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FULL RESEARCH PAPER
Arrhythmias

Influence of sex on efficacy of exercise training for patients with symptomatic atrial fibrillation: insights from the ACTIVE-AF randomized controlled trial

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Aims Exercise training reduces recurrence of arrhythmia and symptom severity amongst patients with symptomatic, non-permanent atrial fibrillation (AF). However, there is little evidence on whether this effect is modified by patient sex. In a sub-analysis from the ACTIVE-AF (A Lifestyle-based, PhysiCal AcTIVity IntErvention for Patients With Symptomatic Atrial Fibrillation) randomized controlled trial, we compared the effects of exercise training on AF recurrence and symptom severity between men and women.

Methods and results The ACTIVE-AF study randomized 120 patients (69 men, 51 women) with paroxysmal or persistent AF to receive an exercise intervention combining supervised and home-based aerobic exercise over 6 months or to continue standard medical care. Patients were followed over a 12-month period. The co-primary outcomes were recurrence of AF, off anti-arrhythmic medications and without catheter ablation, and AF symptom severity scores. By 12 months, recurrence of AF was observed in 50 (73%) men and 34 (67%) women. In an intention-to-treat analysis, there was a between-group difference in favour of the exercise group for both men [hazard ratio (HR) 0.52, 95% confidence interval (CI): 0.29–0.91, $P = 0.022$] and women (HR 0.47, 95% CI: 0.23–0.95, $P = 0.035$). At 12 months, symptom severity scores were lower in the exercise group compared with controls amongst women but not for men.

Conclusion An exercise-based intervention reduced arrhythmia recurrence for both men and women with symptomatic AF. Symptom severity was reduced with exercise in women at 12 months. No difference was observed in symptom severity for men.

Registration Australia and New Zealand Clinical Trials Registry: ACTRN12615000734561

Lay summary This analysis examined the potential benefit of exercise training on arrhythmia recurrence and symptom severity amongst men and women with symptomatic atrial fibrillation enrolled in a randomized controlled trial of exercise and physical activity intervention compared with standard medical care. Previous studies have not provided evidence on whether men and women might benefit from exercise training to a similar degree. Our findings highlight the following key points:

- Both men and women in our study experienced fewer arrhythmia recurrences with exercise training compared with men and women in standard medical care.
- Exercise reduced arrhythmia symptoms in women, but we did not find any evidence of a reduction in symptoms amongst men.

Keywords Exercise • Arrhythmia • Rehabilitation • Symptoms • Women

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Introduction

Atrial fibrillation (AF) is associated with a greater risk of stroke, heart failure, cardiovascular events, and all-cause mortality in women compared with men.[1] Women with AF are more symptomatic with lower quality of life[2] yet referred less frequently and later for catheter ablation.[3] In addition, the distribution of risk factors for AF may differ between men and women, with hypertension, obesity, and type 2 diabetes more frequent, yet lower prevalence of alcohol consumption and obstructive sleep apnoea.[4]

Lifestyle modification and aggressive risk factor management now underpin the treatment pathway in patients with symptomatic AF.[5] This pillar of treatment targets the underlying substrate promoting AF, limiting its progression, and promotes sinus rhythm.[6–8] Although there is accumulating evidence demonstrating the efficacy of risk factor reduction for the secondary prevention of AF, there is limited data on whether underlying differences in the clinical profile and pathophysiology between women and men influence outcomes.

Higher levels of aerobic exercise and physical activity are associated with a lower risk of AF.[9–11] Interestingly, the association between increased physical activity and a lower risk of AF has previously been shown to be greater for women compared with men.[10] Additionally, in participants of endurance sports, there is evidence that women reduce their risk of AF, in contrast to men who develop increased AF risk with endurance sports.[12] In both observational and randomized studies amongst patients with symptomatic AF, exercise intervention improved maintenance of sinus rhythm and lowered AF symptoms.[13,14] Despite this evidence, little attention has been paid to whether sex influences outcomes following exercise intervention.

The ACTIVE-AF (A Lifestyle-based, PhysiCal AcTIVity IntErvention for Patients With Symptomatic Atrial Fibrillation) study was a randomized, controlled trial of a 6-month aerobic exercise intervention compared with standard medical care in patients with symptomatic paroxysmal or persistent AF.[15] The primary study findings demonstrated a reduction in AF recurrence and symptom severity amongst those randomized to exercise intervention. In this sub-study of ACTIVE-AF, we explore whether the effects of exercise intervention may be influenced by patient sex.

