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Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure

HF-ACTION Randomized Controlled Trial

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HEART FAILURE IS A MAJOR AND increasingly common cardiovascular syndrome, and is the end result of many cardiovascular disorders. An estimated 5 million patients in the United States have heart failure, and an additional 500 000 new cases are diagnosed annually.¹ Recent data indicate that the prevalence of heart failure in the Medicare population alone exceeds 4 million, with an annual age-adjusted incidence rate of 29 cases per 1000 person-years.² Although evidence-based pharmacological and device therapies decrease mortality, hospitalizations, and heart failure symptoms and improve quality of life, many patients treated with these regimens often re-

Context Guidelines recommend that exercise training be considered for medically stable outpatients with heart failure. Previous studies have not had adequate statistical power to measure the effects of exercise training on clinical outcomes.

Objective To test the efficacy and safety of exercise training among patients with heart failure.

Design, Setting, and Patients Multicenter, randomized controlled trial of 2331 medically stable outpatients with heart failure and reduced ejection fraction. Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) were randomized from April 2003 through February 2007 at 82 centers within the United States, Canada, and France; median follow-up was 30 months.

Interventions Usual care plus aerobic exercise training, consisting of 36 supervised sessions followed by home-based training, or usual care alone.

Main Outcome Measures Composite primary end point of all-cause mortality or hospitalization and prespecified secondary end points of all-cause mortality, cardiovascular mortality or cardiovascular hospitalization, and cardiovascular mortality or heart failure hospitalization.

Results The median age was 59 years, 28% were women, and 37% had New York Heart Association class III or IV symptoms. Heart failure etiology was ischemic in 51%, and median left ventricular ejection fraction was 25%. Exercise adherence decreased from a median of 95 minutes per week during months 4 through 6 of follow-up to 74 minutes per week during months 10 through 12. A total of 759 patients (65%) in the exercise training group died or were hospitalized compared with 796 patients (68%) in the usual care group (hazard ratio [HR], 0.93 [95% confidence interval {CI}, 0.84-1.02]; $P=.13$). There were nonsignificant reductions in the exercise training group for mortality (189 patients [16%] in the exercise training group vs 198 patients [17%] in the usual care group; HR, 0.96 [95% CI, 0.79-1.17]; $P=.70$), cardiovascular mortality or cardiovascular hospitalization (632 [55%] in the exercise training group vs 677 [58%] in the usual care group; HR, 0.92 [95% CI, 0.83-1.03]; $P=.14$), and cardiovascular mortality or heart failure hospitalization (344 [30%] in the exercise training group vs 393 [34%] in the usual care group; HR, 0.87 [95% CI, 0.75-1.00]; $P=.06$). In prespecified supplementary analyses adjusting for highly prognostic baseline characteristics, the HRs were 0.89 (95% CI, 0.81-0.99; $P=.03$) for all-cause mortality or hospitalization, 0.91 (95% CI, 0.82-1.01; $P=.09$) for cardiovascular mortality or cardiovascular hospitalization, and 0.85 (95% CI, 0.74-0.99; $P=.03$) for cardiovascular mortality or heart failure hospitalization. Other adverse events were similar between the groups.

Conclusions In the protocol-specified primary analysis, exercise training resulted in nonsignificant reductions in the primary end point of all-cause mortality or hospitalization and in key secondary clinical end points. After adjustment for highly prognostic predictors of the primary end point, exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization and cardiovascular mortality or heart failure hospitalization.

Trial Registration clinicaltrials.gov Identifier: NCT00047437

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See also p 1451.

main burdened by dyspnea and fatigue, diminished exercise tolerance, reduced quality of life, recurrent hospitalizations, and early mortality.²⁻⁵

Although rest was traditionally recommended for patients with heart failure, over the past 2 decades it has been recognized that physical deconditioning may play a key role in the progression of symptoms and poor outcomes. Several prior studies have assessed the ability of exercise training to improve functional capacity in patients with heart failure.⁶⁻⁸ Most of these previous studies showed positive effects of exercise training on exercise capacity, quality of life, and biomarkers and observed relatively few complications during training.⁹ These studies also suggested that exercise training might improve survival and decrease heart failure hospitalizations.⁶ Two meta-analyses suggested improved survival and decreased hospitalizations for patients with heart failure undergoing exercise training compared with a non-exercising control group.^{10,11}

Nonetheless, there remains a safety concern regarding exercise training in patients with heart failure. Although the complication rate for all patients participating in cardiac rehabilitation has been reported to be extremely low, the complication rate for patients with heart failure in clinical trials of exercise training has been substantially higher. One potential reason is the 100-fold increased risk for myocardial infarction and 50-fold increased risk of sudden death that exercisers who are habitually sedentary experience when initiating exercise training.¹²

Based on the results of past studies of exercise training, the American College of Cardiology, American Heart Association, European Society of Cardiology, and Canadian Cardiovascular Society have adopted recommendations that physical activity be considered for medically stable patients with systolic dysfunction.^{1,13,14} However, previous studies have been relatively small single-center trials, have not been adequately powered to evaluate mortality and morbidity, and have often lacked an adequate control group. The lack of defini-

tive clinical outcome data has hindered the adoption of this potentially promising treatment modality.

To examine the issue of exercise safety and effectiveness in a large sample of patients with heart failure, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was undertaken to determine whether aerobic-type exercise training reduces all-cause mortality or all-cause hospitalization and improves quality of life (the quality-of-life findings are reported in the accompanying article by Flynn et al¹⁵) in patients with medically stable chronic heart failure due to systolic dysfunction. Our primary hypothesis was that in patients with stable heart failure, regular structured exercise training, when added to usual, evidence-based care in accordance with published guidelines, would significantly reduce the incidence of a combined end point of all-cause mortality or all-cause hospitalization.

