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ORIGINAL INVESTIGATIONS

Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation

The CARDIO-FIT Study

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ABSTRACT

BACKGROUND Obesity begets atrial fibrillation (AF). Although cardiorespiratory fitness is protective against incident AF in obese individuals, its effect on AF recurrence or the benefit of cardiorespiratory fitness gain is unknown.

OBJECTIVES This study sought to evaluate the role of cardiorespiratory fitness and the incremental benefit of cardiorespiratory fitness improvement on rhythm control in obese individuals with AF.

METHODS Of 1,415 consecutive patients with AF, 825 had a body mass index ≥27 kg/m^2 and were offered risk factor management and participation in a tailored exercise program. After exclusions, 308 patients were included in the analysis. Patients underwent exercise stress testing to determine peak metabolic equivalents (METs). To determine a dose response, cardiorespiratory fitness was categorized as: low (<85%), adequate (86% to 100%), and high (>100%). Impact of cardiorespiratory fitness gain was ascertained by the objective gain in fitness at final follow-up (≥2 METs vs. <2 METs). AF rhythm control was determined using 7-day Holter monitoring and AF severity scale questionnaire.

RESULTS There were no differences in baseline characteristics or follow-up duration between the groups defined by cardiorespiratory fitness. Arrhythmia-free survival with and without rhythm control strategies was greatest in patients with high cardiorespiratory fitness compared to adequate or low cardiorespiratory fitness ($p < 0.001$ for both). AF burden and symptom severity decreased significantly in the group with cardiorespiratory fitness gain ≥2 METs as compared to <2 METs group ($p < 0.001$ for all). Arrhythmia-free survival with and without rhythm control strategies was greatest in those with METs gain ≥2 compared to those with METs gain <2 in cardiorespiratory fitness ($p < 0.001$ for both).

CONCLUSIONS Cardiorespiratory fitness predicts arrhythmia recurrence in obese individuals with symptomatic AF. Improvement in cardiorespiratory fitness augments the beneficial effects of weight loss. (Evaluating the Impact of a Weight Loss on the Burden of Atrial Fibrillation [AF] in Obese Patients; ACTRN12614001123639) (J Am Coll Cardiol 2015;66:985–96) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFSS = Atrial Fibrillation Severity Scale

BMI = body mass index

BP = blood pressure

HR = hazard ratio

METs = metabolic equivalents

Atrial fibrillation (AF) is a growing epidemic affecting approximately 33.5 million individuals worldwide (1,2). Cardiac risk factors such as obesity are associated with increased risk of AF and could explain this rising epidemic (3). Several lifestyle factors, including a lack of physical activity, are associated with increased incidence of obesity (4).

Lifestyle modification with weight loss has been shown to reduce AF burden (5). In the Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY), progressive weight loss had a dose-dependent effect on long-term AF freedom (6). Increasing physical activity to enhance cardiorespiratory fitness is an integral component of lifestyle modification. Cardiorespiratory fitness is an independent predictor of cardiovascular outcome and mortality (7). Recent studies have found an inverse relationship between increased physical activity and the risk of incident AF (8,9), but the impact of cardiorespiratory fitness on risk of AF recurrence has not been examined previously. Furthermore, longitudinal improvement in cardiorespiratory fitness is associated with a lower risk of both all-cause and cardiovascular mortality (10). However, the impact of cardiorespiratory fitness gain with a graded exercise program along with weight loss on AF outcome remains unclear and is largely neglected as a therapeutic target.

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We hypothesize that preserved cardiorespiratory fitness at baseline in obese AF patients offsets some of the detrimental effects of obesity and that gain in cardiorespiratory fitness through a structured exercise program has synergistic effect with weight loss on overall freedom from AF.

METHODS

STUDY POPULATION. This study comprised patients referred for management of symptomatic paroxysmal or persistent AF to the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. All patients with a body mass index (BMI) ≥27 kg/m^2 and undergoing an exercise stress test at baseline were included in this analysis. Exclusion criteria were: permanent AF; history of myocardial infarction or cardiac surgery in the previous 12 months; active malignancy; autoimmune or systemic inflammatory diseases; severe renal or hepatic failure; left ventricular ejection fraction <40%; pacemaker in situ; and <24-months of follow-up. In addition, patients who were in AF or could not perform exercise stress test because of neuromuscular or musculoskeletal problems were excluded.

All patients provided written informed consent. The Human Research Ethics Committee of the Royal Adelaide Hospital and University of Adelaide approved the study protocol.

STUDY PROTOCOL AND DESIGN

WEIGHT AND RISK FACTOR MANAGEMENT. All patients were offered attendance at a dedicated physician-led risk factor management clinic at the time of initial assessment. The weight and risk factor management protocol used in our service has been presented previously (6). In brief, a structured motivational, individualized, goal-directed program using face-to-face counseling was used for initiating and reinforcing graded exercise therapy along with weight reduction. Initial weight loss was attempted by a meal plan and behavior modification. Meals consisted of high protein and low glycemic index, calorie-controlled foods. Hypertension, glucose intolerance, dyslipidemia, sleep apnea, and alcohol and tobacco use were screened for and managed

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individually according to American Heart Association/American College of Cardiology guidelines. Changes in metabolic (lipid profile and fasting insulin) and inflammatory state (high-sensitivity C-reactive protein [hsCRP]) levels were monitored.

EXERCISE PROGRAM. Patients were recommended structured physical activity according to American Heart Association guidelines (11). A baseline exercise stress test was used to ascertain cardiorespiratory fitness. Subsequently, a tailored exercise program was designed in which consideration for age and physical ability was made so that targets were achievable without risking injuries. The frequency, intensity, time [duration], and type of exercise principle was used to design a combination of aerobic and resistance/strength exercises for progressive fitness gain to avoid weight plateaus. Low-intensity exercise was prescribed initially for 20 min 3 times weekly increasing to at least 200 min of moderate-intensity exercise per week. For patients with decreased mobility because of weight and or musculoskeletal problems, hydrotherapy, aqua aerobics, upper body training, and physiotherapy sessions were initially used. Participants were advised to use a wearable heart rate monitor and were required to maintain a diet and physical activity diary to log exercise type, frequency, intensity, and duration. After calculating their maximal heart rate (220 − age), patients were advised to avoid reaching heart rate >85% of the maximal predicted heart rate.

