Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial

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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. 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. 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-

See also p 1451.
main burdened by dyspnea and fatigue, diminished exercise tolerance, reduced quality of life, recurrent hospitalizations, and early mortality.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9} These studies also suggested that exercise training might improve survival and decrease heart failure hospitalizations.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 definitive 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 al\textsuperscript{15}) 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.\textsuperscript{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 (\textlesssim 6 weeks) or planned (\textlesssim 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.\textsuperscript{16} Patients were to begin home-based exercise after completing 18 supervised sessions and were...
to fully transition to home exercise af-
ter 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 fol-
low-up, and heart rate monitoring data
(model A1 or S1, Polar USA Inc) dur-
ing the home exercise training phase.

Usual Care

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

All patients were asked to return for
clinics visits every 3 months for the first
2 years of participation and yearly there-
after for up to 4 years. Cardiopulmo-
nary 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. This instrument quantified the
amount of moderate or vigorous activ-
ity in minutes per week completed dur-
ing the preceding week.

Primary, Secondary,
and Safety Outcomes

The primary endpoint was a compos-
ite of all-cause mortality or all-cause
hospitalization. Secondary end points
included all-cause mortality, the com-
posite of cardiovascular mortality or
hospitalization, and the composite of cardiovascular mortality or
heart failure hospitalization.

A post hoc analysis also was per-
formed to compare the 2 study groups
with respect to the composite of cardio-
vascular mortality, heart failure hospi-
talization, 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 dis-
tance 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
assessed as potential mediators.

Although blinding for patients and in-
vestigators was not possible due to the
nature of the exercise training interven-
tions, deaths and cardiovascular hospi-
talizations for each patient were adjudic-
at by a clinical end point committee
blinded to treatment assignment. Once
a patient had an adjudicated heart fail-
u re hospitalization, no further hospital-
izations for that patient were reviewed
by the clinical end point committee.

In addition to mortality and hospital-
ization, other cardiovascular adverse
events were captured, including wors-
ening heart failure, myocardial infar-
cion, unstable angina, serious adverse ar-
rhythmia, stroke, and transient ischemic
attack. Also captured were hospitaliza-
tions for fracture of the hip or pelvis, out-
patient fracture repair, implantable car-
dioverter-defibrillator (ICD) firing events
(for patients with an ICD), all hospital-
izations due to an event that occurred
during or within 3 hours after exercise,
and deaths during or within 3 hours af-
after exercise (or unknown if during or ≤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 ran-
domized to exercise training com-
pared with those randomized to usual
care. This estimate was based on as-
suming an annual primary outcome rate
of 30% in the usual care group, treat-
ment nonadherence rates of 30% in the
first year of follow-up and 12.5% an-
nually 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 Clin-
cial Research Institute, Durham, North
Carolina) using SAS software version
8.2 (SAS Institute Inc, Cary, North
Carolina). Baseline patient character-
istics were summarized using med-
ians and interquartile ranges for con-
tinuous variables and frequencies and
percentages for categorical variables.
Statistical comparisons of the study
groups with respect to clinical out-
comes were performed according to the
intention-to-treat principle. All statis-
tical tests were 2-tailed.