METHODS

Eligibility and Study Design

A complete description of the design of HF-ACTION has been published previously.¹⁶ Briefly, HF-ACTION was a multicenter, randomized controlled trial of patients in the exercise training group vs patients in the usual care group with left ventricular ejection fraction of 35% or less and New York Heart Association (NYHA) class II to IV symptoms despite optimal heart failure therapy for at least 6 weeks. Patients were randomized from April 2003 through February 2007 within the United States, Canada, and France. Exclusion criteria included major comorbidities or limitations that could interfere with exercise training, recent (≤ 6 weeks) or planned (≤ 6 months) major cardiovascular events or procedures, performance of regular exercise training, or use of devices that limited the ability to achieve target heart rates. The protocol was reviewed and approved by the appropriate institutional review board or ethics committee for each participating center and by the coordinating center's institutional review board. All

patients provided written voluntary informed consent.

All patients were to undergo baseline cardiopulmonary exercise testing. Test results were reviewed by investigators to (1) identify significant arrhythmias or ischemia that would prevent safe exercise training, (2) determine appropriate levels of exercise training, and (3) establish training heart rate ranges. Eligible patients were randomized 1:1 using a permuted block randomization scheme, stratified by clinical center and heart failure etiology (ischemic vs nonischemic). At the baseline clinic visit prior to randomization, demographics, socioeconomic status, past medical history, current medications, a physical examination, and the most recent laboratory tests were obtained. Participants reported race and ethnicity at the time of study enrollment using categories defined by the National Institutes of Health. In an analysis to examine the effect of exercise training by subgroup, we used the reported race categories "black or African American" and "white" and combined all others as "other." All cardiopulmonary exercise tests were sent to the HF-ACTION cardiopulmonary exercise core laboratory for review.

Exercise Training Protocol

Patients randomized to the exercise training group first participated in a structured, group-based, supervised exercise program, with a goal of 3 sessions per week for a total of 36 sessions in 3 months. During the supervised training phase, patients performed walking, treadmill, or stationary cycling as their primary training mode. Exercise was initiated at 15 to 30 minutes per session at a heart rate corresponding to 60% of heart rate reserve (maximal heart rate on cardiopulmonary exercise test minus resting heart rate). After 6 sessions, the duration of the exercise was increased to 30 to 35 minutes, and intensity was increased to 70% of heart rate reserve. Details of the exercise training protocol have been reported.¹⁶ Patients were to begin home-based exercise after completing 18 supervised sessions and were

to fully transition to home exercise after 36 supervised sessions.

Patients in the exercise training group were provided home exercise equipment (cycle or treadmill [ICON, Logan, Utah]) and heart rate monitors (Polar USA Inc, New York, New York). The target training regimen for home exercise was 5 times per week for 40 minutes at a heart rate of 60% to 70% of heart rate reserve. Adherence was evaluated by measuring attendance at the supervised training sessions and by activity logs, telephone and clinic follow-up, and heart rate monitoring data (model A1 or S1, Polar USA Inc) during the home exercise training phase.

Usual Care

Patients in the usual care group were not provided with a formal exercise prescription. All patients, regardless of treatment group, received detailed self-management educational materials, in the form of a booklet, at the time of enrollment, including information on medications, fluid management, symptom exacerbation, sodium intake, and activity level of 30 minutes (as tolerated) of moderate-intensity activity on most days of the week, consistent with the guidelines from the American College of Cardiology and the American Heart Association.¹

All patients were asked to return for clinic visits every 3 months for the first 2 years of participation and yearly thereafter for up to 4 years. Cardiopulmonary exercise testing and a 6-minute walk test were performed at the 3-, 12-, and 24-month follow-up visits. The 6-minute walk test also was performed at the 3-year and final visits. Patients made their final visit at the end of the study follow-up period or at 4 years. 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 during the follow-up period.

To provide comparable levels of attention from study personnel in the 2 study groups, all patients were to be called every 2 weeks for the first 9 months, monthly until 24 months of fol-

low-up, and quarterly thereafter. During these calls, patients in the exercise training group were asked questions to determine if they were performing the exercise training regimen as prescribed. During these calls, as well as during the supervised training sessions and at follow-up clinic visits, adherence to the exercise training regimen was promoted by study personnel. Patients in the usual care group were asked if they were exercising, but no further information was obtained due to concerns that more detailed questions about exercise would promote exercise behavior among patients in the usual care group.

In addition, all patients were asked to complete a physical activity questionnaire at the baseline, 6-month, 12-month, 24-month, 3-year, and final visits. This instrument quantified the amount of moderate or vigorous activity in minutes per week completed during the preceding week.

Primary, Secondary, and Safety Outcomes

The primary end point was a composite of all-cause mortality or all-cause hospitalization. Secondary end points included all-cause mortality, the composite of cardiovascular mortality or cardiovascular hospitalization, and the composite of cardiovascular mortality or heart failure hospitalization.

A post hoc analysis also was performed to compare the 2 study groups with respect to the composite of cardiovascular mortality, heart failure hospitalization, left ventricular assist device implantation, or heart transplantation. In addition, change from baseline in peak oxygen consumption per unit of time at 3 months and 1 year, change in distance from baseline in the 6-minute walk test at 3 months and 1 year, and (as a post hoc analysis) change in NYHA class were evaluated as potential mediators.

Although blinding for patients and investigators was not possible due to the nature of the exercise training intervention, deaths and cardiovascular hospitalizations for each patient were adjudicated by a clinical end point committee blinded to treatment assignment. Once

a patient had an adjudicated heart failure hospitalization, no further hospitalizations for that patient were reviewed by the clinical end point committee.

In addition to mortality and hospitalization, other cardiovascular adverse events were captured, including worsening heart failure, myocardial infarction, unstable angina, serious adverse arrhythmia, stroke, and transient ischemic attack. Also captured were hospitalizations for fracture of the hip or pelvis, outpatient fracture repair, implantable cardioverter-defibrillator (ICD) firing events (for patients with an ICD), all hospitalizations due to an event that occurred during or within 3 hours after exercise, and deaths during or within 3 hours after exercise (or unknown if during or \leq 3 hours after exercise).

