

Effects of Exercise Training on Outcomes in Women With Heart Failure

Analysis of HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of Exercise TraiNing) by Sex

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- Objectives** The authors hypothesized that the women enrolled in the HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of Exercise TraiNing) trial and randomly assigned to exercise training (ET) would improve functional capacity as measured by peak oxygen uptake (VO_2) compared with those in the usual care group. Furthermore, they hypothesized that the improvement in peak VO_2 would correlate with prognosis. They explored whether exercise had a differential effect on outcomes in women versus men.
- Background** There is less evidence for the benefit of ET in women with heart failure (HF) compared with men because of the small numbers of women studied.
- Methods** HF-ACTION was a randomized trial of ET versus usual care in 2,331 patients with class II–IV HF and a left ventricular ejection fraction of $\leq 35\%$. Sex differences in the effects of randomized treatment on clinical outcomes were assessed through the use of a series of Cox proportional hazards models, controlling for covariates known to affect prognosis in HF-ACTION.
- Results** Women had lower baseline peak VO_2 and 6-min walk distance than did men (median, 13.4 vs. 14.9 ml/min/kg and 353 vs. 378 m, respectively). An increase in peak VO_2 at 3 months was present in women and men in the ET group (mean \pm SD; median, 0.88 ± 2.2 , 0.80 and 0.77 ± 2.7 , 0.60 , respectively, women vs. men; $p = 0.42$). Women randomly assigned to ET had a significant reduction in the primary endpoint, (hazard ratio: 0.74) compared with men (hazard ratio: 0.99) randomly assigned to ET, with a significant treatment-by-sex interaction ($p = 0.027$).
- Conclusions** Although there is no significant difference between men and women in the effect of ET on peak VO_2 change at 3 months, ET in women with HF is associated with a larger reduction in rate of the combined endpoint of all-cause mortality and hospital stay than in men. (J Am Coll Cardiol HF 2014;2:180–6) © 2014 by the American College of Cardiology Foundation

Cardiovascular disease is responsible for more deaths of women annually than of men in the United States and is the number-one cause of death for women in the United States (1–3). Although the incidence of heart failure (HF) has decreased in the last decade for women, hospital stays continue to increase disproportionately (1,4). Although

women are twice as likely to have HF after a myocardial infarction or revascularization than are their male counterparts, they are less likely to be referred to a cardiac rehabilitation program or complete an exercise training program (5). There is less evidence for benefit of exercise training in women with HF compared with men because of the small

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numbers of women in single-center trials and lack of data on normal functional capacity for women through the use of cardiopulmonary testing. The published nomogram of mostly asymptomatic white women with the use of a Bruce protocol estimated metabolic equivalents of the task by treadmill speed and grade, which may overestimate functional capacity (6). Similarly, there has been a paucity of cardiopulmonary testing data for large clinical cohorts of women with HF (7,8). This underrepresentation of women in the HF clinical trial and functional capacity published data has limited our understanding of potential sex differences that could affect therapy, functional assessment, and recommendations for physical activity and exercise prescription. A large trial was necessary to assess the impact of exercise training on HF outcomes, including mortality, stratified by sex (9).