Cumulative event rates were calcu-
lated using the Kaplan-Meier method.37
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 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Usual Care (n = 1172)</th>
<th>Exercise Training (n = 1159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>59.3 (51.1-68.2)</td>
<td>59.2 (51.2-67.8)</td>
</tr>
<tr>
<td>Female sex</td>
<td>314 (26.8)</td>
<td>347 (29.9)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnicity a</td>
<td>48/1162 (4.1)</td>
<td>40/1147 (3.5)</td>
</tr>
<tr>
<td>Race b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>372/1156 (32.2)</td>
<td>377/1140 (33.1)</td>
</tr>
<tr>
<td>White</td>
<td>728/1156 (63.0)</td>
<td>698/1140 (61.2)</td>
</tr>
<tr>
<td>Other</td>
<td>56/1156 (4.8)</td>
<td>65/1140 (5.7)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>754 (64.3)</td>
<td>723 (62.4)</td>
</tr>
<tr>
<td>III</td>
<td>409 (34.9)</td>
<td>422 (36.4)</td>
</tr>
<tr>
<td>IV</td>
<td>9 (0.8)</td>
<td>14 (1.2)</td>
</tr>
<tr>
<td>Ischemic etiology of heart failure</td>
<td>599 (51.1)</td>
<td>596 (51.6)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, median (IQR), %</td>
<td>24.9 (20.0-30.2)</td>
<td>24.6 (20.0-30.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>370 (31.6)</td>
<td>378 (32.6)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>499 (42.6)</td>
<td>480 (41.4)</td>
</tr>
<tr>
<td>Hypertension b</td>
<td>676/1165 (58.0)</td>
<td>712/1153 (61.8)</td>
</tr>
<tr>
<td>Arterial fibrillation or atrial flutter b</td>
<td>241/1171 (20.6)</td>
<td>247/1159 (21.3)</td>
</tr>
<tr>
<td>Bock Depression Inventory II score, median (IQR)</td>
<td>8 (4-15)</td>
<td>8 (5-15)</td>
</tr>
<tr>
<td>Systolic blood pressure, median (IQR), mm Hg</td>
<td>111 (100-126)</td>
<td>110 (100-126)</td>
</tr>
<tr>
<td>Diastolic blood pressure, median (IQR), mm Hg</td>
<td>70 (60-80)</td>
<td>70 (61-78)</td>
</tr>
<tr>
<td>Sodium, median (IQR), mEq/L c</td>
<td>139 (137-141)</td>
<td>139 (137-141)</td>
</tr>
<tr>
<td>Blood urea nitrogen, median (IQR), mg/dL c</td>
<td>21 (15-28)</td>
<td>20 (15-28)</td>
</tr>
<tr>
<td>Serum creatinine, median (IQR), mg/dL c</td>
<td>1.2 (1.0-1.5)</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Baseline use of medications and devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>1094 (93.3)</td>
<td>1105 (95.3)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1112 (94.9)</td>
<td>1091 (94.1)</td>
</tr>
<tr>
<td>Aldosterone receptor antagonist</td>
<td>528 (45.1)</td>
<td>523 (45.1)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>921 (78.6)</td>
<td>895 (77.2)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>547 (46.7)</td>
<td>499 (43.1)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>448 (38.2)</td>
<td>490 (42.3)</td>
</tr>
<tr>
<td>Biventricular pacemaker</td>
<td>203 (17.3)</td>
<td>216 (18.6)</td>
</tr>
<tr>
<td>Functional measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance of 6-min walk, median (IQR), m</td>
<td>373.2 (300.0-432.5)</td>
<td>365.8 (296.3-436.2)</td>
</tr>
<tr>
<td>Cardiopulmonary exercise time, median (IQR), min</td>
<td>9.7 (7.0-12.1)</td>
<td>9.5 (6.9-12.0)</td>
</tr>
<tr>
<td>Peak oxygen consumption, median (IQR), mL/kg/min</td>
<td>14.5 (11.6-17.8)</td>
<td>14.4 (11.3-17.6)</td>
</tr>
</tbody>
</table>

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

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

b Unless otherwise indicated, Percentages may not sum to 100 because of rounding.

b Indicates the number of patients/number of patients with missing data for the variable (percentage).

c Sodium, 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 mortality (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 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.

Secondary End Points. Exercise training had a nonsignificant reduction in the combined end point of 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).

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 3 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.

Table 2. Patients With Selected Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Usual Care</th>
<th>Exercise Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified cardiovascular adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>340 (29.0)</td>
<td>303 (26.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>45 (3.8)</td>
<td>41 (3.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>88 (7.5)</td>
<td>86 (7.4)</td>
</tr>
<tr>
<td>Serious adverse arrhythmia</td>
<td>164 (14.0)</td>
<td>167 (14.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>28 (2.4)</td>
<td>33 (2.8)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>23 (2.0)</td>
<td>20 (1.7)</td>
</tr>
<tr>
<td>Any of the above events</td>
<td>471 (40.2)</td>
<td>434 (37.4)</td>
</tr>
<tr>
<td>General adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for fracture of the hip or pelvis</td>
<td>7 (0.6)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Outpatient fracture repair</td>
<td>20 (1.7)</td>
<td>13 (1.1)</td>
</tr>
<tr>
<td>ICD firing</td>
<td>151/644 (23.4)</td>
<td>142/641 (22.2)</td>
</tr>
<tr>
<td>Hospitalization after exercise</td>
<td>22 (1.9)</td>
<td>37 (3.2)</td>
</tr>
<tr>
<td>Died after exercise</td>
<td>5 (0.4)</td>
<td>5 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ICD, implantable cardioverter-defibrillator.