ASSESSMENT OF CARDIORESPIRATORY FITNESS. Cardiorespiratory fitness was evaluated in sex-specific metabolic equivalents (METs) estimated from a symptom-limited maximal treadmill exercise test using the standard Bruce protocol at baseline and final follow-up. The test time using this protocol on the treadmill was recorded. If patients achieved only a fraction of the stage of exercise, credit for exercise capacity was "pro-rated." Test time was then used to calculate METs (12). Age- and sex-predicted peak METs were calculated using the St. James model (METs = 14.7 − [0.13 × age]) for women and the Veterans Affairs referral model (METs = 18 − [0.15 × age]) for men (13).

DEFINITIONS. Baseline cardiorespiratory fitness. Study patients were subsequently categorized according to baseline cardiorespiratory fitness into low (<85% predicted METs), adequate (86% to 100% predicted METs), and high (>100% predicted METs) cardiorespiratory fitness groups (13).

Cardiorespiratory fitness gain. To investigate the change in cardiorespiratory fitness on AF outcome, we dichotomized fitness gain into a METs gain ≥2 and a METs gain <2 at final follow-up.

Weight loss and cardiorespiratory fitness gain interaction. We have previously demonstrated effect of weight loss on AF outcome (6). As was presented, no weight loss was defined as <3% weight loss and significant weight loss as ≥10% weight loss. To investigate the interaction between weight loss and METs gain, we divided patients into group 1 (<10% weight loss and <2 METs gain), group 2 (<10% weight loss and ≥2 METs gain), group 3 (≥10% weight loss and <2 METs gain), and group 4 (≥10% weight loss and ≥2 METs gain).

ARRHYTHMIA MANAGEMENT. AF management was undertaken in a separate arrhythmia clinic. The use of rate and rhythm control strategies was at the discretion of the treating physician. In patients who remained symptomatic despite the use of antiarrhythmic agents, AF ablation was offered. The ablation technique used at our institution has been previously described and is outlined in the Online Appendix (14). AF was determined at least annually by clinical review, 12-lead electrocardiogram, and 7-day Holter monitoring. In patients undergoing ablation, procedural success was determined after a 3-month blanking period. AF was taken as any atrial arrhythmia ≥30 s. If patients developed recurrent arrhythmia after the blanking period (3 months), repeat ablation was offered. The earliest date with documented AF was set as the date of arrhythmia recurrence. Only confirmed events were included in the analyses. All patients were anticoagulated if the $CHADS_2$ (measuring congestive heart failure, hypertension, age, diabetes mellitus [DM], and prior stroke) score >1.

Cardiac structural parameters were monitored by serial echocardiographic examinations. All echocardiographic and rhythm evaluations are detailed in the Online Appendix and were performed by operators blinded to the patient's weight and fitness management regimen.

OUTCOMES. The primary outcome was AF burden as determined by symptom burden and freedom from AF. AF symptom burden was determined by the AF Severity Scale (AFSS, University of Toronto, Canada) that quantitates 3 domains of AF-related symptoms: frequency, duration, and severity (15). The AFSS has been clinically validated and used for assessment of AF burden (5,16). In addition, it provides a symptom subscale and global well-being score. The AFSS questionnaire was administered at baseline and final follow-up. Freedom from AF was ascertained with 7-day Holter monitoring. Secondary outcomes included structural parameters of left atrial volume, left

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ventricular wall thickness, and diastolic function from echocardiographic studies.

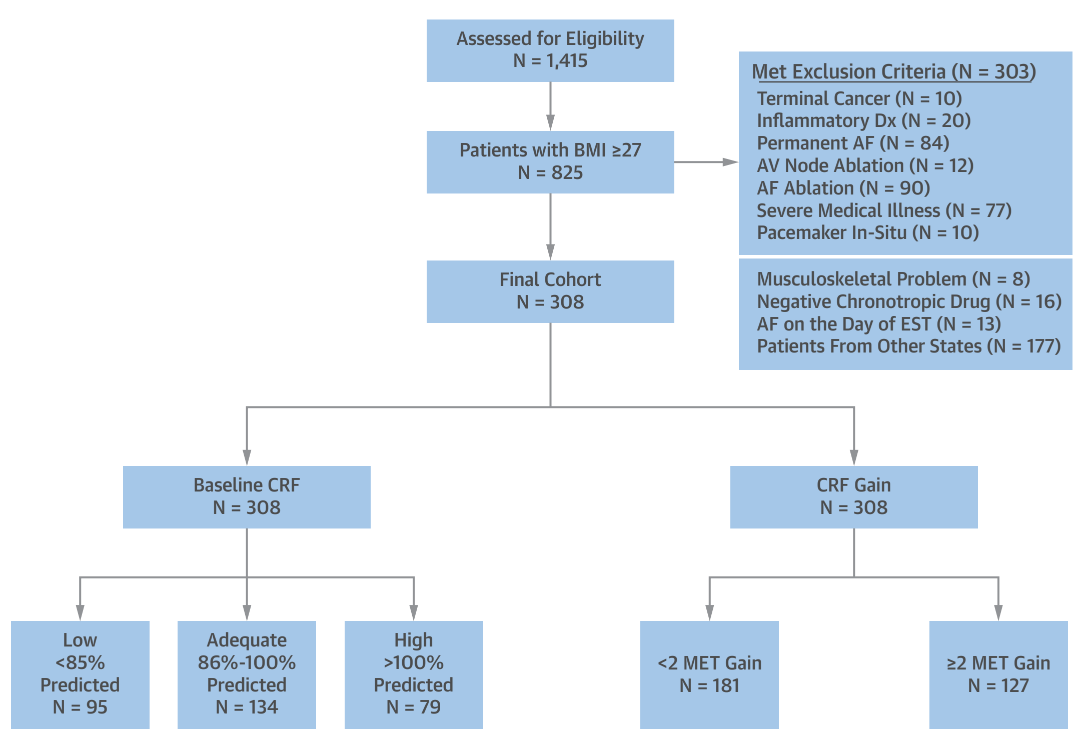
STATISTICAL ANALYSIS. Categorical variables are represented by frequencies and percentages. Continuous variables are summarized by mean ± SD. The differences in baseline characteristics between groups were assessed using analysis of variance procedures for continuous variables and chi-square for categorical variables. A repeated measure analysis of variance was used to assess change over time. For categorical variables, change in status at follow-up was compared between groups using a chi-square test. Time-to-recurrence and event-free survival curves after the last ablation procedure were estimated by the Kaplan-Meier product-limit method. Differences between curves were tested with the log-rank test. Predictors of recurrent AF were assessed using proportional hazards Cox regression models. Candidate variables with $p < 0.1$ in univariate analyses were considered in multivariate regression models. Two-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS, version 21.0 (SPSS, Inc., Chicago, IL).