Methods

Study design

The ACTIVE-AF study was a randomized, controlled trial of patients with symptomatic AF allocated to combined home and supervised exercise intervention or usual medical care for a period of 6 months with an additional 6-month follow-up.[15] All patients were recruited via referral to a single centre for rhythm management from three tertiary hospitals. The study was approved by the Human Research Ethics Committees of the Central Adelaide Local Health Network and the University of Adelaide. All participants provided written informed consent. The trial was prospectively registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12615000734561).

Patient selection and randomization

Patients with symptomatic paroxysmal or persistent AF, aged 18–80 years, referred for rhythm management were screened (*Figure 1*). Exclusion criteria included the absence of AF lasting >30 s in the past 3 months documented by 12-lead electrocardiogram (ECG) or Holter monitoring, AF ablation within the past 12 months, permanent AF, myocardial infarction (MI), or cardiac surgery within the past 12 months, autoimmune or systemic inflammatory disease, left ventricular (LV) ejection fraction of <45%, moderate-to-severe valvular disease, and inability to participate in a structured exercise programme due to a musculoskeletal condition. A computer-generated randomization schedule was used to randomize patients 1:1 to either the exercise arm or the control arm. Randomization was stratified using block sizes of four patients.

Exercise intervention

The exercise intervention has been described previously.[15] Briefly, a personalized exercise programme was developed for each patient according to baseline exercise capacity and current physical activity habits and delivered

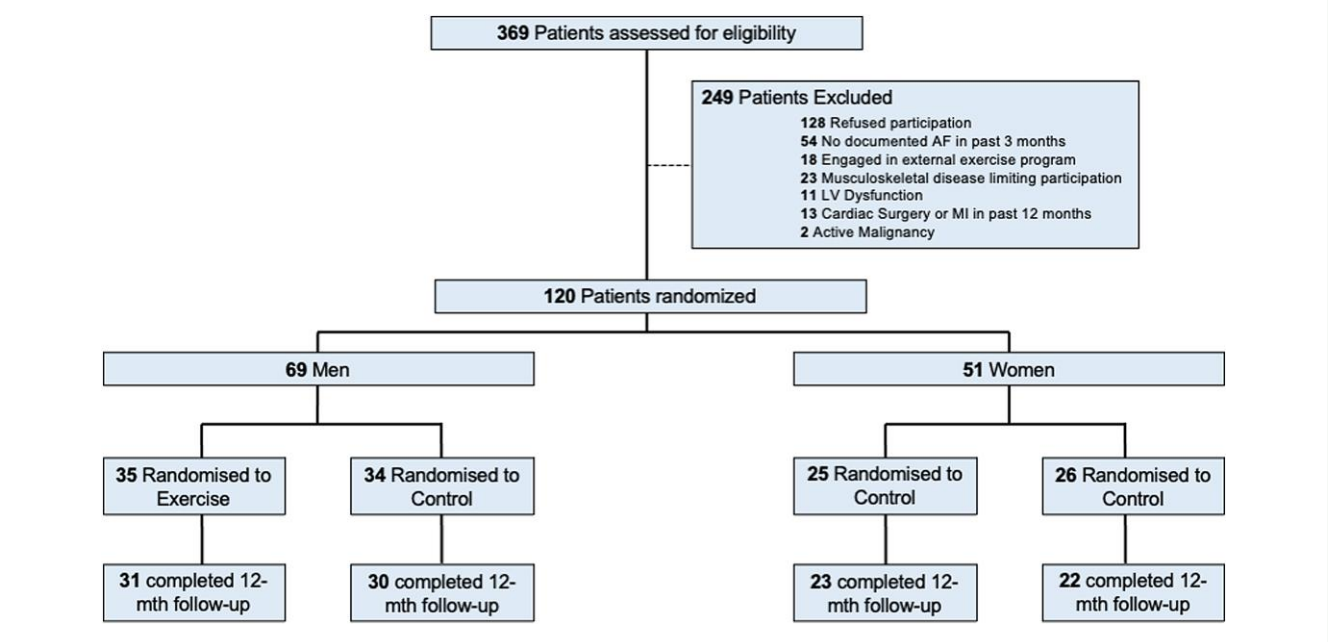

Figure 1 CONSORT diagram of patient recruitment, randomisation, and follow-up. AF, atrial fibrillation; LV, left ventricular; MI, myocardial infarction; mth, month.

