Published in final edited form as:

Am Heart J. 2009 October ; 158(4 Suppl): S72–S77. doi:10.1016/j.ahj.2009.07.014.

Safety of Symptom-Limited Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure due to Severe Left Ventricular Systolic Dysfunction

Steven J. Keteyian, PhD¹, Debra Isaac, MD², Udho Thadani, MD³, Brad A. Roy, PhD⁴, Daniel R. Bensimhon, MD⁵, Robert McKelvie, MD, PhD⁶, Stuart D. Russell, MD⁷, Anne S. Hellkamp, MS⁸, William E. Kraus, MD⁸, and on behalf of the HF-ACTION Investigators

¹ Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI

² Foothills Hospital, Alberta, Canada

³ University of Oklahoma Health Sciences Center, Veterans Administration Medical Center, Oklahoma City, OK

⁴ Kalispell Regional Medical Center, The Summit Medical Fitness Center, Kalispell, MT

⁵ LeBauer Cardiovascular Research Foundation, Durham, NC

⁶ Hamilton Health Sciences, Hamilton, Ontario, Canada

⁷ Division of Cardiology, Johns Hopkins University, Baltimore, MD

⁸ Duke University Medical Center and Duke Clinical Research Institute, Durham, NC

Abstract

Background—To assess the safety of symptom-limited exercise testing in patients with NYHA class II–IV heart failure symptoms due to left ventricular systolic dysfunction, we investigated the frequency of all-cause fatal and non-fatal major cardiovascular (CV) events among subjects enrolled in a prospective clinical trial (HF-ACTION). We hypothesized that exercise testing would be safe, as defined by a rate for all-cause death of < 0.1 per 1,000 tests and a rate of non-fatal CV events < 1.0 per 1,000 tests.

Methods—Prior to enrollment and at three, 12, and 24 months after randomization subjects were scheduled to complete a symptom-limited graded exercise test with open circuit spirometry for analysis of expired gases. To ensure the accurate reporting of exercise test-related events, we report deaths and non-fatal major CV events per 1,000 tests at months three, 12 or 24 after randomization.

Results—2331 subjects were randomized into HF-ACTION. After randomization, 2,037 subjects completed a total of 4,411 exercise tests. There were no test related deaths, exacerbation of heart failure or angina requiring hospitalization, myocardial infarctions, strokes, or transient ischemic attacks. There was one episode each of ventricular fibrillation and sustained ventricular tachycardia. There were no exercise test-related ICD discharges requiring hospitalization. These findings

© 2009 Mosby, Inc. All rights reserved.

Corresponding Author: Steven J. Keteyian, PhD., 6525 Second Avenue, Detroit, MI, 48202; 313–972–1920; fax = 313–972–1921; sketeyi1@hfhs.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

correspond to zero deaths per 1,000 exercise tests and 0.45 non-fatal major CV events per 1,000 exercise tests (95% CI: 0.11,1.81).

Conclusions—In NYHA class II-IV patients with severe left ventricular systolic dysfunction, we observed that symptom-limited exercise testing is safe, based on no deaths and a rate of non-fatal major CV events that is < 0.5 per 1,000 tests.

Introduction

Much literature exists describing the safety of exercise stress testing with ECG monitoring (with or without indirect open-circuit spirometry or cardiac imaging) in both apparently healthy people and those with coronary artery disease. In separate studies, each involving thousands of tests, the reported rate for death during testing ranges between zero and 0.05 per 1,000 tests (1-7). In those same patient groups the combined rates for death and all major cardiovascular (CV) events resulting in hospitalization is between 0.1 and 0.9 events per 1,000 tests.

Conversely, the safety of symptom-limited exercise testing in patients with stable heart failure (HF) due to left ventricular systolic dysfunction is derived from numerous small sample-size trials that were conducted in selected patients to evaluate the pathophysiology of exercise intolerance or response to an exercise training program (8-11). We are unaware of data that specifically reports the safety of such testing in a large multi-center cohort of patients with left ventricular systolic dysfunction.