Statistical Analysis

The study was designed to have 90% power to detect an 11% reduction in the 2-year rate of all-cause mortality or all-cause hospitalization for patients randomized to exercise training compared with those randomized to usual care. This estimate was based on assuming an annual primary outcome rate of 30% in the usual care group, treatment nonadherence rates of 30% in the first year of follow-up and 12.5% annually thereafter, an annual crossover rate of 5% from the usual care group to an active exercise regimen, a planned median follow-up of 2.5 years, and an α level of .05.

Statistical analyses were performed by the coordinating center (Duke Clinical Research Institute, Durham, North Carolina) using SAS software version 8.2 (SAS Institute Inc, Cary, North Carolina). Baseline patient characteristics were summarized using medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Statistical comparisons of the study groups with respect to clinical outcomes were performed according to the intention-to-treat principle. All statistical tests were 2-tailed.

Cumulative event rates were calculated using the Kaplan-Meier method.¹⁷

Event (or censoring) times for all patients were measured from the time of randomization (time zero). All information available on the primary and secondary end points was collected until the time of final contact with the patient, including patients who withdrew consent or were lost to follow-up, at which point follow-up was censored. The log-rank test was used to statistically compare the 2 study groups with respect to the time until the first occurrence of either component of the primary composite end point and the secondary time-to-event outcomes, adjusting for heart failure etiology.¹⁸ Relative risks were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and were calculated using the Cox proportional hazards model.¹⁹ The Cox model also was used to assess the consistency of the treatment effect by testing for interactions between treatment and prespecified baseline characteristics.

As specified in the HF-ACTION protocol, supplementary analyses of the primary end point of all-cause mortality or hospitalization and the secondary end points of cardiovascular mortality or cardiovascular hospitalization and cardiovascular mortality or heart failure hospitalization were performed, adjusting for baseline characteristics strongly predictive of these clinical outcomes. With time-to-event outcomes, adjustment for strong predictors of the outcome enables the analysis to more specifically compare patients of like risk with like risk and thereby increases the statistical power.²⁰

The baseline predictors of the primary outcome of all-cause mortality or hospitalization were objectively selected using a stepwise variable selection based on treatment-blinded data (ie, omitting treatment group from the variable selection process). To avoid introducing bias, the variables selected were required to have little or no missing data. Only the most highly significant variables (all with *P* values < .001) identified in this process were used in the covariate-adjusted treatment comparisons. Heart failure etiology (is-

mic vs nonischemic), which was a stratification factor in the randomization, was included as a covariate in all time-to-event analyses.

Comparisons of the 2 study groups with respect to the change from baseline in physiological end points were performed using Wilcoxon rank sum tests. Changes from baseline in NYHA class were compared between treatment groups using ordinal logistic regression.

An independent data and safety monitoring board was appointed by the National Heart, Lung, and Blood Institute to review the interim results of the study and evaluate patient safety and trial feasibility on a semiannual basis. Interim treatment comparisons were monitored by the data and safety monitoring board using 2-sided symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets α -spending function approach to group-sequential testing.^{21,22} Although the overall significance level was .05, a significance level of .044 was required at the final analysis due to adjustment for the interim analyses.

The data and safety monitoring board allowed the study leadership to have access to the overall primary event rate at some of the data and safety monitoring board meetings during the study. This rate was higher than projected in the study design. After approximately 2000 patients were enrolled, unconditional power calculations based on the higher overall event rate revealed that the number of events required for 90% statistical power could be achieved with 2300 patients rather than the original goal of 3000. The target sample size was therefore reduced accordingly.

RESULTS

Patient Characteristics

A total of 2331 patients were enrolled at 82 participating centers in the United States, Canada, and France. Baseline characteristics of the patients in each randomized group are shown in TABLE 1. The median age of all patients was 59 years; 28% were women and 40% were

racial or ethnic minorities. The median left ventricular ejection fraction was 25%, and 51% of the patients had heart failure with an ischemic etiology. Of patients without an intolerance or contraindication to angiotensin-converting enzyme (ACE) inhibitors or β -blockers, 95% were taking a β -blocker and either an ACE inhibitor or an angiotensin II receptor blocker. Forty-five percent of patients had an ICD or biventricular pacemaker implanted at the time of study enrollment.

Follow-up

The follow-up period ended March 15, 2008. The median duration of follow-up for the primary end point was 30.1 months (goal of a minimum of 1 year and a maximum of 4 years). Thirty-nine patients (1.7%) were lost to follow-up but had a median follow-up of 14.6 months (FIGURE 1). Eighty-three patients (4%) withdrew consent at a median time of 6.8 months following randomization. A total of 736 patients completed 36 supervised training sessions with the median time to completion (for 36 sessions) of 3.9 months (interquartile range, 3.4-4.8 months).

At 12 months of follow-up, the number of patients taking an ACE inhibitor, an angiotensin II receptor blocker, or both, was 93% in the usual care group and 92% in the exercise training group; β -blocker use was 95% in the usual care group and 94% in the exercise training group.

During the first 3 months of follow-up (when patients were still in the supervised training phase of the protocol), patients in the exercise training group exercised for a median of 76 minutes per week (interquartile range, 39-117 minutes per week). The exercise training goal during this time was 90 minutes per week. The exercise time increased to a median of 95 minutes per week (interquartile range, 26-184 minutes per week) at 4 to 6 months following enrollment and subsequently decreased to a median of 74 minutes per week (interquartile range, 0-180 minutes per week) at 10 to 12 months following enrollment, with a training goal

of 120 minutes per week. In the third year of follow-up, patients in the exercise training group were exercising a median of 50 minutes per week (interquartile range, 0-140 minutes per week). At all time points, approximately 30% or more of the patients in the exercise training group exercised at or above the target exercise minutes per week. In these calculations, missing values of minutes per week were conservatively assumed to be no exercise.

