

Exercise Training in Patients With Chronic Heart Failure and Atrial Fibrillation



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ABSTRACT

BACKGROUND The safety and efficacy of aerobic exercise in heart failure (HF) patients with atrial fibrillation (AF) has not been well evaluated.

OBJECTIVES This study examined whether outcomes with exercise training in HF vary according to AF status.

METHODS HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) randomized 2,331 ambulatory HF patients with ejection fraction $\leq 35\%$ to exercise training or usual care. We examined clinical characteristics and outcomes (mortality/hospitalization) by baseline AF status (past history of AF or AF on baseline electrocardiogram vs. no AF) using adjusted Cox models and explored an interaction with exercise training. We assessed post-randomization AF events diagnosed via hospitalizations for AF and reports of serious arrhythmia caused by AF.

RESULTS Of 2,292 patients with baseline rhythm data, 382 (17%) had AF, 1,602 (70%) had sinus rhythm, and 308 (13%) had "other" rhythm. Patients with AF were older and had lower peak $\dot{V}O_2$. Over a median follow-up of 2.6 years, AF was associated with a 24% per year higher rate of mortality/hospitalization (hazard ratio [HR]: 1.53; 95% confidence interval [CI]: 1.34 to 1.74; $p < 0.001$) in unadjusted analysis; this did not remain significant after adjustment (HR: 1.15; 95% CI: 0.98 to 1.35; $p = 0.09$). There was no significant difference in AF event rates by randomized treatment assignment in the overall population or by baseline AF status (all $p > 0.10$). There was no interaction between AF and exercise training on measures of functional status or clinical outcomes (all $p > 0.10$).

CONCLUSIONS AF in patients with chronic HF was associated with older age, reduced exercise capacity at baseline, and a higher overall rate of clinical events, but not a differential response to exercise training for clinical outcomes or changes in exercise capacity. (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]; [NCT00047437](https://doi.org/10.1016/j.jacc.2017.01.032)) (J Am Coll Cardiol 2017;69:1683-91) © 2017 by the American College of Cardiology Foundation.

The disorders of atrial fibrillation (AF) and chronic heart failure (HF) are closely intertwined with aging; both are expected to rise in prevalence, stemming from a continued burgeoning of shared risk factors including hypertension, aging, and obesity (1). More than one-half of patients with HF develop AF, and > one-third with

AF develop incident HF (2). In combination, they portend higher mortality risk compared with either in isolation (2).

Physical activity and exercise training improve symptoms and can have antiarrhythmic effects in individuals with paroxysmal AF and may be protective against the development of AF (3-6). In patients



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ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
CI	= confidence interval
ECG	= electrocardiogram
EF	= ejection fraction
HF	= heart failure
HFrEF	= heart failure with reduced ejection fraction
HR	= hazard ratio
KCCQ	= Kansas City Cardiomyopathy Questionnaire
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association
Vo₂	= oxygen uptake

with chronic heart failure with reduced ejection fraction (HFrEF), as shown in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study, exercise training is associated with improved exercise capacity, improved quality of life, and reduced all-cause mortality and hospitalization (7,8). In the HF-ACTION primary analysis, AF was highly predictive of the primary endpoint of all-cause mortality or hospitalization, independent of treatment arm, and was used in the adjusted model for the primary analysis (7). However, to date, limited data characterize the implications of exercise training in individuals with both HF and AF and their risk for future AF events.

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The HF-ACTION trial is the largest trial to date investigating the effects of aerobic exercise training in stable outpatients with HFrEF (7). Using the HF-ACTION study cohort, we: 1) examine the relationship between baseline AF status and outcomes with exercise training; and 2) describe future AF events, in patients with chronic HF.

METHODS

TRIAL OVERVIEW. The trial design and results of HF-ACTION have been previously reported (7,9). This multicenter, randomized controlled trial compared the long-term safety and efficacy of exercise training plus evidence-based heart failure medical therapy versus medical therapy alone in patients with chronic HF (ejection fraction [EF] <35%) and New York Heart Association (NYHA) functional class II to IV symptoms. There were no inclusion or exclusion criteria regarding the management of AF. Patients were excluded if they had sustained AF with rapid ventricular response on the baseline exercise test performed before enrollment.

Supervised training involved aerobic exercise (walking, treadmill, or cycle ergometer) 3 times weekly for 36 sessions, followed by transition to a home-based exercise program for an additional 2 years. The exercise goal was 90 min per week for the first 3 months, followed by 120 min per week thereafter. Follow-up occurred over a median of 2.6 years. The protocol was approved by the institutional review board or ethics committee at each institution and the coordinating center. All patients provided written informed consent.

AF STATUS AND OUTCOMES. Patient characteristics, medical history, health status, and physiological

parameters at rest and during exercise testing were collected on standardized forms at baseline and repeated at 3 months, 12 months, and 24 months. Health status was measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Beck Depression Inventory II (10,11). All patients underwent graded cardiopulmonary exercise testing to evaluate safety and exercise capacity at baseline, including a 12-lead electrocardiogram (ECG) for assessment of baseline rhythm, and this testing was repeated at 3 months, 12 months, and 24 months. Performed using a modified Naughton treadmill protocol or a leg ergometer, exercise continued until sign- or symptom-limited maximal exertion was reached. Peak oxygen uptake (Vo₂) was defined as the Vo₂ at peak exercise, either within the last 90 s of exercise or the first 30 s of recovery, whichever was higher. Exercise volume was calculated for the subpopulation randomized to exercise therapy. Using metabolic equivalent hours of exercise per week to represent the product of exercise intensity (where 1 metabolic equivalent is ~3.5 ml O₂ · kg⁻¹ · min⁻¹), exercise volume was derived during months 1 to 3 for patients who did not experience a clinical event or were not censored in that time period (12).

For the present study, AF status was determined by presence on ECG at baseline cardiopulmonary stress test or an investigator-reported past medical history of AF. Patients with and without AF were compared. In the AF study groups, the composite primary endpoint of all-cause mortality and all-cause hospitalization, and secondary endpoints of all-cause mortality alone and cardiovascular mortality or HF hospitalization were assessed with and without adjustment for variables found to be significantly associated with outcomes in prior HF-ACTION analyses (13,14). The occurrence of new or recurrent AF events after randomization was diagnosed through investigator reports of AF hospitalizations or serious adverse arrhythmia caused by AF.

STATISTICAL METHODS. Baseline characteristics were reported by AF status. Categorical variables were reported as frequencies and percentages and compared using Pearson chi-square or Fisher exact tests. Continuous variables were reported as median (25th and 75th percentile) and compared using the Wilcoxon rank sum test.

We used unadjusted and adjusted Cox proportional hazards models to assess the association between exercise training and each clinical outcome stratified by baseline AF status. Adjusted general linear models were also used to assess the association between exercise training and exercise capacity and health status outcomes stratified by baseline AF status.

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