Patients with impaired left ventricular systolic function have a high incidence of ventricular arrhythmia, which is often the cause of sudden death in this group of patients (12-14). Also, these patients are often sedentary (15) and, when compared to habitually active people, such behavior is known to increase one's risk for a cardiac event during strenuous physical activity (16). Given that symptom-limited peak exercise testing is routinely performed in patients with left ventricular systolic dysfunction to determine the need for cardiac transplantation (17-19), it is prudent to better understand the safety of conducting such testing in these patients. To accomplish this, we investigated the frequency of both all-cause fatal and non-fatal major CV events that resulted from symptom-limited exercise testing in patients that were enrolled in the prospective Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial. Our primary hypothesis in the present study was that exercise testing would be safe, as defined by a rate for all-cause deaths of < 0.1 per 1,000 tests. We also hypothesized that the frequency of all non-fatal major CV events requiring hospitalization would be less than 1.0 per 1,000 tests.

Methods

Study Sample

The design of HF-ACTION has been previously described (20). Briefly, between April 2003 and February 2007, subjects were enrolled from 82 participating clinical sites within the United States, Canada, and France. The minimum planned follow-up period was one year. Inclusion criteria included New York Heart Association (NYHA) Class II, III or IV heart failure (HF) and a left ventricular ejection fraction $\leq 35\%$. Clinical site personnel were also strongly encouraged to enroll subjects currently on stable optimal guideline-based pharmacologic therapy for at least six weeks prior to randomization. Patients were excluded if they were experiencing a co-morbid disease or behavioral condition that might interfere with exercise training; were regularly exercising more than one time per week at a moderate-to-vigorous level over the prior 6 weeks; underwent a CV procedure or experienced a major CV event within the prior 6 weeks; or were scheduled to undergo a CV procedure (e.g., implantable cardioverter defibrillator, ICD) in the future. After providing informed consent to participate

in HF-ACTION (approved by the institutional review board at each participating center), subjects underwent baseline exercise testing with open circuit spirometry for analysis of expired gases. Subjects that met or completed all qualifications were randomized to usual care or usual care plus regular exercise training. At trial entry, usual care included the one-time receipt of a self-management education manual that included recommendations from the American College of Cardiology and American Heart Association (17). Subjects randomized to the intervention arm received usual care plus 36 supervised exercise training sessions, followed by the recommendation to regularly exercise at home at the prescribed level of 30 to 40 minutes, five days per week at an intensity equivalent to 60% to 70% of heart rate reserve.

Exercise Testing

Prior to randomization and at 3, 12 and 24 months after randomization into the trial subjects were scheduled to complete a sign- and symptom-limited graded exercise test, performed in accordance with American College of Sports Medicine (21) guidelines. To assess for and minimize any re-test related familiarization effect, the first five subjects to undergo exercise testing at each participating site performed two such tests within one week at baseline (22).

Details of the exercise testing have been previously reported (20,22). Briefly, all tests at all time points were terminated due to symptoms (i.e., fatigue, dyspnea, angina, other), adverse changes in blood pressure, orthopedic/musculoskeletal complaints, or electrocardiographic evidence of ischemia or arrhythmia. All tests were directly supervised by a physician or an allied health professional (e.g., clinical exercise physiologist or nurse) with medical supervision available nearby. Subjects were asked to take their medications as usual on the day of testing, with a specific request that they take their beta-adrenergic blocking agent between three and 10 hours before the test.

The primary mode of testing was a treadmill; however, a stationary cycle ergometer was used for subjects unable to walk on the treadmill or at those testing sites that routinely used this modality for exercise testing. In 97% of subjects the same testing mode was used throughout the trial. Ninety-seven percent of exercise tests also included simultaneous analysis of expired air for determination of peak exercise capacity (peak oxygen consumption, VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and other pertinent cardiorespiratory parameters. Site testing personnel were instructed to exercise patients to a Borg rating of exertion (RPE) level that was >16 (scale 6 to 20) and/or an RER of >1.1 . However, exercise testing staff were asked to not use achievement of either of these criteria as a reason to stop a test.

Clinical Outcomes

Any occurrence of death or first non-fatal CV event requiring hospitalization was adjudicated by a clinical endpoint committee. Once a patient had an adjudicated heart failure hospitalization, no further hospitalizations for that patient were reviewed by the clinical endpoint committee. Non-fatal CV events requiring hospitalization were worsening HF, myocardial infarction, unstable angina, serious arrhythmia (i.e., supraventricular or ventricular tachycardia lasting more than 30 seconds), stroke, transient ischemic attack, or ICD discharge. To be considered as either a fatal or non-fatal event related to the exercise test, the event must have occurred on the same day or the next calendar day after the test.