RESULTS

Of 1,415 patients with symptomatic AF, 825 had a BMI ≥27 kg/m^2. Only patients who did not meet exclusion criteria, had regular follow-up, and underwent stress testing were included in the analysis. Patients were excluded for: predefined criteria (n = 303); interstate patients (n = 177); premature termination of test because of a musculoskeletal problem (n = 8); beta-blocker or calcium channel blocker use on the day of procedure (n = 16); or those with AF on the exercise stress test (n = 13) (Figure 1). The final cohort included 308 patients with a mean follow-up of 49 ± 19 months.

BASELINE CARDIORESPIRATORY FITNESS. The characteristics of each group are shown in Table 1. Ninety-five patients had low, 134 had adequate, and 79 had high cardiorespiratory fitness at baseline. Mean METs achieved in the low cardiorespiratory fitness group were 5.2 ± 1.6, in the adequate cardiorespiratory fitness group 7.9 ± 1.6, and in the high cardiorespiratory fitness group 8.8 ± 1.7 (p = 0.008). Mean duration of follow-up was 47 ± 18.3, 48 ± 17, and 48.2 ± 18 months, respectively (p = 0.8).

FIGURE 1 **Patient Selection**



Flow diagram demonstrating patient recruitment and attrition. AF = atrial fibrillation; AV = atrioventricular; BMI = body mass index; CRF = cardiorespiratory fitness; Dx = disease; EST = exercise stress test; MET = metabolic equivalent.

EFFECT OF BASELINE CARDIORESPIRATORY FITNESS ON AF OUTCOMES. Freedom from AF without the use of rhythm control strategies. Figure 2A demonstrates "ablation- and drug-free" AF freedom. At final follow-up, 12% of the low, 35% of the adequate, and 66% of the high cardiorespiratory fitness group ($p < 0.001$) remained free from arrhythmia without antiarrhythmic drugs or ablation. Univariate predictors of AF recurrence were as follows: cardiorespiratory fitness group ($p < 0.001$), no weight loss group ($p = 0.001$), and left ventricular hypertrophy group ($p = 0.05$). On multivariable analysis, the cardiorespiratory fitness group (compared with the high cardiorespiratory fitness and low cardiorespiratory fitness groups: HR: 2.75; 95% CI: 1.61 to 4.68; adequate cardiorespiratory fitness: HR: 1.89; 95% CI: 1.14 to 3.12; $p = 0.001$), no weight loss (HR: 2.95; 95% CI: 1.8 to 4.8) remained an independent predictor of AF recurrence. Each unit increase in METs of baseline cardiorespiratory fitness was associated with a 13% decline in the risk of AF recurrence (HR: 0.87; 95% CI: 0.80 to 0.94; $p < 0.001$), even after adjusting for weight loss during follow-up.

Total arrhythmia-free survival. Figure 2B demonstrates the total arrhythmia-free survival with significant attrition in the low cardiorespiratory fitness group compared with the adequate and high cardiorespiratory fitness groups. At final follow-up, total arrhythmia-free survival rates was 17% in the low, 76% in the adequate, and 84% in the high cardiorespiratory fitness groups ($p < 0.001$). Univariate predictors of AF recurrence were: cardiorespiratory fitness group ($p < 0.001$), no weight loss ($p < 0.001$), DM ($p = 0.01$), and smoking status ($p = 0.04$). On multivariable analysis, the low cardiorespiratory fitness but not the adequate cardiorespiratory fitness (compared with the high cardiorespiratory fitness and low cardiorespiratory fitness groups: HR: 5.94; 95% CI: 3.15 to 11.23; $p < 0.001$; adequate cardiorespiratory fitness group: HR: 1.17; 95% CI: 0.60 to 2.26; $p < 0.65$) and no weight loss group (HR: 3.64; 95% CI: 1.95 to 6.76) remained an independent predictor of AF recurrence. For cardiorespiratory fitness expressed as a continuous variable, even after adjusting for weight loss during follow-up, there was a 20% reduction in total arrhythmia recurrence for each additional MET achieved during baseline cardiorespiratory fitness assessment (HR: 0.80; 95% CI: 0.74 to 0.87; $p < 0.001$).

CARDIORESPIRATORY FITNESS GAIN. Cardiorespiratory fitness gain was 2.9 ± 0.9 versus 0.5 ± 1.4 METs in the $\geq$2 METs and <2 METs gain groups, respectively ($p < 0.001$). This corresponded with higher participation in the dedicated risk factor management clinic (83% in the $\geq$2 METs gain vs. 39% in the <2 METs gain group; $p < 0.001$). The characteristics of both groups are shown in Table 2.