The HF-ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise TraiNing) trial randomly assigned 2,331 patients with HF caused by systolic dysfunction (ejection fraction $\leq 35\%$) to either a formal exercise program in addition to optimal medical therapy or to optimal medical therapy alone without any formal exercise training. The median age was 59 years, 28% were women, and 37% had New York Heart Association class III or IV symptoms. The underlying cause of heart failure was ischemia in 51%, and median left ventricular ejection fraction (LVEF) was 25%. Median follow-up was 30 months. Exercise training was associated with a non-significant reduction in the primary endpoint of all-cause mortality or hospital stay (hazard ratio [HR]: 0.93 [95% CI: 0.84 to 1.02]; $p = 0.13$) and non-significant reductions in the secondary endpoints of mortality (HR: 0.96 [95% CI: 0.79 to 1.17]; $p = 0.70$), cardiovascular mortality or cardiovascular hospitalization (HR: 0.92 [95% CI: 0.83 to 1.03]; $p = 0.14$), and cardiovascular mortality or heart failure hospital stay (HR: 0.87 [95% CI: 0.75 to 1.00]; $p = 0.06$) (10,11). After adjusting for four covariates, duration of the cardiopulmonary exercise test (CPX), LVEF, Beck Depression Inventory II score, and history of atrial fibrillation or flutter, which were identified as highly prognostic of the primary endpoint independent of treatment assignment, plus HF cause, exercise training was found to be associated with a reduction in the event rate of the primary endpoint by 11% (HR: 0.89 [95% CI: 0.81 to 0.99]; $p = 0.03$) and the combined secondary end-point of cardiovascular (CV) mortality or HF hospital stay (15%, $p = 0.03$) but not the combined secondary endpoint of CV death or CV hospital stay (9%, $p = 0.09$) (11). The HF-ACTION trial also demonstrated that in patients with HF, regular aerobic exercise is safe and modestly improves health-related quality of life as measured by the Kansas City Cardiomyopathy Questionnaire instrument as early as 3 months after random assignment and remained stable at 12 months (12).

In the primary analysis, 64% of the women had the combined primary endpoint versus 68% of the men. The primary subgroup analysis (adjusted only for cause) for

women and men showed an HR of 0.83 (95% CI: 0.68 to 1.00) for the women and 0.97 (95% CI: 0.87 to 1.09), $p = 0.17$ for the interaction.

The HF-ACTION trial is unique in several ways: 1) it is a pre-specified analysis of women; 2) it has study sites with adequate representation of women; 3) it is the largest CPX testing database ever acquired in women at baseline and during trial conduct, and 4) it has the optimization of background medical therapy.

Therefore, the HF-ACTION trial is uniquely positioned to review outcome by sex to determine the effects of exercise training on the primary and secondary endpoints in women with HF and compare them to the male cohort, for example, does exercise have a differential effect on clinical outcomes in women versus men? We hypothesized for this exploratory analysis that the women enrolled in the HF-ACTION trial and randomly assigned to exercise would improve functional capacity as measured by peak oxygen uptake (VO_2) compared with those in the usual care group. Furthermore, we hypothesized that the improvement in peak VO_2 would correlate with prognosis.

Methods

Study design. The full design of the trial and the training protocol have been described elsewhere, as have the baseline data by sex (13,14). In brief, HF-ACTION was a multi-center trial that enrolled outpatients in stable condition with left ventricular dysfunction (ejection fraction $\leq 35\%$) and New York Heart Association class II to IV HF symptoms. Patients were recruited from 82 centers in the United States, Canada, and France. The relevant institutional review boards, research ethics boards, and ethics committees of the participating centers and the coordinating center approved the protocol, and all patients provided written consent to participate. To assess both exercise capacity, as measured by peak VO_2 , and one's ability to safely undergo exercise training, patients were scheduled to undergo a symptom-limited cardiopulmonary exercise test before random assignment. Patients randomly assigned to the exercise arm ($n = 1,159$) were scheduled to participate in supervised walking or stationary cycling 3 days per week. After completing 18 sessions, patients were asked to add a 2-day-per-week home-based exercise program. They were fully transitioned to a 5-day-per-week home-based exercise program after completing 36 supervised sessions. The duration for supervised exercise was 30 minutes; intensity was initially set at a heart rate of 60% by use of the heart rate reserve method ($[\text{peak heart rate} - \text{resting heart rate}] \times 0.6 + \text{resting heart rate}$) (15) and then titrated to 70% of heart rate reserve. Home exercise was prescribed for 40 minutes at 60% to 70% of heart rate reserve. Among patients in

Abbreviations and Acronyms

HF = heart failure

ET = exercise training

LVEF = left ventricular ejection fraction

whom heart rate alone was invalid as a measure of exercise intensity (e.g., atrial fibrillation), the Borg Rating of Perceived Exertion scale was used and set at a level of 12 to 14 (i.e., fairly light to somewhat difficult) (16). Consistent with the main HF-ACTION trial, the primary outcome in this analysis was a composite of all-cause mortality or hospital stay and the secondary clinical outcomes were mortality alone, the composite of CV mortality or CV hospital stay, and the composite of CV mortality or HF hospital stay. Any death or first nonfatal CV event requiring hospital stay was adjudicated by a blinded Clinical End Points Committee.