Statistical Analysis

To describe and characterize our subjects, they were divided into two groups based on the reason for stopping their exercise test at baseline (musculoskeletal complaints vs. all other reasons, the latter labeled as sign- or symptom-limited maximum). For the 438 subjects that completed two tests at baseline to assist in the determination of any re-test related

familiarization effect, the reason for stopping their first test was used. Baseline demographics, clinical history, and exercise test parameters were compared between these groups using likelihood ratio chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Two-year CV-related hospitalization rates were calculated using Kaplan-Meier methods.

A patient was classified as non-compliant for follow-up exercise testing if they were alive and in the study (i.e., had not withdrawn consent, been lost to follow-up, nor completed the study) at the time of a scheduled test, but failed to complete at least one test. Candidate predictors for non-compliance were the same as those listed in Table 1. All candidate predictors were entered into a multivariable logistic regression model, and backwards selection used to determine the set of independent predictors.

Exercise testing at baseline was conducted for study screening purposes and occurred prior to subject enrollment. Among those subjects that did not qualify for the study due to exercise testing results, data identifying the reason for trial exclusion and complete demographic information were not systematically recorded. Therefore, to ensure the more the accurate reporting of exercise test-related events, the rates we report here-in do not reflect any events (known or unknown) associated with baseline tests. Instead, we only describe those events that occurred after enrollment and during a follow-up exercise test conducted at months three, 12 or 24. Safety data are reported as (a) deaths per 1,000 tests and (b) non-fatal major CV events per 1,000 tests, both with a 95% confidence interval given for any non-zero event rate. To account for the multiple tests per patient, generalized estimating equations were used in the calculation of confidence intervals.

Results

Main Study Outcomes and Patient Characteristics

2331 subjects were randomized into the HF-ACTION study. The median follow-up period in HF-ACTION was 2.5 yr. Overall there were 387 (17%) total deaths, with 274 of these due to CV disease. 1,489 subjects (64%) experienced at least one hospitalization, of which 1,222 (52%) were related to CV disease. The two-year event rate for a CV-related hospitalization among all subjects enrolled in HF-ACTION was 44%. In the 1,285 subjects with an ICD implanted before or during the trial, 293 subjects experienced at least one ICD firing and there were 688 ICD firings in total.

Table 1 summarizes the demographic/clinical characteristics and exercise response parameters at baseline for the 2329 subjects who underwent a pre-enrollment symptom-limited exercise test and then subsequently enrolled into HF-ACTION; two subjects were enrolled into the trial but did not perform a graded exercise test beforehand. Eighty-eight percent of these baseline exercise tests were discontinued due to sign- or symptom-limited criteria (median peak RER: 1.09), with the balance of these tests stopped due to musculoskeletal reasons (median peak RER: 1.08). Subjects who stopped exercising due to musculoskeletal reasons tended to be older, white, and less physically fit; achieved a lower heart rate at peak exercise; and had a clinical history of diabetes, ischemic HF, atrial fibrillation/flutter, or a pacemaker implant. Ninety-one percent of subjects used the treadmill (versus stationary cycle ergometer) for testing.

After randomization, 2,037 of the 2331 subjects that were enrolled in the main trial completed one or more of the three follow-up tests, yielding a total of 4,411 exercise tests for analysis. Among this cohort of 2037 subjects, the two-year event rate for a CV-related hospitalization was 43%. Forty-two percent of subjects in our cohort completed all three of their scheduled follow-up exercise tests and 33% and 25% completed two and one of their scheduled follow-

up exercise tests, respectively. There were 1,048 subjects who were alive at the time of a scheduled test but failed to complete at least one test. Using the same baseline demographic/clinical characteristics and exercise test parameters shown in Table 1, the variables that were significantly and independently associated with an increased risk for non-compliance to completing a follow-up exercise test are shown in Table 2. In general, subjects < 55 years of age; with a history of diabetes or NYHA class III/IV symptoms; with a higher ejection fraction or lower fitness level (as measured by peak VO_2); and with the inability to sufficiently increase RER during the baseline exercise test were more likely not to comply with one or more of their scheduled follow-up exercise tests.