TABLE 1 Baseline Characteristics for Baseline Cardiorespiratory Fitness Groups

	Low CRF (<85%) (n = 95)	Adequate CRF (86% to 100%) (n = 134)	High CRF (>100%) (n = 79)	p Value
Age, yrs	58 ± 13	56 ± 10	69 ± 9	0.10
Male	46 (49)	64 (48)	40 (51)	0.20
Follow-up duration, months	47 ± 18.3	48 ± 17.0	48.2 ± 18.0	0.80
Anthropometric measures				
BMI, kg/m^{-2}	34.0 ± 4.8	32.7 ± 4.5	32.8 ± 5.1	0.08
SBP, mm Hg	145 ± 16	144 ± 18	149 ± 18	0.10
Atrial fibrillation				
Paroxysmal AF	46 (48)	69 (52)	49 (62)	0.18
Nonparoxysmal	49 (52)	65 (48)	30 (38)	
Metabolic risk factors				
Hypertension	73 (77)	98 (73)	61 (78)	0.67
DM	32 (34)	34 (25)	18 (23)	0.28
IGT	5 (5)	13 (10)	10 (13)	
Hyperlipidemia	38 (41)	51 (38)	31 (40)	0.40
Coronary artery disease	17 (18)	12 (9)	10 (13)	0.14
Valvulopathy	5 (5)	5 (4)	5 (6)	0.68
AHI >30	47 (49)	76 (57)	40 (51)	0.50
Alcohol excess (>30 g/week)	27 (28)	48 (36)	21 (27)	0.29
Smoker	8 (8)	47 (35)	20 (25)	0.06
Medication use				
Mean number of AAD	1.0 ± 0.7	0.9 ± 0.7	0.9 ± 0.7	0.34
Mean number of anti-HTN	0.9 ± 1.1	0.7 ± 0.7	0.8 ± 0.9	0.19
Serology and lipid profile				
hsCRP, mg/L	4.4 ± 6.0	4.9 ± 11.9	4.8 ± 7.6	0.95
Fasting insulin level, U	14.9 ± 6.6	16.4 ± 6.9	16.0 ± 6.0	0.54
LDL level, mmol/l	2.7 ± 1.0	2.9 ± 0.8	3.0 ± 1.0	0.22
TG level, mmol/l	1.6 ± 0.5	1.7 ± 0.8	1.5 ± 0.7	0.45
Echocardiographic measures				
LA volume index, ml/m^2	38.9 ± 3.8	38.1 ± 5.4	39.4 ± 6.4	0.21
IVS, mm	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	0.10
LVEDD, cm	5.0 ± 0.6	5.0 ± 0.5	4.9 ± 0.6	0.37
E/E' ratio	11.9 ± 3.5	11.4 ± 4.1	13.0 ± 4.8	0.06
AFSS				
Frequency (scale: 1-10)	6.9 ± 1.8	7.0 ± 1.6	7.3 ± 1.2	0.28
Duration (scale: 1-10)	6.8 ± 1.9	7.1 ± 1.8	6.6 ± 1.7	0.17
Severity (scale: 1-10)	6.7 ± 1.4	6.9 ± 1.9	7.1 ± 1.8	0.47
Symptom (scale: 0-35)	17.6 ± 5.5	18.0 ± 5.5	19.6 ± 5.8	0.07
Global well-being (scale: 1-10)	2.7 ± 0.8	2.4 ± 0.9	2.5 ± 0.9	0.4

Values are mean ± SD or n (%).

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFSS = Atrial Fibrillation Severity Scale; anti-HTN = antihypertensive medication; AHI = Apnea Hypopnea Index; BMI = body mass index; CRF = cardiorespiratory fitness; DM = diabetes mellitus; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; IGT = impaired glucose tolerance; IVS = interventricular septum; LA = left atrium; LDL = low-density lipoprotein; LVEDD = left ventricular end-diastolic diameter; SBP = systolic blood pressure; TG = triglyceride.

EFFECT OF CARDIORESPIRATORY FITNESS GAIN ON RISK FACTOR PROFILE. Table 3 shows the impact of cardiorespiratory fitness gain on various cardiac risk factors.

Weight loss. Weight decreased in both groups, but significantly more in patients who gained $\geq$2 METs

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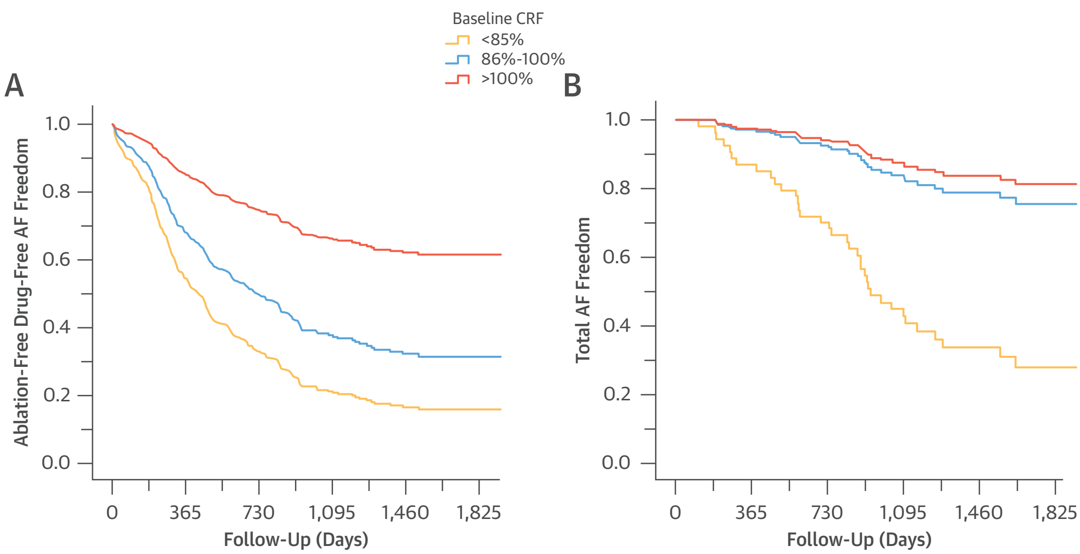
FIGURE 2 **AF Freedom Outcome According to Baseline Cardiorespiratory Fitness (Baseline METs Achieved)**



Time (Days)	0	365	730	1,095	1,460	1,825	0	365	730	1,095	1,460	1,825
<85% Predicted	95	54	36	16	12	6	95	78	58	33	20	11
86%-100% Predicted	134	93	56	34	19	11	134	133	119	86	56	33
>100% Predicted	79	63	50	36	26	18	79	78	63	51	36	21

(A) Kaplan-Meier curve for AF-free survival without the use of rhythm control strategies. **(B)** Kaplan-Meier curve for AF-free survival for total AF-free survival (multiple ablation procedures ± drugs; right). Abbreviations as in Figure 1.

compared with those with <2 METs gain (−12 ± 8.8 vs. −3 ± 7.6 kg; p = 0.001). Additionally, the ≥2 METs gain group had more sustained weight loss compared to the <2 METs gain group (54% vs. 46%; p = 0.006), and fewer patients fluctuated >5% in their weight during the yearly follow-up (37% vs. 63%; p = 0.001).

Blood pressure control. There was a greater decline in systolic blood pressure (BP) in patients who gained ≥2 METs compared to those with a <2 MET gain (14 ± 16.4 vs. 10 ± 18 mm Hg; p = 0.05). The number of antihypertensive agents used for BP control decreased in patients with a ≥2 METs gain (0.8 ± 0.8 to 0.5 ± 0.5; p = 0.01) and remained unchanged in those with a <2 METs gain (0.8 ± 1.0 to 0.9 ± 0.7; p = 0.2).

Lipid profile. At baseline, 46% of the ≥2 METs and 48% of the <2 METs gain groups had dyslipidemia (p = 0.7). Drug therapy was required in 29% and 35% of patients in each group, respectively (p < 0.001). Both low-density lipoprotein cholesterol and plasma triglycerides declined significantly in patients who gained ≥2 METs (p < 0.001), but did not differ in those with a <2 METs gain.