Statistical methods. Baseline patient characteristics were presented by sex, with continuous variables summarized using the median (and interquartile range), and categorical data were summarized by frequencies and percents. Probability values for continuous variables were obtained by means of the *t* test, except when the assumption of normality was not satisfied, in which case the Wilcoxon rank-sum test was used. For categorical variables, the chi-square test was used when appropriate; otherwise, the Fisher exact test was used. Change in peak VO₂ from baseline to 3 months was summarized by sex and treatment group, by use of the mean, standard deviation, median, minimum and maximum values in each group. Adjusted linear and Cox proportional hazards models were used to assess the role of sex in the relationship between exercise treatment and outcomes. The clinical outcomes were analyzed with Cox models and the linear model was used to model change in peak VO₂ from baseline to 3 months.

Separate models were developed for each of the clinical endpoints through the use of the same methodology. Sixty-one potential predictors, including treatment group, were considered. First, missing data of potential predictors were imputed when necessary by means of a multiple imputation procedure, although most of the potential predictors had <1% missing data. The independent relationship of each individual continuous variable with outcome was checked for linearity of the log hazard ratio, and piecewise linear splines were used as transformations when appropriate. A

bootstrapped backwards selection algorithm of a Cox proportional hazards model was used for model selection, and the C-index was used to choose the final model. Lists of covariates identified by this method for modeling each clinical endpoint are noted in Table 1.

Although treatment group does not appear in any of the lists of strong predictors listed previously, treatment was added to each model to investigate its interaction with sex and to separately estimate the associated HR for men and women. Similarly, race was added and peak VO₂ was substituted for Weber class in the primary endpoint model to investigate their respective interactions with sex.

In Cox models, the relative risk of exercise versus usual care was estimated by HR with 95% confidence intervals, calculated separately for male and female patients. In addition to exercise treatment, the relative roles of race and baseline peak VO₂ among men and women were analyzed in the primary endpoint model. On the basis of the observed univariate relationship between baseline peak VO₂ and the primary endpoint, peak VO₂ values >20 ml/kg/min were modeled as if they were 20 ml/kg/min to model the hazard as constant for peak VO₂ >20 ml/kg/min. In the linear model used to analyze the endpoint of change in peak VO₂ at 3 months, the relative effect of exercise among male and female patients was estimated by use of the difference in least-squares mean response (exercise vs. usual care) with 95% CI, among male and female patients. Interaction tests with male and female patients in the same Cox model were performed to check for differential treatment effect by sex. No adjustment was made for multiple comparisons in this exploratory analysis. Statistical analyses were performed by the coordinating center (Duke Clinical Research Institute, Durham, North Carolina) with the use of SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Demographics and baseline parameters. Of the 2,331 patients recruited into the HF-ACTION trial, 28% were women. The baseline demographics and clinical

Table 1 Results From Adjusted Proportional Hazards Models: Hazard Ratios for Specified Effects Among Men and Women, With Tests for Corresponding Interactions of Interest

Model Endpoint	Sex Interaction Effect	Estimated Effect in Women	Estimated Effect in Men	p Value for Interaction
All-cause death/hosp*	HR (95% CI): exercise (vs. control)	0.74 (0.59–0.92)	0.99 (0.86–1.13)	0.027
All-cause death†	HR (95% CI): exercise (vs. control)	0.71 (0.43–1.15)	1.01 (0.79–1.29)	0.20
CV-death/CV-hosp‡	HR (95% CI): exercise (vs. control)	0.79 (0.62–1.00)	0.96 (0.83–1.11)	0.17
CV-death/HF-hosp§	HR (95% CI): exercise (vs. control)	0.76 (0.55–1.05)	0.91 (0.75–1.10)	0.36
All-cause death/hosp*	HR (95% CI): non-white (vs. white)	1.01 (0.81–1.27)	1.25 (1.08–1.45)	0.11
All-cause death/hosp*	HR (95% CI): baseline peak VO ₂ (up to 20)	0.92 (0.90–0.95)	0.92 (0.90–0.94)	0.74