Safety of Exercise Testing

During the 4,411 total exercise tests completed at months three, 12, or 24 and during the recovery period following each of these tests, there were no deaths; no exacerbation of HF or angina requiring hospitalization; and no myocardial infarctions, sustained ventricular tachycardia, strokes or transient ischemic attacks. There was one episode of ventricular fibrillation that occurred later on during the day after testing and this was successfully treated. There was one bout of sustained ventricular tachycardia, also successfully treated, that occurred while the subject was hospitalized for a non-cardiac reason during the calendar day that immediately followed the day of the exercise test. There were no exercise test-related ICD discharges requiring hospitalization. In sum, the above corresponds to zero deaths per 1,000 exercise tests and 0.45 non-fatal, major CV events per 1,000 exercise tests (95% CI: 0.11, 1.81).

The two subjects that experienced a major CV event associated with exercise testing were both white men under 70 years of age and had a history of non-ischemic cardiomyopathy and prior ICD implant. Of the 4,411 follow-up exercise tests, 27 (6.1 per 1,000 tests) were stopped due to non-sustained (e.g., 3, 4, or 5 beat) supraventricular or ventricular tachycardia. Thirteen percent ($n = 575$) of all follow-up exercise tests were stopped due to orthopedic/musculoskeletal complaints.

Discussion

In this sample of 2,037 patients with left ventricular systolic dysfunction that completed 4,411 symptom-limited exercise tests during a nearly five year clinical trial, there were no deaths and only two non-fatal, major CV events (0.45 events/1,000 tests). There were no test-related ICD discharges requiring hospitalization and no evidence that severity of disease (i.e., per NYHA functional class) was related to frequency of test-related events. Based on these findings we accept our hypotheses that symptom-limited maximal exercise testing can be safely conducted in patients with systolic HF who are being treated in accordance with evidence-based guidelines.

Our event rates for death and major non-fatal CV events in stable patients with left ventricular systolic dysfunction are consistent with previously published exercise test-related event rates for both death (0 to 0.05 per 1,000 tests) and other major CV events (0.1 to 0.9 per 1,000 tests) in patients with coronary artery disease and no HF or left ventricular dysfunction (1,2,4-7). The extremely low event rates associated with exercise testing in this study might be considered surprising, when one considers that the primary mechanism of death in patients with left ventricular systolic dysfunction is malignant arrhythmia (12-14). We speculate that the favorable event rates in our study might reflect, in part, the fact that well over 90% of our subjects were taking evidenced-based medical therapy (e.g., ACE-inhibitors, beta-adrenergic blocking agents), better than what is currently observed in the general cardiology ambulatory care setting (23,24).

An important strength of our data lies in the fact that it was derived from more than 4,400 exercise tests, yielding a sample that was sufficiently large, demographically diverse (e.g., 40% minority, 28% women), and clinically impaired (e.g., median ejection fraction of 25%; median peak VO_2 $14.4 \text{ mL kg}^{-1}\text{min}^{-1}$) at baseline to generalize our findings to many other patients with HF due to left ventricular systolic dysfunction that are referred to exercise testing laboratories for the determination of prognosis or exercise capacity. There are; however, limitations associated with this study. First, although there were 688 total ICD discharges that required hospitalization during this trial, none of which occurred on the same day or next day after exercise testing, it is possible that an ICD firing did occur on the same day or the day after an exercise test but the patient was not hospitalized (i.e., device interrogated in ambulatory care setting) or the patient did not report the event to their study coordinator. As a result, our event rate for non-fatal major CV events could be higher than 0.45 per 1000 tests. Additionally, in a few patients with an ICD that was set to discharge at a ventricular rate that might be achieved during exercise testing, the ICD was turned off, the ventricular discharge rate was increased prior to the test or the test was stopped at a heart rate of five to ten beats below the first treatment zone on the ICD.