Safety of Exercise Training

Overall, the performance of exercise training was well tolerated and safe. In the exercise training group, 37 patients had at least 1 hospitalization due to an event that occurred during or within 3 hours after exercise (TABLE 2). In the usual care group, 22 patients had such a hospitalization, despite not undergoing a formal exercise program. During the initial 36 sessions of supervised training, the percentages of patients with an event that caused at least 1 session to be cut short (goal duration not achieved) or the goal training intensity to not be achieved were as follows: 10% for angina, 7% for arrhythmia, 4% for presyncope or syncope, and 2% for hypoglycemia. Only 1 patient had an ICD discharge that caused at least 1 supervised exercise training session to fail to reach the target duration or intensity.

Usual Care Crossover

A minority of patients in the usual care group also exercised, based on self-report. For the eight 3-month windows in the first 2 years, 22% to 28% of patients, depending on time point, stated during every telephone call in the 3-month window that they were exercising. As an estimate of the fraction of patients in the usual care group exercising continuously throughout the trial, 8% of usual care patients reported they were exercising on all telephone follow-up calls after the first 3 months. Based on data elicited from the physical activity questionnaire, the median time spent walking at baseline was 40 minutes per week in the usual care

group vs 45 minutes per week in the exercise training group. At 6 months, the median time walking in the usual care group was 65 minutes per week vs 140 minutes per week in the exercise training group. At 12 months, the median time spent walking was 75 minutes per week in the usual care group

vs 140 minutes per week in the exercise training group. Notably, at the time of randomization, 627 of the patients in the usual care group (55%) expressed that they were somewhat or very dissatisfied with treatment assignment vs 22 patients in the exercise training group (2%).

Table 1. Baseline Characteristics

Characteristics	No. (%) of Patients ^a	
	Usual Care (n = 1172)	Exercise Training (n = 1159)
Age, median (IQR), y	59.3 (51.1-68.2)	59.2 (51.2-67.8)
Female sex	314 (26.8)	347 (29.9)
Hispanic or Latino ethnicity ^b	48/1162 (4.1)	40/1147 (3.5)
Race ^b		
Black or African American	372/1156 (32.2)	377/1140 (33.1)
White	728/1156 (63.0)	698/1140 (61.2)
Other	56/1156 (4.8)	65/1140 (5.7)
NYHA class		
II	754 (64.3)	723 (62.4)
III	409 (34.9)	422 (36.4)
IV	9 (0.8)	14 (1.2)
Ischemic etiology of heart failure	599 (51.1)	598 (51.6)
Left ventricular ejection fraction, median (IQR), %	24.9 (20.0-30.2)	24.6 (20.0-30.0)
Diabetes mellitus	370 (31.6)	378 (32.6)
Previous myocardial infarction	499 (42.6)	480 (41.4)
Hypertension ^b	676/1165 (58.0)	712/1153 (61.8)
Atrial fibrillation or atrial flutter ^b	241/1171 (20.6)	247/1159 (21.3)
Beck Depression Inventory II score, median (IQR)	8 (4-15)	8 (5-15)
Systolic blood pressure, median (IQR), mm Hg	111 (100-126)	112 (100-126)
Diastolic blood pressure, median (IQR), mm Hg	70 (60-80)	70 (61-78)
Sodium, median (IQR), mEq/L ^c	139 (137-141)	139 (137-141)
Blood urea nitrogen, median (IQR), mg/dL ^c	21 (15-28)	20 (15-28)
Serum creatinine, median (IQR), mg/dL ^c	1.2 (1.0-1.5)	1.2 (1.0-1.5)
Baseline use of medications and devices		
ACE inhibitor or ARB	1094 (93.3)	1105 (95.3)
β -Blocker	1112 (94.9)	1091 (94.1)
Aldosterone receptor antagonist	528 (45.1)	523 (45.1)
Loop diuretic	921 (78.6)	895 (77.2)
Digoxin	547 (46.7)	499 (43.1)
Implantable cardioverter-defibrillator	448 (38.2)	490 (42.3)
Biventricular pacemaker	203 (17.3)	216 (18.6)
Functional measures		
Distance of 6-min walk, median (IQR), m	373.2 (300.0-432.5)	365.8 (296.3-436.2)
Cardiopulmonary exercise time, median (IQR), min	9.7 (7.0-12.1)	9.5 (6.9-12.0)
Peak oxygen consumption, median (IQR), mL/kg/min	14.5 (11.6-17.8)	14.4 (11.3-17.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IQR, interquartile range; NYHA, New York Heart Association.

SI conversion factors: To convert blood urea nitrogen to mmol/L, multiply by 0.357; creatinine to μ mol/L, multiply by 88.4; sodium to mmol/L, multiply by 1.0.

^aUnless otherwise indicated. Percentages may not sum to 100 because of rounding.

^bIndicates the number of patients/number of patients with nonmissing data for the variable (percentage).

^cSodium, blood urea nitrogen, and serum creatinine values are based on standard-of-care laboratory tests measured up to 1 year prior to randomization.

Clinical Outcomes

Primary End Point and Its Components.

Kaplan-Meier curves depicting the primary end point of death or hospitalization from any cause for each randomized group are shown in FIGURE 2. During follow-up, 759 patients in the exercise training group (65%) and 796 patients in the usual care group (68%) experienced a primary clinical event. In the primary analysis (adjusted for heart failure etiology), exercise training resulted in a nonsignificant reduction in the primary end point of all-cause mor-

tality or hospitalization (HR, 0.93 [95% CI, 0.84-1.02]; $P = .13$). The absolute reduction in the primary event rate at 3 years was 4%.