*All-cause death/hosp covariates are Weber class, sex, region, mitral regurgitation grade, ventricular conduction before CPX, BUN, LVEF, BB dose (<50), baseline KCCQ Symptom Stability Score, and treatment group. †All-cause mortality covariates are sex, BMI (<25), loop diuretic dose (<100), Canadian Angina Class, ventricular conduction before CPX, LVEF, exercise duration on CPX test, serum creatinine (<2.3), and treatment group. ‡CV-death/CV-hosp covariates are sex, race, LVEF (>17), mitral regurgitation grade, ventricular conduction before CPX, BUN (<26), baseline KCCQ Symptom Stability Score, heart rate at peak exercise on baseline CPX (>142), nitrates, Weber class, baseline KCCQ Total Symptom Score, and treatment group. §CV-death/HF-hosp covariates are sex, race, age (<62), loop diuretic dose (<100), LVEF, mitral regurgitation grade, BUN (<39), VE/VCO₂ (<80), baseline KCCQ Symptom Stability Score, peak VO₂ (<28), ventricular conduction before CPX, and treatment group.

BB = β-blocker; BMI = body mass index; BUN = blood urea nitrogen; CPX = cardiopulmonary exercise test; CV = cardiovascular; HF = heart failure; hosp = hospitalization; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; VE/VCO₂ = ventilatory equivalents of CO₂; VO₂ = peak oxygen uptake (ml/kg/min).

characteristics of the study group by sex are depicted in Table 2. Full baseline variables have been published previously (14). The median LVEF for women was the same as for men, but, because of the distribution, the p value was 0.01. Women were less likely to have an ischemic cause of disease. Of interest, a slightly higher percent of women had a left bundle-branch block on baseline electrocardiogram than men. Women had significantly better renal function. The dosages of β -blockers in women were lower on average but not significantly different. The Kansas City Cardiomyopathy Questionnaire health status assessment scores were similar in men and women. However, both the peak VO₂ and 6-min walk distance were lower at baseline in the women when compared with that in men.

Functional capacity by peak VO₂. Table 3 presents the changes in peak VO₂ at 3 months in both randomized groups by sex. There were no apparent differences between men and women within either treatment arm with respect to change in peak VO₂. Adjusted model estimates (with 95% CIs) of the

least-squares mean difference in peak VO₂ change between exercise patients and usual care patients were similar for men (0.50, 0.22 to 0.79) and women (0.73, 0.27 to 1.19), and the sex-by-treatment interaction was not statistically significant in the adjusted model (p = 0.42) (see Table 4 with model specifications included). The target ET for the study was 90 min/week. Adherence to ET was higher among men than women, with 45% of men maintaining the goal of 90 minutes of exercise per week during the first 3 months of study (median, 81 min per week; Q₁ = 41 min, Q₃ = 122 min) versus 37% of women (median, 70 minutes per week; Q₁ = 37 min, Q₃ = 108 min).

Endpoints. The unadjusted absolute 2-year Kaplan-Meier rate estimates for the primary endpoint by sex and treatment were (exercise vs. usual care) 0.37 (95% CI: 0.33 to 0.40) versus 0.37 (95% CI: 0.34 to 0.41) for men and 0.50 (95% CI: 0.44–0.55) versus 0.40 (95% CI: 0.34 to 0.46) for women. Table 1 illustrates the estimated effect of treatment on outcomes by sex, after adjustment for covariates