by clinical exercise physiologists. Participants were given access to supervised, one-on-one exercise sessions on a weekly basis for the first 3 months and then fortnightly from 3 to 6 months. Additional sessions were offered if required. A weekly physical activity plan was developed at each session to promote home-based participation in moderate-to-vigorous aerobic physical activity tailored to their ability. All home-based physical activity was recorded by participants in a diary, in which mode, duration, and intensity of activities were recorded. During the initial training phase, participants were encouraged to increase their weekly physical activity time by ~20% per week until a target of 210 min per week was reached. Weekly physical activity time included periods of moderate-to-vigorous aerobic activity of ≥10 min. Supervised exercise sessions followed the aerobic interval training structure consisting of 4 × 4 min intervals, each interspersed by 2 min of active recovery, as demonstrated elsewhere.[13] The target exercise intensity for each interval was 85–90% of the heart rate reserve (HRR) established during baseline cardiopulmonary exercise testing (CPET).[16] For patients in AF, a modified Borg Scale using the rating of perceived exertion (1–10) was used to guide exercise intensity, with a target rating of 9 identified for aerobic intervals.

Control group

Participants in the control group were provided with two education sessions on the benefits of physical activity for the management of AF. Each session was delivered one-on-one by a clinical exercise physiologist. Specifically, patients in the control group were encouraged to achieve 150 min of moderate physical activity per week but did not attend any supervised exercise sessions or receive any individualized exercise programme.

Guideline-directed, standard medical care was provided to all patients throughout the study period from their treating cardiologist blinded to the randomization group. Arrhythmia management, including decisions regarding rate control, rhythm control, and anticoagulation, was at the discretion of the treating cardiologist. In addition, all patients received advice on management of lifestyle-based risk factors, consistent with current guidelines. No specific weight loss intervention was initiated during the study period.

Follow-up

All patients underwent a standardized follow-up that included study visits at baseline and 6, 9, and 12 months post-randomization. Study outcomes were assessed by research and clinical staff blinded to treatment allocation.

Study outcomes

The co-primary outcomes of the primary study were freedom from AF, off anti-arrhythmic medications and without AF ablation, and AF symptom severity, quantified using the symptom severity domain of the University of Toronto AF Symptom Severity (AFSS) questionnaire.

Atrial fibrillation monitoring

Ambulatory monitoring was undertaken for 4 days in all patients at baseline and 6 and 12 months. Additional 4-day Holter monitoring was performed in patients who report symptoms consistent with AF. Furthermore, all patients underwent 12-lead ECG and clinical review at 3 and 9 months post-randomization to screen for any potential arrhythmia or arrhythmia-related clinical events. A team of two independent cardiac scientists blinded to patient randomization assessed Holter recordings, with final review by a cardiac electrophysiologist also blinded to patient randomization. Episodes of AF lasting 30 s or longer[17] on Holter monitoring, AF documented with 12-lead ECG following symptomatic episodes, and ongoing symptomatic episodes requiring anti-arrhythmic medication or AF ablation were considered recurrence of AF.

Atrial fibrillation symptom severity

The AFSS questionnaire is a validated questionnaire that assesses the frequency, duration, and severity of AF-related symptoms. The co-primary outcome focused on the symptom severity domain that questions patients on the severity of seven AF-related symptoms over the preceding 4-week period.[18] The AFSS questionnaire asks the patients to rate the extent to which each symptom has bothered them on a scale of 0–5 (0 being 'No symptom', 5 representing 'A great deal'). The sum of all symptom scores was used to compute the total symptom severity score. In addition, three additional domains from the AFSS questionnaire were assessed: arrhythmia frequency (scored 1–10) and duration (scored 1.25–10). Using all components, the total AF symptom burden was computed on a scale ranging from 3.25 (lowest symptom burden) to 30 (highest symptom burden). The AFSS questionnaire was administered at baseline and 6 and 12 months by staff blinded to patient randomization.

Cardiopulmonary exercise testing

At baseline and 6 and 12 months, all patients underwent treadmill-based maximal CPET using breath-by-breath pulmonary gas exchange (Jaeger Oxycon Pro, CareFusion, San Diego, CA, USA) following current guidelines.[19] The treadmill protocol followed a standardized protocol with a fixed walking speed and a 1% increase in gradient each minute until exhaustion. Twelve-lead ECG (Mortara, USA) was used to assess the rhythm and heart rate. Peak oxygen consumption (VO_{2peak}) was defined as the highest oxygen uptake averaged over 20 s intervals. Maximal effort was determined by a peak respiratory exchange ratio (RER) of ≥1.05.

