Structured Exercise for Heart Failure Patients Is Safe But Does Not Significantly Reduce Mortality or Hospitalizations

O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

Study Overview

Objective. To determine whether a structured exercise regimen is safe and improves clinical outcomes in patients with stable chronic heart failure.

Design. Multicenter randomized controlled trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]).

Setting and participants. 2331 medically stable outpatients with chronic heart failure and reduced left ventricular ejection fraction (< 35%) from 82 centers in the United States, Canada, and France were enrolled from April 2003 to February 2007. Patients were excluded if they had major comorbidities that could interfere with exercise training, recent (≤ 6 weeks) or planned (≤ 6 months) major cardiovascular events or procedures, had already participated in regular exercise training, used devices that would limit their ability to achieve target exercise heart rates, or if baseline cardiopulmonary exercise testing revealed significant arrhythmias or ischemia that would prevent safe exercise training.

Intervention. Patients were randomized to usual care plus aerobic exercise training or usual care alone. Patients randomized to exercise training received 3 months of structured, group-based, supervised 15- to 30-minute exercise sessions 3 times per week (for a total of 36 supervised sessions), followed by home-based exercise for 40 minutes 5 times per week using specialized equipment and heart rate monitors. Exercise adherence was monitored, and approximately 30% of patients in the exercise training arm exercised at or above their weekly target time durations at any given time during the study.

Main outcome measures. The primary outcome was a composite endpoint of all-cause mortality or hospitalization. Secondary outcomes were all-cause mortality, the composite of cardiovascular mortality or cardiovascular hospitalization, and cardiovascular mortality or heart failure hospitalization. Exercise safety was assessed by hospitalizations for fracture of the hip or pelvis, outpatient fracture repair, implantable cardioverter-defibrillator firing events, and all hospitalizations due to an event or deaths that occurred during or within 3 hours after an exercise session. Outcomes were adjudicated by a committee blinded to treatment assignment.

Main results. Median age was 59 years, 28% were women, and 51% had heart failure of ischemic etiology. By the end of the study period (median follow-up, 30.1 months), there were no significant reductions in primary and secondary outcomes in the exercise group. 65% of patients in the exercise training group died or were hospitalized compared with 68% in the usual care group (hazard ratio [HR], 0.93 [95% confidence interval {CI}, 0.84–1.02]; $P = 0.13$). 16% of patients in the exercise training group died compared with 17% in usual care (HR, 0.96 [95% CI, 0.79–1.17]). Cardiovascular mortality or cardiovascular hospitalization occurred in 55% of patients in the exercise training group and 58% in the usual care group (HR, 0.92 [95% CI, 0.82–1.03]), and cardiovascular mortality or heart failure hospitalization occurred in 30% of patients receiving exercise and 34% receiving usual care (HR, 0.87 [95% CI, 0.75–1.00]). In safety assessment, hospitalization after exercise was the only outcome that was more frequent in exercise training patients compared with patients in usual care (3.2% vs. 1.9%).

Conclusion. A structured exercise regimen is safe for patients with chronic heart failure and reduced left ventricular ejection fraction. However, it is unclear what effect this particular exercise regimen had on important clinical outcomes. If beneficial effects on mortality and hospitalization exist, they are likely to be modest in magnitude or, alternatively, a different "dose" of exercise may be required.

Commentary

Heart failure is an increasingly common problem, and despite treatment with drugs and medical devices, the risks of early mortality and recurrent hospitalizations among patients with heart failure remain high [1]. Because physical conditioning has been recognized as a potential contributor to poor outcomes among heart failure patients, exercise training has been incorporated into guidelines for heart failure

care [2]. However, these guidelines have been based on meta-analyses of relatively small, single-institution studies of exercise training [3–5], and the safety of exercise training has been unclear, with 1 older study finding significant increases in the risk of sudden death among exercisers who were previously sedentary [6].

The current study by O'Connor et al presents results from the largest multicenter randomized controlled trial of exercise training for patients with chronic heart failure. After approximately 3 months of supervised aerobic exercise followed by home exercise (with the provision of specialized exercise equipment), there were no significant differences between exercise and usual care for the primary endpoint of all-cause mortality or hospitalization. However, there were trends towards lower rates of adverse outcomes, but statistical significance was not achieved for this primary endpoint or for the secondary endpoints. Exercise therapy also appeared to be safe, with very few deaths or hospitalizations immediately following exercise.

After statistical adjustment for highly prognostic baseline characteristics, the HF-ACTION investigators found statistically significant reductions in all-cause mortality or hospitalization (HR, 0.89 [95% CI, 0.81–0.99]) as well as significant reductions in the adjusted risk of secondary endpoints. The effect magnitudes are in the same range observed in trials of angiotensin receptor blockers in heart failure [7,8]. However, it is difficult to know what to make of these supplementary analyses. The strength of a randomized controlled trial lies in its ability to evenly distribute all confounding patient characteristics, measured and unmeasured. Even if by chance more high-risk patients were randomized to the exercise intervention, statistical adjustment can only account for measured risk factors (and may unintentionally introduce new confounding by risk factors that are not measured). In addition, the study's 90% statistical power to detect an 11% reduction in the primary endpoint was not affected by lower-than-expected event rates or subject enrollment. The most likely explanation for the null study results is that the benefits of exercise training for this patient population are smaller than expected.

This study has limitations. First, the degree of crossover was high. Among patients randomized to usual care, over 50% expressed dissatisfaction with their treatment assignment, and during 3-month follow-up measurements, 22% to 28% reported that they exercised on their own. Second, adherence with the exercise training protocol declined as the trial progressed into the home-based exercise phase. Finally, the dose of the exercise intervention may have been limited by inclusion of the home-based component rather than continuation of supervised group exercise. The investigators posited that supervised, group-based exercise could be adopted in practice, even as increasingly expensive and technical treatments for heart failure are readily provided by the U.S. health care system. Any impracticality of continued supervised exercise (efficacious for conditions such as peripheral artery and coronary artery disease) is more likely to result from barriers of payment policy than from laws of natural science [9,10].

Applications for Clinical Practice

This study provides important guidance for the prescription of exercise to patients with chronic heart failure by showing that exercise training is safe and indicating that the effect of exercise training on mortality and hospitalization may be quite small in magnitude. However, the lack of significant outcomes improvement in this trial may be partially attributable to the particular exercise regimen that was studied.

—Review by Mark W. Friedberg, MD, MPP

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