Variable	Women (n = 661)	Men (n = 1,670)	p Value
Age, yrs	57 (49, 66)	60 (52, 69)	<0.001 NP
Race			
African American	303 (47)	446 (27)	<0.001
White	316 (49)	1,110 (67)	
Other	30 (5)	91 (6)	
Country			
United States	614 (93)	1,454 (87)	<0.001
Canada	31 (5)	157 (9)	
France	16 (2)	59 (4)	
BMI, kg/m ²	30 (25, 36)	30 (26, 34)	0.12 NP
New York Heart Association class			
II	410 (62)	1,067 (64)	0.40
III/IV	251 (38)	603 (36)	
HF cause			
Ischemic	209 (32)	988 (59)	<0.001
LVEF %	25 (20, 31)	25 (20, 30)	0.012 NP
Mitral regurgitation			
Moderate to severe or severe	96 (16)	160 (11)	0.001
Ventricular conduction before baseline CPX			
Normal	321 (49)	658 (41)	<0.001
LBBB	139 (21)	240 (15)	
RBBB	13 (2)	72 (4)	
IVCD	71 (11)	221 (14)	
Paced	105 (16)	431 (27)	
Serum creatinine, mg/dl	1.0 (0.8, 1.2)	1.3 (1.1, 1.5)	<0.001 NP
BB dose, mg/day carvedilol equivalent	25 (13, 50)	37 (13, 50)	0.090 NP
Loop (diuretic) dose, mg/day furosemide equivalent	40 (10, 80)	40 (20, 80)	0.001 NP
Peak VO ₂ , ml/kg/min	13.4 (10.8, 16.3)	14.9 (11.9, 18.2)	<0.001 NP
CPX duration, min	8.8 (6.3, 11.2)	10.0 (7.1, 12.2)	<0.001 NP
Six-min walk distance, m	353 (287, 415)	378 (301, 442)	<0.001 NP
Biventricular pacemaker	92 (14)	327 (20)	0.001
Kansas City Cardiomyopathy Questionnaire overall score	69 (50, 83)	68 (51, 83)	0.89 NP

Values are median (Q1, Q3) or n (%).
 NP = nonparametric; other abbreviations as in Table 1.

Table 3 Peak VO₂ Change at 3 Months by Sex and Treatment Group

Peak VO ₂ change at 3 Months	Women, Usual Care	Men, Usual Care	Women, Exercise	Men, Exercise
N	229	668	290	682
Mean ± SD	0.15 ± 2.1	0.26 ± 2.6	0.88 ± 2.2	0.77 ± 2.7
Median	0.2	0.2	0.8	0.6
(Min, Max)	(-6.0, 7.8)	(-11.6, 13.5)	(-10.7, 10.2)	(-8.9, 12.5)

VO₂ = peak oxygen uptake.

from previously developed models (10,17). The women randomly assigned to exercise had a significant reduction in the primary endpoint (HR: 0.74; 95% CI: 0.59 to 0.92) when compared with the men randomly assigned to exercise, (0.99; 95% CI: 0.86 to 1.13), with a significant treatment-by-sex interaction ($p = 0.027$) after adjustment. For all the secondary endpoints, the HR was lower in women compared with men, although the associated treatment-by-sex interactions were not statistically significant. There was no significant interaction of sex with baseline peak VO₂ (truncated at 20 ml/kg/min, as described previously) on the primary endpoint ($p = 0.74$). Figure 1 illustrates the endpoint analysis by sex subgroup of exercise versus usual care.

Discussion

We found a significant 26% reduction in the primary endpoint of all-cause death or all-cause hospital stay in women and no reduction in the men randomly assigned to exercise training in the HF-ACTION trial. This prospectively planned analysis, by sex, of the primary endpoint of HF-ACTION is the first, to our knowledge, to link the effects of exercise training to reduction in risk for subsequent all-cause death or all-cause hospital stay in women. Although sex-by-treatment interaction reported initially in the trial manuscript was not significant ($p = 0.17$ adjusted only for cause of HF), the current analysis included additional covariate adjustment, and we observed a significant risk reduction among women randomly assigned to exercise training (HR: 0.74; 95% CI: 0.59 to 0.92) and virtually no risk reduction in the men (HR: 0.99; 95% CI: 0.86 to 1.13). It has been shown that covariate adjustment can lead to more accurate estimates in Cox models, even when there are no baseline imbalances. To date, the HF-ACTION trial not only comprises the largest prospective study to examine