1Unless otherwise indicated.
2Follow-up data forms were not available for 1 patient.
3Defined 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).
4Indicates the number fired/number of patients with an ICD (percentage).
5Head at least 1 hospitalization due to an event that occurred during or within 3 hours after exercise.
6Patient died or not known if patient died during or within 3 hours after exercise.
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 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

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors Exercise</th>
<th>Favors Usual Care</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2331</td>
<td>1555</td>
<td>0.90 (0.84-1.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>1896</td>
<td>1226</td>
<td>0.92 (0.82-1.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>435</td>
<td>329</td>
<td>0.96 (0.78-1.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>661</td>
<td>420</td>
<td>0.83 (0.68-1.00)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>1670</td>
<td>1135</td>
<td>0.97 (0.87-1.09)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>749</td>
<td>523</td>
<td>0.96 (0.80-1.12)</td>
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<tr>
<td>White</td>
<td>1426</td>
<td>906</td>
<td>0.94 (0.83-1.07)</td>
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<tr>
<td>Other</td>
<td>127</td>
<td>84</td>
<td>0.86 (0.56-1.33)</td>
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<td></td>
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<tr>
<td>Etiology of heart failure</td>
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<td></td>
<td></td>
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<tr>
<td>Ischemic</td>
<td>1197</td>
<td>634</td>
<td>0.94 (0.82-1.08)</td>
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<tr>
<td>Nonischemic</td>
<td>1134</td>
<td>721</td>
<td>0.91 (0.78-1.05)</td>
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<tr>
<td>Baseline NYHA class</td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>1477</td>
<td>907</td>
<td>0.95 (0.83-1.08)</td>
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<tr>
<td>III/IV</td>
<td>854</td>
<td>648</td>
<td>0.85 (0.73-1.00)</td>
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<tr>
<td>LVEF, %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤25</td>
<td>1217</td>
<td>865</td>
<td>0.94 (0.83-1.08)</td>
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<tr>
<td>&gt;25</td>
<td>1110</td>
<td>687</td>
<td>0.91 (0.78-1.06)</td>
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<td>Previous revascularization</td>
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<tr>
<td>No</td>
<td>1428</td>
<td>925</td>
<td>0.94 (0.83-1.07)</td>
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<tr>
<td>Yes</td>
<td>903</td>
<td>630</td>
<td>0.90 (0.77-1.06)</td>
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<tr>
<td>History of MI</td>
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<td>No</td>
<td>1352</td>
<td>869</td>
<td>0.91 (0.79-1.03)</td>
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<tr>
<td>Yes</td>
<td>979</td>
<td>698</td>
<td>0.96 (0.82-1.11)</td>
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<td>ACE inhibitor use at baseline</td>
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<tr>
<td>No</td>
<td>595</td>
<td>415</td>
<td>0.81 (0.67-0.99)</td>
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<tr>
<td>Yes</td>
<td>1736</td>
<td>1143</td>
<td>0.97 (0.87-1.09)</td>
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<tr>
<td>β-Blocker use at baseline</td>
<td></td>
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<tr>
<td>No</td>
<td>128</td>
<td>94</td>
<td>1.08 (0.72-1.62)</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>2203</td>
<td>1461</td>
<td>0.91 (0.83-1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

HR, 0.92 (95% CI, 0.83-1.03); P = .14
Adjusted HR, 0.91 (95% CI, 0.82-1.01); P = .09

CI indicates confidence interval; HR, hazard ratio.

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but can occur when the treatment differences are close to significance. The overall interpretation of the results, then, is that this structured exercise training intervention had at best a modest effect on clinical endpoints in a large cohort of patients. The changes in cardiovascular 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 theValsartan Heart Failure Trial (HR, 0.87; 95% CI, 0.77-0.97). 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. 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 cardiac rehabilitation model, followed by regular home exercise. Unlike the study by Belardinelli et al., 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, 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 al. (18% increase in peak oxygen consumption) and the study by McKelvie (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.\textsuperscript{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.\textsuperscript{34}

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 investigators 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 al\textsuperscript{35}), 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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ing on the board of directors of Cancer Consultants, and having equity in and serving on the executive board of Family Connection LLC (a more detailed listing of Dr Schulman's financial disclosures is available at http://www.dcri.duke.edu/research/coi.jsp). Dr Piha reported receiving grants or funding from the National Institutes of Health, receiving personal income for consulting from the Food and Drug Administration, and receiving honoraria from AstaRezeca, Innovia, Merck, Novartis, Sanofi-Aventis, and Solvay. Drs Lee, Cooper, Lefter, Kitzman, R. McKevie, and Zannad did not report any financial disclosures.

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EXERCISE TRAINING IN PATIENTS WITH CHRONIC HEART FAILURE

Previous Presentation: Presented as a late-breaking clinical trial at the American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society; ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology; ESC Committee for Practice Guidelines; Document Reviewers. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388-2442.


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