GLYCEMIC CONTROL. At baseline, 29% of the ≥2 METs and 25% of the <2 METs gain groups had a history of DM (p = 0.8). At final follow-up, DM patients in the ≥2 METs group had a significantly better glycemic control compared to those in the <2 METs gain group (glycated hemoglobin <7% in 12% vs. 3%, respectively; p = 0.001).

Inflammation. Patients with a ≥2 METs gain demonstrated a decrease in mean hsCRP (p < 0.001) from baseline to follow-up. There was no change in hsCRP in patients with a <2 METs gain (p = 0.8).

EFFECT OF CARDIORESPIRATORY FITNESS GAIN ON CARDIAC STRUCTURE. Table 3 shows the effect of cardiorespiratory fitness gain on cardiac structure. The left atrial volume indexed for body surface area decreased significantly in both groups. There was a greater decline in left atrial volume index with a ≥2 METs gain (p < 0.001). A similar trend was seen in left ventricular end-diastolic diameter, in which a ≥2 METs gain corresponded to greater reductions in left ventricular end-diastolic diameter. Lateral E/E′ declined in patients with a ≥2 METs gain, but did not change in the <2 METs gain group.

EFFECT OF CARDIORESPIRATORY FITNESS GAIN ON AF SYMPTOM BURDEN. At baseline, both groups had comparable and high AFSS subscale scores (Table 3).

AF frequency, duration, symptom, and symptom severity were reduced at final follow-up in both groups, with a significantly greater reduction seen in the ≥2 METs gain group ($p < 0.001$).

Freedom from AF without the use of rhythm control strategies. Figure 3A demonstrates the "ablation- and drug-free" AF freedom based on METs gain groups. At final follow-up, 61% of patients who gained ≥2 METs remained free from arrhythmia without antiarrhythmic drugs or ablation compared to 18% of patients in the <2 METs gain group. Change in cardiorespiratory fitness was a significant univariate predictor of AF recurrence ($p < 0.001$). On multivariable analysis, a <2 METs gain (HR: 2.1; 95% CI 1.3 to 3.3; $p = 0.001$), no weight loss (HR: 1.7; 95% CI 1.0 to 3.1; $p = 0.005$), and low baseline cardiorespiratory fitness (HR: 2.7; 95% CI 1.57 to 4.52; $p < 0.001$) remained independent predictors of AF recurrence. As a continuous variable, every METs gained from baseline to follow-up was associated with a 9% decline in the risk of arrhythmia recurrence even after adjustment for weight loss and baseline cardiorespiratory fitness (HR per 1-MET change: 0.90; 95% CI: 0.83 to 1.00; $p = 0.036$).

Total arrhythmia-free survival. Figure 3B demonstrates the total arrhythmia-free survival for the 2 groups. At final follow-up, patients who gained ≥2 METs had higher arrhythmia-free survival rates compared to patients who gained <2 METs (89% vs. 40%; $p < 0.001$). Change in cardiorespiratory fitness was a significant univariate predictor of AF recurrence ($p < 0.001$). On multivariable analysis, a <2 METs gain (HR: 3.9; 95% CI: 2.1 to 7.3; $p < 0.001$), no weight loss (HR: 1.9; 95% CI: 1.1 to 3.70; $p = 0.008$), low baseline cardiorespiratory fitness (HR: 5.12; 95% CI: 2.67 to 9.84; $p < 0.001$), and DM (HR: 1.77; 95% CI: 1.2 to 2.6; $p = 0.003$) remained independent predictors of AF recurrence. As a continuous variable, every MET gained from baseline to follow-up was associated with a 12% decline in the risk of total arrhythmia recurrence after multivariate adjustment (HR 1-MET change: 0.88; 95% CI: 0.80 to 0.96; $p = 0.005$).

TABLE 2 Baseline Characteristics for CRF Gain Groups

	<2 METs Gain (n = 181)	≥2 METs Gain (n = 127)	p Value
Age, yrs	58 ± 11	59 ± 12	0.40
Male	118 (65)	87 (69)	0.54
Follow-up duration, months	48.0 ± 18.0	47.6 ± 17.1	0.72
CRF gained, METs	0.5 ± 1.4	2.9 ± 0.9	<0.001
Anthropometric measures			
Weight, kg	101 ± 17	99 ± 16	0.36
BMI, kg/m^{-2}	33.4 ± 5.0	32.7 ± 4.5	0.20
SBP, mm Hg	146 ± 18	145 ± 17	0.71
AF			
Paroxysmal AF	99 (54)	66 (52)	0.67
Nonparoxysmal	82 (46)	61 (48)	
Metabolic risk factors			
Hypertension	140 (78)	92 (72)	0.28
DM	52 (29)	32 (25)	0.79
IGT	16 (9)	12 (9)	
Dyslipidemia	87 (48)	58 (46)	0.65
Coronary artery disease	25 (14)	14 (11)	0.49
Valvulopathy	8 (4)	7 (6)	0.66
AHI >30	90 (50)	73 (57)	0.18
Alcohol excess (>30 g/week)	90 (50)	73 (57)	0.55
Smoker	12 (7)	3 (2)	0.22
Medication use			
% on beta-blocker or CCB	72 (40)	54 (43)	0.82
Mean number of AAD	0.9 ± 0.7	0.9 ± 0.6	0.90
Mean number of anti-HTN	0.8 ± 1.0	0.8 ± 0.8	0.88
Serology and lipid profile			
Mean hsCRP, mg/l	4.8 ± 9.7	4.6 ± 9.0	0.91
Mean fasting insulin level, U	15.7 ± 6.9	16.2 ± 6.1	0.67
Mean LDL level, mmol/l	2.8 ± 1.0	2.9 ± 0.9	0.38
Mean TG level, mmol/l	1.6 ± 0.7	1.6 ± 0.6	0.90
Echocardiographic measures			
LA volume indexed, ml/m^2	39.2 ± 4.6	38.0 ± 6.0	0.08
IVS, mm	1.1 ± 0.3	1.0 ± 0.2	0.9
LVEDD, cm	5.1 ± 0.6	5.0 ± 0.4	0.5
Lateral E/E' ratio	11.7 ± 3.5	12.5 ± 4.8	0.10
AFSS			
Frequency (scale: 1-10)	7.2 ± 1.5	6.8 ± 1.6	0.50
Duration (scale: 1-10)	6.8 ± 1.8	7.0 ± 1.8	0.48
Severity (scale: 1-10)	6.8 ± 1.6	7.0 ± 1.8	0.51
Symptom (scale: 0-35)	17.9 ± 5.4	18.7 ± 5.8	0.25
Global well-being (scale: 1-10)	2.5 ± 0.9	2.4 ± 0.9	0.9

Values are mean ± SD or n (%).
CCB = calcium-channel blocker; METs = metabolic equivalents; other abbreviations as in Table 1.

