely to engage in exercise. An adequately powered and appropriately designed dose-response trial would be needed to determine the optimal dose of exercise needed to reduce depressive symptoms to clinically significant levels.

Third, because of missing data for some of the clinical parameters measured in HF-ACTION, we used simple median imputation for the time-to-event analyses, which allowed us to include a greater number of cases. However, the results of these analyses differed very little from simply omitting variables for which complete data were unavailable.

Fourth, we used the BDI-II to assess depressive symptoms. Although the BDI-II is widely recognized as a valid and reliable psychometric instrument for assessing depressive symptoms and has been associated with increased risk of morbidity and mortality in other studies involving patients with cardiac disease,^{4,5,7} the BDI-II should not be used to diagnose clinical depression. The extent to which exercise could improve depressive symptoms in patients with major depression was not assessed in this trial. The BDI-II scores were also somewhat lower than expected. Using the BDI-I, Sherwood et al³² reported that more than half of the sample in that study exhibited significant levels of depressive symptoms compared with only 28% in the present sample.

Fifth, Sherwood et al³² reported that the level of risk associated with elevated BDI scores was greater than the risk we observed in HF-ACTION. The reasons for this discrepancy are not obvious.

Sixth, unplanned crossover may have affected our findings. Only about 40% of patients assigned to the aerobic exercise condition were fully adherent to the exercise program in achieving pre-specified target exercise volumes (ie, 90 min/wk for months 1-3 and 120-minute/wk for months 4-12), and 40% to 50% of usual care patients reported that they had engaged in at least some exercise during the first year of the trial.

Finally, although we suggested that worsening depressive symptoms may contribute to deteriorating heart failure, it also is possible that increasing depressive symptoms may reflect worsening heart failure. Whether worsening depression is a cause or conse-

quence of increased heart failure symptoms could not be determined.

Conclusion

In this ancillary study from the HF-ACTION trial, patients with heart failure who participate in exercise training, compared with usual care, had modest reductions in depressive symptoms at 12 months, although the clinical significance of these small improvements is unknown.

Author Contributions: Dr Babyak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Babyak, O'Connor, Keteyian, Howlett, Gottlieb, Blackburn, Swank, Whellan, Blumenthal.

Acquisition of data: O'Connor, Keteyian, Howlett, Kraus, Gottlieb, Blackburn, Swank, Whellan, Blumenthal.

Analysis and interpretation of data: Babyak, O'Connor, Keteyian, Landzberg, Howlett, Gottlieb, Blackburn, Swank, Whellan, Blumenthal.

Drafting of the manuscript: Babyak, O'Connor, Keteyian, Landzberg, Howlett, Blackburn, Swank, Blumenthal.

Critical revision of the manuscript for important intellectual content: Babyak, O'Connor, Keteyian, Howlett, Kraus, Gottlieb, Blackburn, Swank, Whellan. **Statistical analysis:** Babyak, Howlett, Blumenthal.

Obtained funding: O'Connor, Swank, Whellan, Blumenthal.

Administrative, technical, or material support: Keteyian, Landzberg, Howlett, Blackburn, Swank, Whellan, Blumenthal.

Study supervision: O'Connor, Landzberg, Kraus, Blackburn, Blumenthal.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr O'Connor reported that he has received honoraria for consulting from Merck, Amgen, Pfizer, and Novartis; served as a consultant for which either he or is academic institution received fees from Merck, Medtronic, GE Healthcare, Amgen, Medpace, Roche Diagnostics, Actelion, Novella, Trevena, Martek Biosciences, Pfizer, Nile, Novartis, Heartware, Ikaria, ResMed, Pozen, Johnson & Johnson, Gilead, Critical Diagnostics, BG Medicine, Otsuka, Acorn, and Hoffman Roche. Dr Keteyian reported that he has served as consultant to Johnson & Johnson and receives textbook royalties from McGraw-Hill. Dr Gottlieb reported serving as a consultant and receiving institutional grant support from Duke Clinical Research Institute. No other financial conflicts were reported.

Funding/Support: Dr Blumenthal reported that he was compensated for his work by grant HL080664 from the National Heart, Lung, and Blood Institute. The HF-ACTION was funded by 13 National Heart, Lung, and Blood Institute grants: 5U01-HL063747 to the Duke Clinical Research Institute Coordinating Center (Dr C. O'Connor, principal investigator); 5U01HL066461 to the Economic and Quality of Life (K. Schulman, principal investigator); HL068973 to the U grant enrolling centers—Boston Medical Center (W. Colucci, principal investigator); HL066501 to Case Western Reserve University (I. Piña, principal investigator); HL066482 to Emory University (A. Smith, principal investigator); HL064250 to the Henry Ford Hospital (S. Keteyian, principal investigator); HL066494 to the Ohio State University (W. Abraham, principal investigator);

HL064257 to Oregon Health Science University (R. Hershberger, principal investigator); HL066497 University of Alabama (V. Bittner, principal investigator); HL068980 to University of California—Los Angeles (G. Fonarow, principal investigator); HL064265 to the University of Colorado (E. Wolfel, principal investigator); HL066491 to Wake Forest University (D. Kitzman, principal investigator); and HL064264 to Washington University of St Louis (G. Ewald, principal investigator).

Role of the Sponsor: The National Heart, Lung, and Blood Institute was involved in the design and conduct of the study; and in the collection and management and oversight of the data analysis. However, the funding source had no formal role in the interpretation of the data or in the preparation, review, or approval of the manuscript.

The complete list of collaborators in HF-ACTION has been reported previously in reference 15.

Online-Only Material: The eTable, eFigure, and Author Audio Interview are available at <http://www.jama.com>.

Additional Contributions: We especially wish to thank Stephen J. Ellis, PhD from the Duke Clinical Research Institute (DCRI) for assembling the dataset used in this analysis and for providing statistical advice, for which he was compensated as part of his employment at the coordinating center, Yanhong Li, MA, also from the DCRI who provided end point data for this analysis, and Andrew Sherwood, PhD, from the Department of Psychiatry and Behavioral Sciences at Duke University for his comments and suggestions on an earlier version of this manuscript.

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