Four baseline characteristics (duration of the cardiopulmonary exercise test, left ventricular ejection fraction, Beck Depression Inventory II score, and history of atrial fibrillation or flutter) were identified as highly prognostic of the primary end point of all-cause mortality or hospitalization, independent of treatment assignment. After adjusting for these covariates and heart failure etiology, exercise training was found to reduce the incidence of all-cause mortality or all-cause hospitalization (the primary end point) by 11% (HR, 0.89 [95% CI, 0.81-0.99]; $P = .03$) (Figure 2).

There was no significant difference in the number of deaths (189 patients [16%] in the exercise training group vs 198 patients [17%] in the usual care group; HR, 0.96 [95% CI, 0.79-1.17]; $P = .70$) (TABLE 3 and Figure 2). At least 1 hospitalization was experienced in 729 patients (63%) in the exercise training group vs 760 (65%) in the usual care group.

The HRs and 95% CIs for the comparison of study groups within selected subgroups are shown in FIGURE 3. As reflected by the interaction P values, there was no significant interaction of exercise training with any of the factors defining these subgroups; that is, the overall study result was consistent among the various subgroups.

Secondary End Points. Exercise training had a nonsignificant reduction in the combined end point of cardiovascular mortality or cardiovascular hospitalization in the main analysis (632 patients [55%] in the exercise training group vs 677 [58%] in the usual care group; HR, 0.92 [95% CI, 0.83-1.03]; $P = .14$) and after adjustment for prognostic factors (HR, 0.91 [95% CI, 0.82-1.01]; $P = .09$) (FIGURE 4). There was a nonsignificant reduction in cardiovascular mortality or heart failure hospitalization (344 patients [30%] in the exercise training group vs 393 [34%] in the usual care group; HR, 0.87 [95% CI, 0.75-1.00]; $P = .06$), which was statistically significant after adjustment for prognostic factors (HR, 0.85 [95% CI, 0.74-0.99]; $P = .03$) (Figure 4).

Figure 1. Flow of Participants Through the Trial

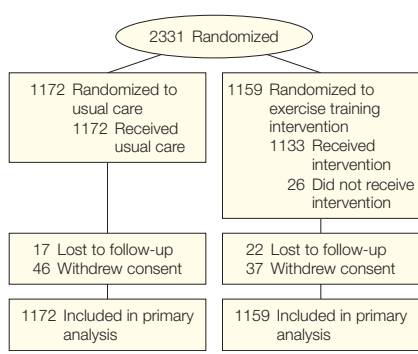


Table 2. Patients With Selected Adverse Events

Adverse Event	No. (%) of Patients ^a	
	Usual Care (n = 1171) ^b	Exercise Training (n = 1159)
Prespecified cardiovascular adverse events		
Worsening heart failure	340 (29.0)	303 (26.1)
Myocardial infarction	45 (3.8)	41 (3.5)
Unstable angina	88 (7.5)	86 (7.4)
Serious adverse arrhythmia ^c	164 (14.0)	167 (14.4)
Stroke	28 (2.4)	33 (2.8)
Transient ischemic attack	23 (2.0)	20 (1.7)
Any of the above events	471 (40.2)	434 (37.4)
General adverse events		
Hospitalization for fracture of the hip or pelvis	7 (0.6)	3 (0.3)
Outpatient fracture repair	20 (1.7)	13 (1.1)
ICD firing ^d	151/644 (23.4)	142/641 (22.2)
Hospitalization after exercise ^e	22 (1.9)	37 (3.2)
Died after exercise ^f	5 (0.4)	5 (0.4)

Abbreviation: ICD, implantable cardioverter-defibrillator.

^aUnless otherwise indicated.

^bFollow-up data forms were not available for 1 patient.

^cDefined as sustained ventricular tachycardia lasting longer than 30 seconds, ventricular fibrillation, supraventricular tachycardia with rapid ventricular response lasting longer than 30 seconds, cardiac arrest, or bradycardia (heart rate <50/min, symptomatic, and not felt to be related to medication).

^dIndicates the number fired/number of patients with an ICD (percentage).

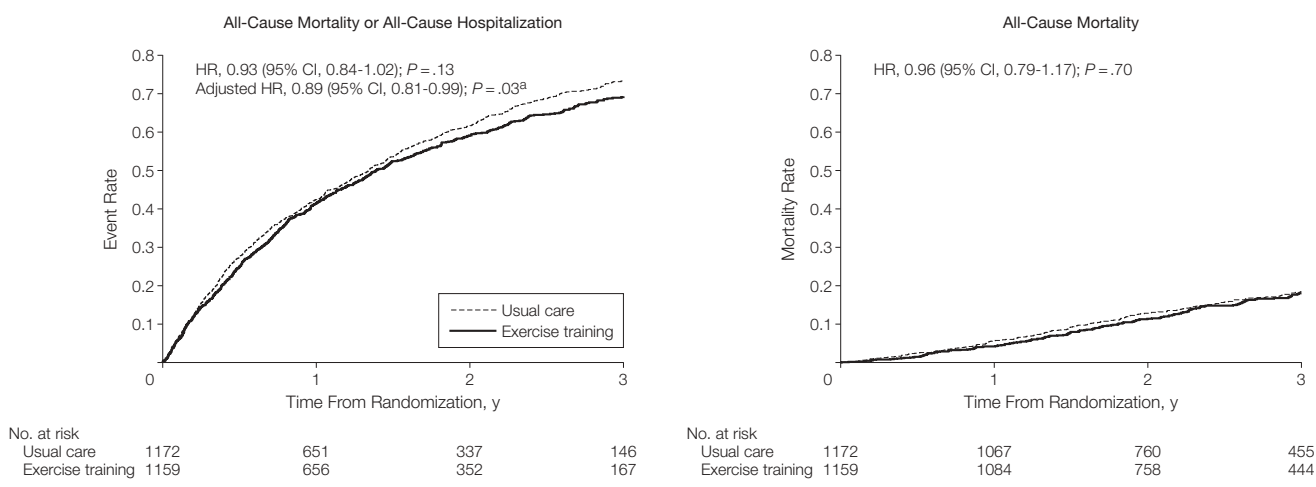
^eHad at least 1 hospitalization due to an event that occurred during or within 3 hours after exercise.