WEIGHT LOSS AND CARDIORESPIRATORY FITNESS GAIN INTERACTION: SYNERGISTIC EFFECT. A total of 152 patients had <10% weight loss and <2 METs gain (group 1), 49 had <10% weight loss and ≥2 METs gain (group 2), 29 had ≥10% weight loss with <2 METs gain (group 3), and 78 had ≥10% weight loss with ≥2 METs gain (group 4). Cardiorespiratory fitness gain provides additional benefit above that conferred by weight loss alone. Figure 4A demonstrates the "ablation- and drug-free" AF freedom for the 4 groups. At final follow-up, 13.2% of group 1, 36.7% of group 2, 44.8% of group 3, and 75.6% of group 4 ($p < 0.001$) remained free from arrhythmia without antiarrhythmic drugs or ablation. Figure 4B demonstrates the total arrhythmia-free survival for the 4 groups. At final follow-up, 34% of group 1, 69% of group 2, 81% of group 3, and 94% of group 4 ($p < 0.001$) remained free from arrhythmia.

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TABLE 3 Cardiorespiratory Fitness Gain

Risk Factors	<2 METs Gain Group (N = 181) Baseline	Follow-Up‡	p Value*	≥2 METs Gain Group (N = 127) Baseline	Follow-Up‡	p Value*	p Value†
Weight, kg	101 ± 17	98 ± 19	<0.001	99 ± 16	87 ± 14	<0.001	<0.001
BMI, kg/m^{-2}	33.5 ± 5.0	32.5 ± 5.3	<0.001	32.7 ± 4.5	28.8 ± 4.2	<0.001	<0.001
Mean SBP, mm Hg	146 ± 18	136 ± 14	<0.001	145 ± 17	131 ± 13	<0.001	0.047
DM with HbA_{1c} ≥7	40 (22)	21 (12)		30 (24)	4 (3)		<0.001
Medication use							
Mean number of anti-HTN, n	0.8 ± 1.0	0.9 ± 0.7	0.20	0.8 ± 0.8	0.5 ± 0.5	0.001	<0.001
On lipid Rx	68 (38)	63 (35)		51 (40)	36 (29)		<0.001
Mean number of AAD	0.9 ± 0.7	0.4 ± 0.6	<0.001	0.9 ± 0.7	0.2 ± 0.5	<0.001	0.04
Serology and lipid profile							
Mean hsCRP, mg/l	4.1 ± 5.9	3.9 ± 4.5	0.75	4.6 ± 9.0	1.6 ± 2.7	<0.001	0.02
Mean fasting insulin level, U	15.9 ± 6.8	15.3 ± 10.2	0.54	16.6 ± 5.9	9.5 ± 4.7	<0.001	<0.001
Mean LDL level, mmol/l	2.8 ± 1.0	2.7 ± 0.8	0.09	3.0 ± 0.8	2.3 ± 0.7	<0.001	<0.001
Mean TG level, mmol/l	1.6 ± 0.7	1.5 ± 0.7	0.22	1.6 ± 0.6	1.2 ± 0.5	<0.001	<0.001
Echocardiogram							
Indexed LA volume, ml/m^2	39.1 ± 4.6	37.9 ± 6.8	0.03	38.0 ± 6.0	32.0 ± 9.5	<0.001	<0.001
IV septum, mm	1.1 ± 0.3	1.1 ± 0.2	0.7	1.0 ± 0.2	0.9 ± 0.1	0.02	0.01
LVEDD, cm	5.1 ± 0.6	4.9 ± 0.6	0.01	5.0 ± 0.4	4.7 ± 0.8	<0.001	0.01
Lateral E/E′ ratio	11.7 ± 3.5	11.4 ± 5.0	0.55	12.5 ± 4.8	8.7 ± 3.3	<0.001	<0.001
AFSS							
AF frequency (scale: 1-10)	7.2 ± 1.4	4.3 ± 1.8	<0.001	6.8 ± 1.6	2.8 ± 1.6	<0.001	<0.001
AF duration (scale: 1.25-10)	6.8 ± 1.8	5.4 ± 2.3	<0.001	7.0 ± 1.8	3.9 ± 2.2	<0.001	<0.001
AF episode severity (scale: 1-10)	6.9 ± 1.6	4.7 ± 2.0	<0.001	6.9 ± 1.7	3.6 ± 1.7	<0.001	<0.001
AF symptom subscale (scale: 0-35)	18.2 ± 5.1	12.2 ± 5.1	<0.001	18.8 ± 5.9	9.1 ± 4.6	<0.001	<0.001
Global well-being (1-10)	2.5 ± 0.9	5.7 ± 2.0	<0.001	2.4 ± 0.9	7.6 ± 1.7	<0.001	<0.001

Values are mean ± SD or n (%). Impact of cardiorespiratory fitness gain on cardiac risk factors, cardiac structure, and AF severity from baseline to follow-up. *p value refers to within group difference (baseline to follow-up). †p value refers to between group differences over time (group-time interaction). ‡Median follow-up: 48.0 ± 18.0 months for <2 METs gain group and 47.6 ± 17.1 months for ≥2 METs gain group.