Second, our cohort of subjects may represent a “slightly healthier” sample of ambulatory patients with left ventricular systolic dysfunction, as compared to patients usually seen in a general cardiology or HF clinic. Possible reasons for this include (a) like other patients routinely referred to an exercise testing laboratory, our exercise tests were conducted on patients that the consenting physician felt were well enough to undergo such testing and (b) despite rigorous behavioral and/or modest monetary incentive strategies aimed at facilitating compliance with exercise testing at months three, 12 and 24, the observed decrease in compliance with exercise testing over time may preferentially reflect those subjects that were alive but did not feel well enough to undergo testing. Additionally, although we have no evidence of such, there may have been subjects that were not enrolled into HF-ACTION because they died or experienced a major CV event or other complication (e.g., hypotensive response, atrial fibrillation) in conjunction with the exercise test they completed during the screening process to determine study eligibility. Evidence that our study cohort ($n = 2037$) was not differentially more healthy than all patients enrolled into HF-ACTION ($n = 2331$) is evident in the fact that the 43% two-year CV-related hospitalization rate among our cohort is essentially the same as the 44% two-year CV-related hospitalization rate experienced by all subjects enrolled into HF-ACTION. Also, in routine clinical practice it is common that patients who feel they are too sick to undergo exercise testing for clinical reasons often cancel their scheduled appointment, thus making any impact that illness had on test compliance in our study similar to what occurs in contemporary non-invasive laboratories.

In conclusion, in NYHA class II-IV patients with severe left ventricular systolic dysfunction who were treated with guideline-based therapy are able to undergo symptom-limited exercise testing, we observed that such testing is safe. This is demonstrated by the absence of any test-related deaths and a rate of non-fatal, major CV events that is < 0.5 per 1,000 tests.

Acknowledgments

Funding Source: National Institutes of Health; National Heart, Lung, and Blood Institute

References

1. American Thoracic Society and American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med* 2003;165:211–277.

2. Gibbons RJ, Balady GJ, Bricker JT, et al. American College of Cardiology/American Heart Association 2002 update for exercise testing: summary article. *Circulation* 2002;106:1883–1892. [PubMed: 12356646]
3. Gordon NF, Kohl KH. Exercise testing and sudden cardiac death. *J Cardiopulm Rehabil* 1993;13:381–386.
4. Hamm LF, Crow RS, Stull GA, et al. Safety and characteristics of exercise testing early after acute myocardial infarction. *Am J Cardiol* 1989;63:1193–1197. [PubMed: 2711988]
5. Knight JA, Laubach CA Jr, Butcher RJ. Supervision of clinical exercise testing by an exercise physiologist. *Am J Cardiol* 1995;75:390–391. [PubMed: 7856534]
6. Myers J, Voodi L, Umann T, Froelicher V. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. *J Cardiopulm Rehabil* 2000;20:251–258. [PubMed: 10955267]
7. Stuart RJ Jr, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;77:94–97. [PubMed: 7351157]
8. McKelvie RS. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. *Heart Failure Rev* 2008;13:3–11.
9. Mezzani A, Corra U, Giannuzzi P. Central adaptations to exercise training in patients with chronic heart failure. *Heart Fail Rev* 2008;13:13–20. [PubMed: 17932747]
10. Braith RW, Beck DT. Resistance exercise: training adaptations and developing a safe exercise prescription. *Heart Fail Rev* 2008;13:69–79. [PubMed: 17932746]
11. Weber KT, Kinasweitz GT, Janicki JS, et al. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982;65:1213–23. [PubMed: 6804111]
12. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverterdefibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37. [PubMed: 15659722]
13. Kadish A, Dryer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151–2058. [PubMed: 15152060]
14. Moss AJ, Zareba W, Hall J, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–883. [PubMed: 11907286]
15. Crespo CJ, Keteyian SJ, Snelling A, et al. Prevalence of non leisure-time physical activity in persons with chronic disease. *Clinical Exercise Physiology* 1999;1:68–73.
16. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of myocardial infarction onset study investigators. *N Engl J Med* 1993;329:1677–83. [PubMed: 8232456]
17. Jessup M, Abraham WT, Casey DE, et al. Writing on behalf of the 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult Writing Committee. 2009 Focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009;119:1977–2016. [PubMed: 19324967]
18. Heart Failure Society of America. Surgical approaches to the treatment of heart failure. *J Cardiac Failure* 2006;12:e76–e79.
19. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant* 2006;25:1024–42. [PubMed: 16962464]
20. Whellan DJ, O'Connor CM, Lee KL, et al. Heart failure and a controlled trial investigating outcomes of exercise training (hf-action): design and rationale. *Am Heart J* 2007;153:201–211. [PubMed: 17239677]
21. American College of Sports Medicine: Guidelines for Exercise Testing and Prescription. Vol. 7th Ed.. Lippincott Williams & Wilkins; Philadelphia: 2000. GETP7
22. Bensimhon DR, Leifer ES, Ellis SJ, Fleg JL, Keteyian SJ, Pina IL, Kitzman DW, McKelvie RS, Kraus WE, Forman DE, Kao AJ, Whellan DJ, O'Connor CM, Russell SD. HF-ACTION Trial Investigators. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training). *Am J Cardiol* Sept 15;2008 102:712–7. [PubMed: 18773994]