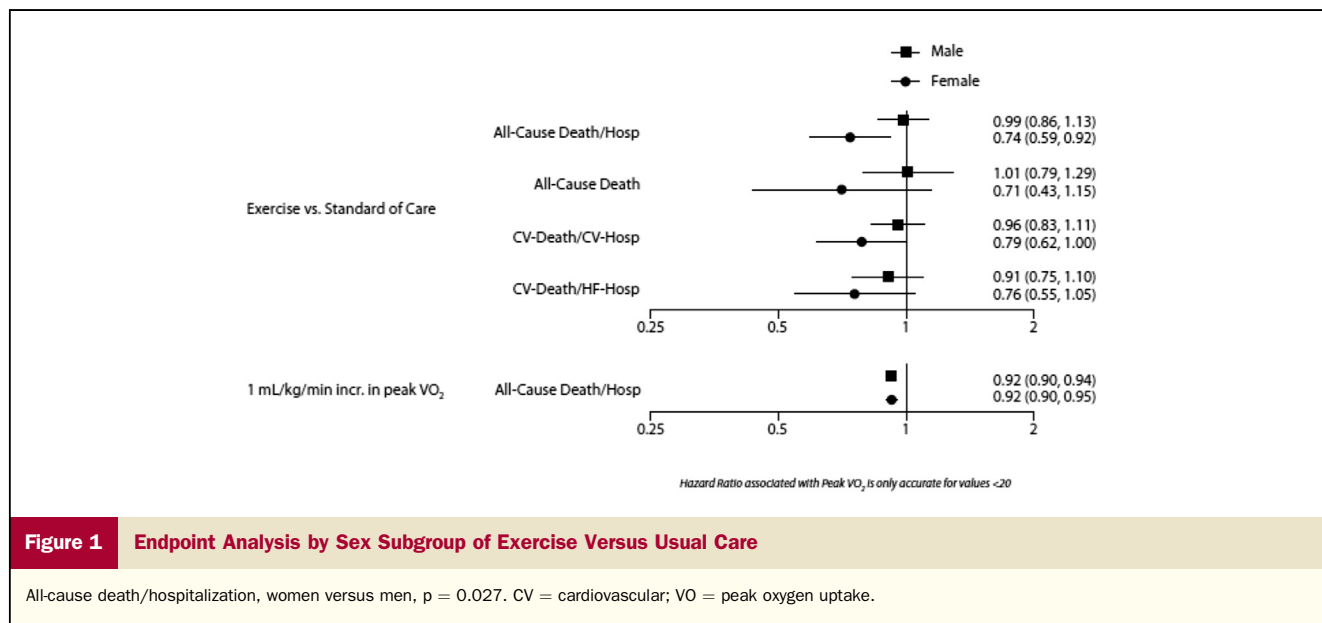
the effects of exercise training in patients with HF, but it also includes the largest cohort of women with HF to undergo exercise training. Our finding of a greater reduction in risk among women than men parallels the observations of Suaya et al. (18), who reported that the reduction in 5-year cumulative mortality rate among cardiac rehabilitation users (vs. non-users) was greater in older women versus older men. The differences in baseline characteristics have been previously reported (14). However, there are differences by sex presented in this study that support previous work and are also worth reviewing. As reported by others, the women had less ischemic disease than the men, better renal function, and similar quality of life (19). The lower risk of adverse outcomes in women has also been noted in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) trial (20) and in the analysis of the BEST (Beta-Blocker Evaluation of Survival Trial) trial by sex (21). In the A-HeFT (African-American Heart Failure Trial), which included 40% women, hypertension was more prevalent in the women than in the men (22). In addition, there was a trend in β -blocker dosing toward being lower in the women. Suboptimal dosing of medical therapy in women has also been previously noted (2,6,14). As recently published, we also observed that left bundle-branch block was slightly more common in the women (23). Exercise capacity at baseline, as measured by both peak VO₂ and 6-min walk distance, was approximately 7% to 10% lower in women versus men and similar to those reviewed by Haykowsky et al. (24). Women have significantly lower baseline values of peak VO₂ and experience a greater (but not significantly greater) increase in peak VO₂ after 3 months of treatment. The women in HF-ACTION had a change in peak VO₂ that was similar to that in men, although the change for either sex was modest. As demonstrated in Figure 1, a higher peak VO₂ is associated