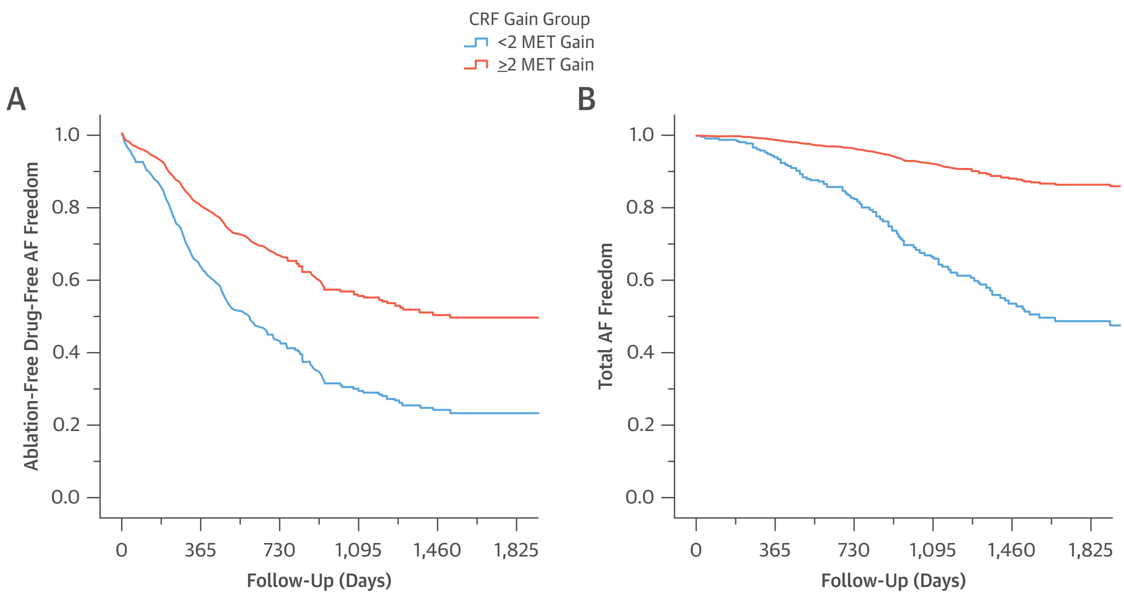
HbA_{1c} = glycated hemoglobin; Rx = prescription; other abbreviations as in Tables 1 and 2.

DISCUSSION

This study demonstrates that in overweight and obese individuals with symptomatic AF, preserved baseline cardiorespiratory fitness predicts long-term freedom from AF. We found a significant dose-response relationship between baseline cardiorespiratory fitness with a 20% reduction in the risk of AF recurrence for each MET increase in baseline cardiorespiratory fitness. Cardiorespiratory fitness gain with a structured exercise program (**Central Illustration**) has an additive effect to weight loss in improving the long-term outcome of AF. METs gain in cardiorespiratory fitness ≥2 on top of weight loss were associated with 2-fold greater freedom from AF. Specifically, participation in a dedicated risk factor management clinic was associated with increased cardiorespiratory fitness gain. These findings highlight the prescriptive role of exercise in managing patients with AF, particularly as a strategy for rhythm control.

Several population-based studies have demonstrated a robust relationship between obesity and AF (3). Modifiers of this association such as weight loss have been shown to reduce AF recurrence (6,16). Physical activity has previously been suggested to mitigate some of the cardiovascular hazards associated with excess body weight (17,18). However, the relationship between physical activity and AF is highly contentious (18,19) because it is mostly based on the results from population-based longitudinal studies with self-reported data (18,20). Recent studies have suggested that increased leisure time physical activity may be protective against AF even in the presence of obesity (8,21). In the current study, we used objective measures of cardiorespiratory fitness to demonstrate the prognostic benefits in patients with symptomatic AF. This remains significant even after adjustment for change in BMI observed throughout the follow-up. Our results suggest that cardiorespiratory fitness may partially offset the adverse effects of obesity.

FIGURE 3 **Outcomes of AF Freedom According to Cardiorespiratory Fitness Gain (<2 METs Gain vs. ≥2 METs Gain)**



Time (Days)	0	365	730	1,095	1,460	1,825
≥2 MET Gain	127	105	78	52	38	19
<2 MET Gain	181	104	63	36	20	16

	0	365	730	1,095	1,460	1,825
≥2 MET Gain	127	124	109	84	62	33
<2 MET Gain	181	166	132	86	51	32

(A) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures ± drugs) according to weight trend. **(B)** Kaplan-Meier curve for total AF-free survival (multiple ablation procedures ± drugs) according to weight fluctuation. Abbreviations as in Figure 1.

Few studies have examined the role of exercise training per se on arrhythmia burden in those with symptomatic AF. Short-term exercise intervention has been shown to improve health-related quality of life and exercise capacity in patients with permanent AF (22,23). In the present study, a gain in cardiorespiratory fitness (≥2 METs) associated with a reduction in AF burden marked improvement in long-term freedom from AF. Indeed, 61% previously symptomatic AF patients no longer required antiarrhythmic medications or ablation. We observed a 9% gain in long-term freedom from AF for each unit gain in METs. This gain is independent from the benefit conferred by weight loss alone in these patients. The seminal finding that the change in cardiorespiratory fitness over a follow-up period reduces AF recurrence supports a possible role for the prescription of exercise in this cohort. Notably, participation in a dedicated risk factor management clinic was associated with a greater increase in cardiorespiratory fitness.

Obesity is associated with various electrical and structural remodeling leading to genesis and perpetuation of AF (24–26). Our prior work demonstrated that weight loss has a beneficial effect on cardiac risk factors and structural remodeling (6). In this study, we have found an additive effect of cardiorespiratory fitness over weight loss. It is probable that common mechanisms contribute to this synergistic effect of cardiorespiratory fitness on reduction of the AF burden. Regular exercise has been shown to improve autonomic function (27), BP (28), insulin sensitivity (29), vascular function (30), and inflammation (31). In this study, we observed beneficial effects of cardiorespiratory fitness gain on BP, diabetic control, lipid profile, and inflammation, all of which may have contributed to reduced AF burden. This results in a better outcome and freedom from AF.