^fPatient died or not known if patient died during or within 3 hours after exercise.

Exercise Training Effects

The changes from baseline in peak oxygen consumption and distance in the 6-minute walk test at 3 months and 1 year are presented in TABLE 4. Compared with patients in the usual care group at 3 months of follow-up, patients in the exercise training group had a greater improvement in distance in the 6-minute walk test (median, 20 vs 5 meters; $P < .001$), in exercise time on the cardiopulmonary exercise test (1.5 minutes vs 0.3 minutes; $P < .001$), and in peak oxygen consumption (0.6 vs 0.2 mL/min/kg; $P < .001$).

The number of patients who had a 50-meter or greater improvement in distance in the 6-minute walk test at 3 months was 166 (19%) in the usual care group and 273 (28%) in the exercise training group. The number of patients with a 1-mL/min/kg or greater improvement in peak oxygen consumption was 297 (33%) in the usual care group and 423 (44%) in the exercise training group.

Figure 2. Time to All-Cause Mortality or All-Cause Hospitalization and to All-Cause Mortality

CI indicates confidence interval; HR, hazard ratio.
^aAdjusted for key prognostic factors.

The median percentage improvement of 4% in peak oxygen consumption in the exercise training group fell short of the 10% improvement targeted in the protocol, which is customarily used as a clinically relevant improvement. At 12 months, the differences in cardiopulmonary exercise test results remained but there was no significant difference in distance in the 6-minute walk test. The analyses presented are complete cases only and do not take into account missing data (33% at 12 months).

Post Hoc Analyses

For the post hoc end point of cardiovascular mortality, heart failure hospitalization, heart transplantation, or left ventricular assist device implantation, the reduction in HR was 13% with exercise training (353 patients [30%] in the exercise training group vs 403 [34%] in the usual care group; HR, 0.87 [95% CI, 0.75-1.00]; $P=.06$). A post hoc analysis of NYHA class showed a difference between the 2 study groups, with 30% of the exercise training cohort improving by 1 class or more vs 25% of the usual care cohort (ordinal regression $P=.03$).

COMMENT

HF-ACTION is the largest multicenter, randomized controlled trial of

Table 3. Clinical Events

Event	No. (%) of Patients		HR (95% CI)	<i>P</i> Value
	Usual Care (n = 1171) ^a	Exercise Training (n = 1159)		
All-cause mortality or all-cause hospitalization (primary end point)	796 (68)	759 (65)	0.93 (0.84-1.02)	.13
Cardiovascular mortality or cardiovascular hospitalization	677 (58)	632 (55)	0.92 (0.83-1.03)	.14
Cardiovascular mortality or heart failure hospitalization	393 (34)	344 (30)	0.87 (0.75-1.00)	.06
Cardiovascular mortality or heart failure hospitalization or cardiac transplantation or left ventricular assist device	403 (34)	353 (30)	0.87 (0.75-1.00)	.06
All-cause mortality, all-cause hospitalization, emergency department visit, or urgent clinic visit for heart failure exacerbation	906 (77)	885 (76)	0.99 (0.90-1.08)	.79
All-cause mortality	198 (17)	189 (16)	0.96 (0.79-1.17)	.70
Cardiovascular mortality	143 (12)	131 (11)	0.92 (0.74-1.15)	.47

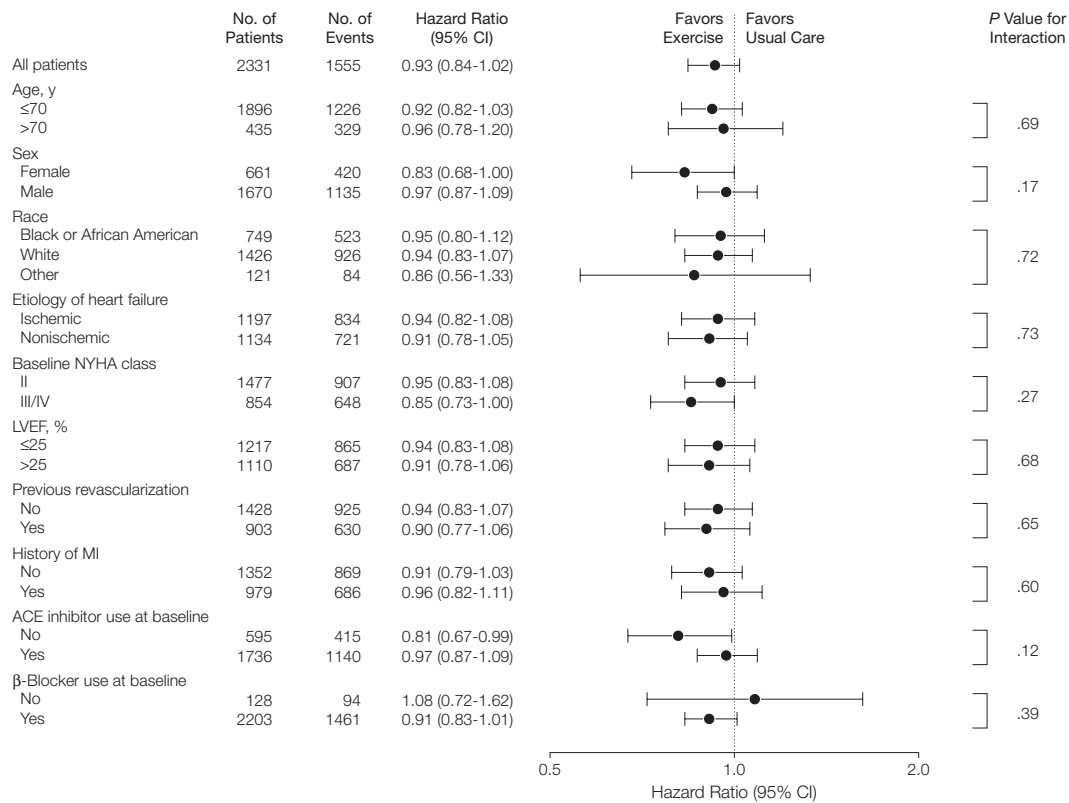
Abbreviations: CI, confidence interval; HR, hazard ratio.
^aFollow-up data forms were not available for 1 patient.