Table 4 Results From Adjusted Linear Model of Change in Peak VO₂ at 3 Months: Least-Squares Mean Differences Between Treatment Groups Among Men and Women, With Sex-by-Treatment Interaction Test

Model Endpoint	Sex Interaction Effect	Estimated Effect, Women	Estimated Effect, Men	p Value
Change in peakVO ₂ at 3 months	Least-squares mean differences (95% CI): Exercise-control	0.73 (0.27–1.19)	0.50 (0.22–0.79)	0.42

Covariates for 3-month change in peak VO₂ are baseline peak VO₂, days from baseline to 3-month visit, age, sex, race, BMI (≥ 30 kg/m²), ischemic cause, BUN, ventricular conduction prior to CPX, income, education, insulin use, adjusted heart rate (beats/min) at the end of WL 2 on CPX test, exercise duration on CPX test (< 18 min), heart rate reserve on CPX test, peak respiratory exchange ratio on CPX test (< 1), number of HF hospital stays in 6 months before baseline, and treatment.

Abbreviations as in Table 1.



with a better outcome (at least for the primary endpoint) in men and women. Nevertheless, no significant interaction was found ($p = 0.85$) between 3-month change in peak VO₂ and sex in a primary outcome model that adjusted for these two covariates along with baseline peak VO₂; therefore we cannot conclude that differences in peak VO₂ over time translated to different death/hospital stay outcomes for men and women. Mechanisms responsible for this benefit at this time are unknown. However, regardless of mechanisms, the finding of a better clinical outcome in the women carries significant implications for dissemination and for clinical practice. There may be other benefits to exercise training in women that are different than in the men and not related to peak VO₂. We could postulate that a cohort with primarily a non-ischemic underlying cause may derive a greater benefit from rehabilitation. Historically, women are referred less often to cardiac rehabilitation and are less likely to complete a program (25,26). The barriers for women often include transportation, family responsibilities, and lack of the clinician's support and encouragement, in addition to lower rates of referral. Our findings suggest that exercise training for women with HF might appropriately be considered a useful addition to medical therapy. It should be pointed out that the study emphasized optimal guideline-driven medical therapy and achieved significant levels of background medical therapy, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β -blockers. Thus, the benefit of the training occurred in addition to medical therapy. The training in our trial did not require electrocardiographic monitoring but had a concrete recommendation for exercise prescription individualized by the baseline CPX. Home exercise training guided by an initial in-center phase, as in this study, can represent lower cost and a more accessible adjunctive treatment option for patients with HF

and impaired LVEF than facility-based training. The safety of exercise training in patients with HF was previously reported for the HF-ACTION trial, as was the improvement in health status (11,12).

Study limitations. The results of this study should be seen in the light of some of the limitations of the HF-ACTION trial. The patients were younger than the general population with HF. In addition, blinding was impossible in this trial construct. Therefore, although investigators made every attempt to minimize preferential care, patients in the exercise arm may have received differential attention when compared with the control group. Some baseline differences by sex may have been, in part, a function of the patients who self-selected for entry into an exercise trial. Unmeasured confounding variables may have affected the relationships observed between sex and clinical outcomes. Also, no adjustment was made for multiple comparisons; therefore p values of borderline significance should be interpreted with caution.

Conclusions

We present the largest database of women with HF enrolled in an exercise trial, and the data suggest that exercise training may reduce the risk of all-cause mortality and all cause hospital stay in women. If confirmed, this result might recommend the addition of exercise training to other evidence-based medical therapy for women with HF and impaired left ventricular function.

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