The strength of this study is that cardiorespiratory fitness was measured by a commonly performed, highly reproducible, and well-validated test. The relative and combined contributions of fitness and fatness to AF remain controversial, but our results suggest that fitness may partially offset the adverse effects of body fatness. Evidently, the compounded benefit of "alliance of cardiorespiratory fitness with weight loss" is over and above the strategic gain

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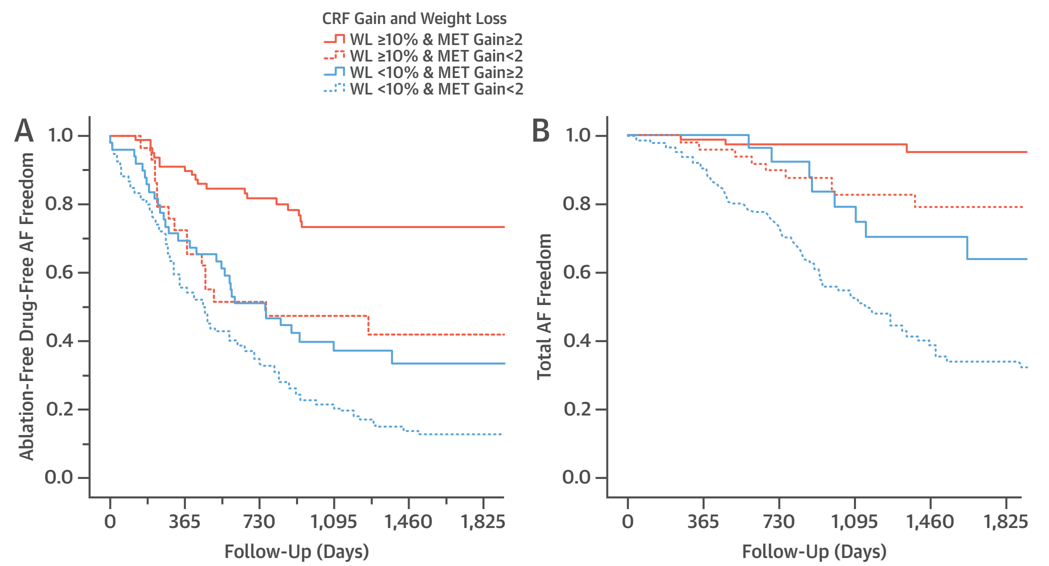
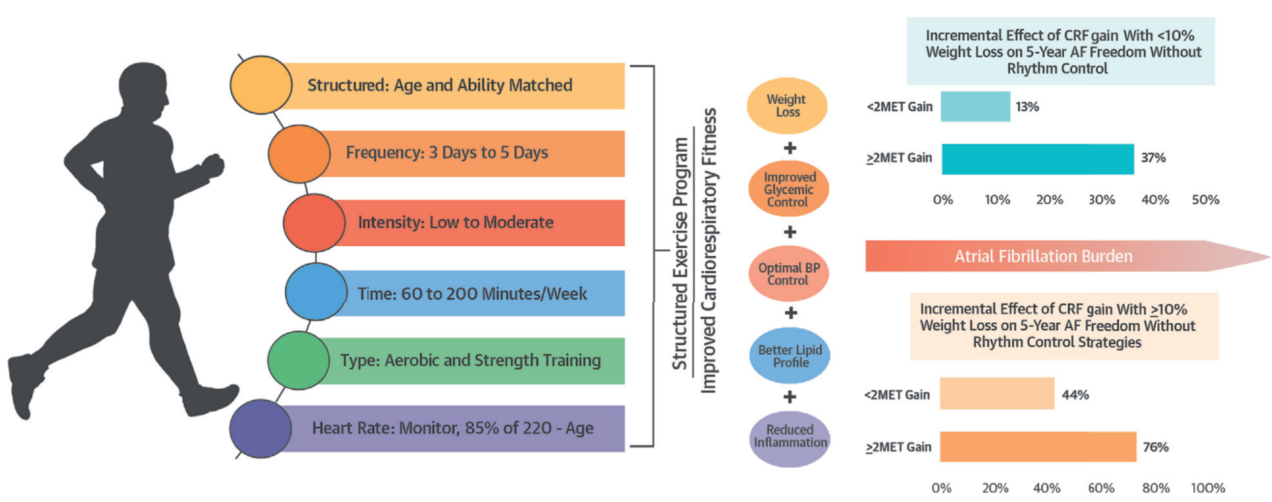
FIGURE 4 Outcomes of AF Freedom According to Cardiorespiratory Fitness Gain (<2 METs Gain vs. ≥2 METs Gain) and Weight Loss (<10% vs. ≥10% Weight Loss)



Time (Days)	0	365	730	1,095	1,460	1,825	0	365	730	1,095	1,460	1,825
≥10% WL+ MET Gain ≥2	77	71	53	37	28	13	77	76	66	51	40	20
≥10% WL+ MET Gain <2	28	20	11	9	7	6	28	28	22	16	15	8
<10% WL+ MET Gain ≥2	48	33	24	14	8	4	48	47	42	31	22	11
<10% WL+ MET Gain <2	151	84	50	26	12	10	151	136	109	74	36	23

(A) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures ± drugs) according to weight trend. **(B)** Kaplan-Meier curve for total AF-free survival (multiple ablation procedures ± drugs) according to weight fluctuation. WL = weight loss; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Cardiorespiratory Fitness and AF Recurrence: CARDIO-FIT trial



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AF = atrial fibrillation; BP = blood pressure; CARDIO-FIT = CARDIOrespiratory FITness; CRF = cardiorespiratory fitness; MET = metabolic equivalent.

provided by each individually. These data highlight the prognostic role for exercise testing in predicting AF outcomes and importance of interventions to improve physical activity and cardiorespiratory fitness in overweight and/or obese symptomatic AF patients.

STUDY LIMITATIONS. This study has the potential for bias inherent in observational studies. However, measurement bias has been reduced through standardized processes in our clinic and the evaluation by operators blinded to the patients' risk factor management regimens. AF burden assessment using 7-day Holter may miss some AF episodes; however, it was used for AF freedom assessment in both the groups and was a limitation for all. Ascertainment bias was reduced through the routine collection of outcome data. Although there are clinical limitations of using BMI as a surrogate measure of body fatness, this was used because of its wide applicability, noninvasiveness, and simple measure. Improvement in individual risk factors for AF such as obesity, hypertension, and DM is likely to vary between patients, but the specific contribution of these risk factors in AF-related outcomes is beyond the scope of this study.

CONCLUSIONS

Increased cardiorespiratory fitness was associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm. Cardiorespiratory fitness gain provides a 12% incremental gain over weight loss in long-term freedom from total AF burden. This occurs in conjunction with favorable changes in cardiometabolic risk factor profile, inflammatory state, and cardiac remodeling.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Increased cardiorespiratory fitness is synergistic with weight loss as part of the management strategy for rhythm control in overweight and obese patients with AF.

TRANSLATIONAL OUTLOOK: Additional studies are needed to better understand the mechanism by which cardiorespiratory fitness reduces the risk of recurrent AF and to determine whether particular regimens used to achieve or maintain fitness are more or less effective than others.

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KEY WORDS atrial fibrillation, fitness, obesity, physical activity, risk factors, weight loss

APPENDIX For a supplemental appendix, please see the online version of this article.