23. Cox JL, Ramer SA, Lee DS, et al. Canadian Cardiovascular Outcomes Research Team Investigators. Pharmacological treatment of congestive heart failure in Canada: a description of care in five provinces. *Canadian J Cardiol* 2005;21:337–43.
24. Philbin EF, Jenkins PL. Differences between patients with heart failure treated by cardiologists, internists, family physicians, and other physicians: analysis of a large, statewide database. *Am Heart J* 2000;139:491–496. [PubMed: 10689264]

Table 1

Demographic and clinical characteristics and exercise test responses gathered prior to randomization among subjects enrolled into the study.

Baseline characteristic	All patients (N=2329)	Reason for stopping first test [*]	
		Sign- or Symptom-Limited Maximum (N=2050)	Stopped Due to Musculoskeletal Complaints (N=279)
Age (yr)	59 (51, 68)	59 (51, 68)	64 (55, 71) ^{**}
Race (%)			
Black or African American	33	34	23 ^{**}
White	62	61	72
Other	5	5	5
Female (%)	28	29	24
Ejection fraction (%)	25 (20,30)	25 (20,30)	26 (20,31)
NYHA Class II/III/IV (%)	63/36/1	64/35/1	60/39/1
Ischemic HF (%)	51	50	63 ^{**}
Atrial fibrillation or atrial flutter (%)	21	20	28 ^{**}
Diabetes mellitus (%)	32	31	39 [*]
Beck Depression Inventory II	8.0 (4.0,15.0)	8.0 (4.5, 15.0)	8.0 (4.0, 14.0)
ACEi or ARB (%)	94	95	92
Beta-adrenergic blocking Agent (%)	95	94	95
ICD (%)	40	40	39
Pacemaker (%)	18	17	25 ^{**}
Bi-ventricular pacemaker (%)	18	17	23 [*]
HR at peak exercise (min ⁻¹)	120 (104, 134)	120 (105, 135)	115 (97, 129) ^{**}
Peak VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	14.4 (11.5, 17.7)	14.5 (11.6, 17.8)	13.7 (10.6, 16.6) ^{**}
Respiratory exchange ratio	1.09 (1.02, 1.16)	1.09 (1.02, 1.16)	1.08 (1.01, 1.15)

Continuous variables are shown as median (25th, 75th percentile)

HF = heart failure; NYHA = New York Heart Association; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HR = heart rate; ICD = implantable cardioverter defibrillator; VO₂ = volume of oxygen consumed per minute

^{*}
p < 0.05

^{**}
p < 0.01

Table 2

Demographic and clinical characteristics at baseline that are independently associated with increased risk for non-compliance to one or more of the follow-up exercise tests

Baseline Characteristic	Category	Odds Ratio (95% CI)	P-value for Association with Non-compliance
NYHA class	III/IV vs II	1.36 (1.13,1.64)	0.0012
Diabetes	Yes vs No	1.29 (1.07,1.56)	0.0069
Age	Per every 5 yr decrease below 55	1.17 (1.10,1.26)	<0.0001
Respiratory exchange ratio	Per 0.1 unit decrease	1.13 (1.05,1.23)	0.0017
Ejection fraction	Per every 5% increase	1.07 (1.01,1.14)	0.019
Peak VO_2 ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	Per every 1 mL decrease	1.06 (1.04,1.08)	<0.0001

NYHA = New York Heart Association; VO_2 = volume of oxygen consumed per minute