Transthoracic echocardiography

Transthoracic echocardiography was performed by an experienced sonographer blinded to patient randomization at baseline and 6 and 12 months. All images were obtained and analysed as per current guidelines.[20,21]

Clinical follow-up

All patients were followed up by a clinical cardiac electrophysiologist blinded to treatment allocation. Furthermore, study investigators were blinded to decisions on rate and rhythm control medication. The prescribed medications for each patient were evaluated and recorded at baseline and 6 and 12 months. Additionally, in-office blood pressure, height, and weight were obtained during each study visit by experienced cardiac scientists blinded to randomization.

Statistical analysis

All data are presented as percentages for discrete variables and median [interquartile range (IQR)] or mean ± standard deviation for continuous variables. For analysis of the co-primary outcome of AF freedom, we first constructed a single Cox regression model including both the randomization group and sex, and their interaction, as input variables. Survival curves were subsequently estimated by the Kaplan–Meier method and compared by the log-rank test within each sex. The hazard ratio (HR) and 95% confidence interval (CI) of the group effect were derived using the Cox proportional hazards model. All participants were analysed using the intention-to-treat principle according to initial randomization and by sex. The proportional hazards assumption was assessed by correlating scaled Schoenfeld residuals with time to test for independence between residuals and time. Proportionality of hazards was confirmed using Schoenfeld's global test with $P > 0.05$, indicating that this assumption was met. For analysis of the co-primary outcome of AF symptom severity, pairwise mean comparisons at 6 and 12 months were performed with adjustment for baseline values using analysis of covariance, with $\alpha = 5\%$ set as the significance level. To account for missing values, a multiple imputation approach was performed using the predictive mean matching method with 50 iterations taken to impute missing values. Five imputed datasets were created, which were subsequently pooled for analysis. In addition, a secondary analysis was performed using complete cases only. All other secondary outcomes were analysed using analysis of covariance to compare mean differences and 95% CI at 6 and 12 months, with baseline measures added as a covariant. The CI of secondary endpoints is presented without adjustment for multiplicity. All statistical analyses were performed using R Statistical Software (R Foundation for Statistical Computing) using the 'mice', 'rms', 'survival', and 'emmeans' packages. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

From November 2015 to December 2019, 369 symptomatic AF patients were assessed for eligibility and 120 patients were enrolled in the study. Of these, 69 (57.5%) were men and 51 (42.5%) were women. The baseline characteristics of enrolled patients are shown in *Table 1*. On average, women were older (68 vs. 63 years) and more likely to have paroxysmal AF than men (75% vs. 52%). The prevalence of coronary artery disease was lower amongst women (20.3% vs. 5.9%). There were no differences between men and women for prescribed medications. Fourteen patients did not complete follow-up (eight men, six women; *Figure 1*). For men, four patients withdraw from each of the exercise and control groups. Amongst women, two patients withdrew from the exercise group and four withdraw from the control group.

Primary outcome: atrial fibrillation recurrence

Recurrence of AF, off anti-arrhythmic therapy, was observed in 50 (73%) men and 34 (67%) women (HR 1.38, 95% CI: 0.89–2.14). In a Cox regression model including both the randomization group and sex, we found no evidence of an interaction between the group and sex ($P = 0.99$). In an intention-to-treat analysis, there was a between-group difference in favour of the exercise group for both men (HR 0.52, 95% CI: 0.29–0.91, $P = 0.022$) and women (HR 0.47, 95% CI: 0.23–0.95, $P = 0.035$; *Figure 2*). These findings did not differ when only complete cases were included in this analysis (see Supplementary material online, *Table S1*).

Sex differences in atrial fibrillation symptoms

At enrolment, women and men reported comparable AF symptom severity scores (11 ± 7 vs. 9 ± 7), and this similarity remained after adjustment for between-sex differences in age, AF type, and coronary artery disease ($P = 0.08$). The change in AF symptom severity over the 12-month study period is shown in *Figure 3*. We did not observe any statistically significant interaction between the group and sex on AF symptom severity. At 6 months after randomization, the mean AF symptom severity score for women was 7 ± 4 and 12 ± 9 for the exercise and control groups, respectively, with a mean adjusted difference of −2.6 (95% CI: −5.6 to 0.5, *Table 2*). At 12 months, the AF symptom severity score for women was 6 ± 5 and 11 ± 9 for the exercise and control groups (adjusted mean difference −3.4, 95% CI: −6.6 to −0.2). In men, the 6-month symptom severity scores for the exercise and control groups were 7 ± 6 and 7 ± 6, corresponding to an adjusted mean difference of −0.95 (95% CI: −3.6 to 1.7). At 12 months, symptom severity scores were 6 ± 5 and 6 ± 5, corresponding to an adjusted mean difference of −0.3 (95% CI: −3.0 to 2.5, *Table 2*). These findings did not differ when only complete cases were included in this analysis (see Supplementary material online, *Table S2*).