exercise training in heart failure to date. The size and duration of this trial are sufficient to examine for the first time the effect of exercise training on the combined primary end point of all-cause death or all-cause hospitalization in patients with left ventricular systolic dysfunction. In this cohort of patients with reduced left ventricular function, NYHA class II to IV symptoms, and treated with optimal, guideline-based background

heart failure therapy, exercise training was safe, but provided a nonsignificant reduction in the risk for the primary end point of all-cause mortality or all-cause hospitalization and key secondary clinical end points. However, the reduction in risk for the primary end point and for the risk of cardiovascular mortality or heart failure hospitalization was significant after adjusting for highly prognostic predictors of the primary end point.

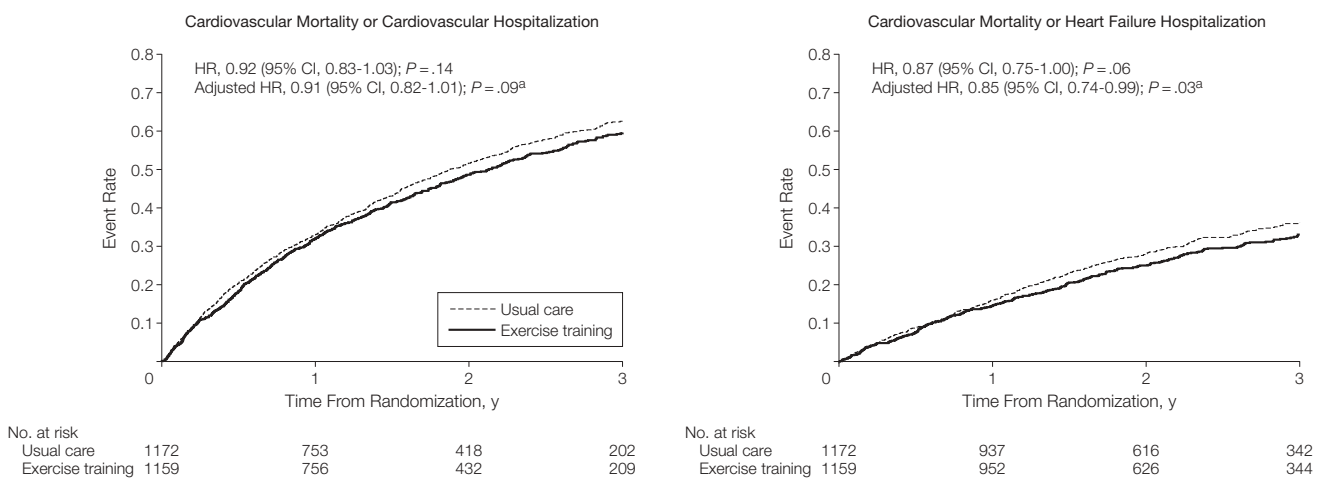
It is important to recognize that the main or primary analysis for the study that adjusted only for heart failure etiology did not result in a significant reduction in the primary end point or secondary end points. The change from a nonsignificant to a significant result after adjustment for strongly predictive factors is unusual in large clinical trials,

Figure 3. Subgroup Analysis of All-Cause Mortality or All-Cause Hospitalization



ACE indicates angiotensin-converting enzyme; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Figure 4. Time to Cardiovascular Mortality or Cardiovascular Hospitalization and to Cardiovascular Mortality or Heart Failure Hospitalization



CI indicates confidence interval; HR, hazard ratio.
^aAdjusted for key prognostic factors.

but can occur when the treatment differences are close to significance.²⁰ The overall interpretation of the results, then, is that this structured exercise training intervention had at best a modest effect on clinical end points in a large cohort of patients. The changes in cardiopulmonary exercise testing parameters and distance in the 6-minute walk test at 3 months were consistent with the finding of a modest benefit in reducing clinical events.

The ability to achieve a 13% risk reduction for the end point of cardiovascular mortality or heart failure hospitalization is important, given the exceptional use of evidence-based therapies among the patients in this study at baseline and throughout the trial. HF-ACTION arguably represents the largest trial to date with nearly uniform adherence to guideline-based therapy. In this study, 95% of patients without a contraindication or intolerance to β -blockers or ACE inhibitors received optimal heart failure therapy, defined as a β -blocker and either an ACE inhibitor or an angiotensin II receptor blocker. In addition, 45% of the patients were treated with an ICD or biventricular pacemaker prior to randomization.

The magnitude of effect of exercise training on the combined end point of cardiovascular mortality or heart failure hospitalization was similar to that observed with candesartan treatment in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM; HR, 0.84 [95% CI, 0.77-0.91]) and valsartan treatment in the Valsartan Heart Failure Trial (HR, 0.87; 95% CI, 0.77-0.97).^{23,24} In the CHARM trial and the Valsartan Heart Failure Trial, only 55% and 35% of patients, respectively, received β -blocker therapy, and an ICD was reported in only 2.4% to 2.6% of patients enrolled in CHARM.^{23,24}

A major challenge of HF-ACTION was to design and implement an exercise training protocol in patients with heart failure that could be translated into clinical practice. We based the study design on the traditional 36-session car-

Table 4. Change in 6-Minute Walk Test and Cardiopulmonary Exercise Test Results

	Median (IQR)		P Value
	Usual Care	Exercise Training	
Baseline to 3 mo ^a			
Distance of 6-minute walk, m (n = 1835)	5 (-28 to 37)	20 (-15 to 57)	<.001
Cardiopulmonary exercise time, min (n = 1914)	0.3 (-0.6 to 1.4)	1.5 (0.3 to 3.0)	<.001
Peak oxygen consumption, mL/kg/min (n = 1870)	0.2 (-1.2 to 1.4)	0.6 (-0.7 to 2.3)	<.001
Baseline to 12 mo ^b			
Distance of 6-minute walk, m (n = 1444)	12 (-30 to 55)	13 (-28 to 61)	.26
Cardiopulmonary exercise time, min (n = 1476)	0.2 (-1.0 to 1.7)	1.5 (0 to 3.2)	<.001
Peak oxygen consumption, mL/kg/min (n = 1442)	0.1 (-1.5 to 1.8)	0.7 (-1.0 to 2.5)	<.001

Abbreviation: IQR, interquartile range.

^aComplete case analysis. Expected 2284 patients at 3 months.

^bComplete case analysis. Expected 2159 patients at 12 months.

diac rehabilitation model, followed by regular home exercise. Unlike the study by Belardinelli et al,⁶ evaluating a strategy of only supervised training was not feasible, and it is unlikely that such a strategy would be adopted in practice. As expected in an unblinded study of a behavioral intervention, the HF-ACTION investigators had to deal with issues of crossover, adherence, and site variation. In fact, based on a survey of the patients after randomization, 55% of patients in the usual care group were not satisfied with the study group to which they were randomly assigned, and many continued some level of physical activity.

It is not easy for participants in an exercise training program, particularly for patients such as those in this study who have chronic symptomatic heart failure and multiple comorbid conditions, to continue exercise training during long-term follow-up. Although the study invested substantial effort and resources into optimizing adherence, we understand that lack of compliance is likely due to many factors, including a limitation of the disease state and concomitant comorbid conditions, diminishing motivation, or other factors, some of which are not easily modifiable.

The level of adherence achieved in HF-ACTION likely approaches the

maximal amount that could be achieved in a broad population of patients with heart failure, given the extensive attention provided by study personnel to promoting compliance, the provision of exercise equipment and heart rate monitors, and other adherence optimization efforts. By implementing these additional strategies, we were able to improve, in a significantly larger and broadly representative cohort of patients with heart failure, to a median of 1.8 supervised exercise training sessions per week from the 1.7 sessions per week seen in the study by McKelvie,⁹ which used a similar design of initial supervised training followed by home-based training.

At 3 months, patients in the exercise training group did have changes in exercise parameters (median 4% increase in peak oxygen consumption), which were less than those seen in the study by Belardinelli et al⁶ (18% increase in peak oxygen consumption) and the study by McKelvie⁹ (10% increase in peak oxygen consumption). All 3 studies had patients engaged in supervised training during the early phases. The differences between studies may be due to adherence during the early stages or differences in baseline characteristics, including β -blocker use. The observed 1-minute difference between groups in exercise time is simi-

lar to the changes in exercise time observed in the early ACE inhibitor trials.²⁵⁻²⁷

The lack of change in exercise testing parameters at 12 months may have been due to an insufficient training stimulus in most patients. A potential cause for the blunted training effect was the high use of β -blockers, which have been shown to limit peak oxygen consumption changes in healthy patients. The improvement at 12 months seen in the usual care group that reduced the differences between the 2 study groups was potentially due to crossover to exercise training by patients in the usual care group. Differences in health status between those who returned for the 12-month cardiopulmonary exercise test and those who did not also may have played a role. Also, there is significant variability in peak oxygen consumption measurements, particularly when obtained from multiple centers.²⁸

The results of HF-ACTION should be interpreted in the context of the following potential limitations. The patients enrolled in this trial were relatively young compared with the general population with heart failure and did not have heart failure with preserved left ventricular function (or diastolic heart failure). The only measure of exercise for patients in the usual care group was the Physical Activity Questionnaire, which provided a snapshot of activity over the prior 7 days. Blinding of the patients and the research personnel was not possible. More than 50% of the patients randomized to the usual care group were either somewhat or very dissatisfied with their treatment assignment; a number of these patients likely crossed over and initiated exercise training.

Despite the extensive efforts of the study, adherence to the exercise training regimen and crossovers to exercise in the usual care group may have diminished the study's ability to detect a significant effect of exercise training on the primary outcome. The lack of blinding also may have caused differential attention to patients by the study personnel. However, the inves-

tigators attempted to control for the inherent differences in the amount of contact with caregivers by regular telephone contact and follow-up of the patients in both study groups of the trial. Due to the fact that not all patients underwent cardiopulmonary exercise testing at 3-month and 12-month follow-up visits, changes in peak oxygen consumption should be interpreted with caution. The level of missing data on home exercise makes adherence in the exercise training group difficult to quantify. Some safety end points were measured only in the exercise training group and thus have no within-trial comparator group.

CONCLUSION

Regular exercise training in patients with systolic heart failure was safe. Based on the main analysis adjusted for heart failure etiology only, exercise training produced nonsignificant reductions in the primary end point (all-cause mortality or all-cause hospitalization) and in key secondary clinical end points. However, in protocol-specified supplementary analyses adjusted for prognostic factors, the treatment effect was statistically significant for the primary end point and for the secondary end point of cardiovascular mortality or heart failure hospitalization. These findings are consistent with the 33 previous trials and the meta-analyses showing improved outcomes. Based on the safety of exercise training and the modest reductions in clinical events in addition to the modest increases in health-related quality of life (reported in the accompanying article by Flynn et al¹⁵), the HF-ACTION results support a prescribed exercise training program for patients with reduced left ventricular function and heart failure symptoms in addition to evidence-based therapy.

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