At 6 and 12 months, the AF symptom burden was lower in the exercise group amongst women only. Similarly, we observed a reduced AF frequency at 12 months in women only. We found no evidence of a reduced AF symptom burden, duration, or frequency in men randomized to exercise at either time point.

Sex differences in cardiorespiratory fitness

At enrolment, VO_{2peak} was lower in women compared with men (16.0 ± 4.1 vs. 22.3 ± 5.1 mL/kg/min, $P < 0.001$). These differences persisted following adjustment for sex differences in age, type of AF, and coronary artery disease. We did not observe any statistically significant interaction between the group and sex on VO_{2peak}. Upon completion of the intervention period, the between-group difference in VO_{2peak} for

Table 1 Baseline clinical characteristics

Characteristic	Men ($n = 69$)	Women ($n = 51$)	*P*-value
Demographics and baseline measures			
Age (years)	63 ± 11	68 ± 7	0.003
Body mass (kg)	98 ± 18	83 ± 17	<0.001
Height (cm)	180 ± 8	164 ± 6	<0.001
Body mass index (kg/m^2)	30.2 ± 5.3	30.8 ± 6.6	0.59
Systolic blood pressure (mmHg)	134 ± 17	130 ± 20	0.28
Diastolic blood pressure (mmHg)	79 ± 10	71 ± 14	<0.001
Medical history			
Persistent AF (*n*, %)	33 (48)	13 (25)	0.022
Hypertension (*n*, %)	44 (64)	36 (71)	0.56
Type 2 diabetes (*n*, %)	10 (14)	6 (12)	0.87
Obstructive sleep apnoea (*n*, %)	29 (42)	20 (39)	0.90
Coronary artery disease (*n*, %)	14 (20)	3 (6)	0.049
Previous stroke/TIA (*n*, %)	3 (4)	3 (6)	0.99
CHA_2DS_2-VASc (median, IQR)	1 (1–2)	2 (1–2.5)	0.12
Medications			
Beta-blocker (*n*, %)	30 (43)	21 (41)	0.85
Calcium channel blocker (*n*, %)	22 (32)	18 (35)	0.66
Sotalol (*n*, %)	11 (16)	8 (16)	1.0
Flecainide (*n*, %)	19 (28)	13 (26)	1.0
Amiodarone (*n*, %)	6 (9)	2 (4)	0.52
ACE inhibitor (*n*, %)	18 (26)	12 (24)	0.96
Angiotensin receptor blockade (*n*, %)	24 (35)	17 (33)	1.0
Statin (*n*, %)	30 (43)	20 (39)	0.8
Oral anticoagulation (*n*, %)	55 (80)	41 (80)	1.0
Echocardiography and exercise testing			
LA volume (mL/m^2)	33.8 ± 9.7	29.8 ± 8.0	0.024
LV ejection fraction (%)	61.1 ± 7.8	62.9 ± 6.4	0.20
LV mass (g/m^2)	88.7 ± 23.3	77.1 ± 16.2	0.003
E/*e*′	9.5 ± 4.5	10.6 ± 4.0	0.16
VO_{2peak} (mL/kg/min)	22.3 ± 5.1	16.0 ± 4.1	<0.001
AF symptom scores			
Symptom severity	8.9 ± 7.4	11.3 ± 7.3	0.08
Symptom frequency	4.5 ± 3.6	4.6 ± 3.0	0.84
Symptom duration	5.5 ± 3.5	4.9 ± 3.0	0.35
Symptom burden	15.5 ± 7.0	15.4 ± 4.8	0.92

LA volume and LV mass were indexed to the body surface area. VO_{2peak} was indexed to body mass.

ACE, angiotensin converting enzyme; AF, atrial fibrillation; TIA, transient ischaemic attack; LA, left atrial; LV, left ventricular; *E*, early mitral filling; *e*′, mitral annular early diastolic velocity; VO_{2peak}, peak oxygen consumption; IQR, interquartile range.

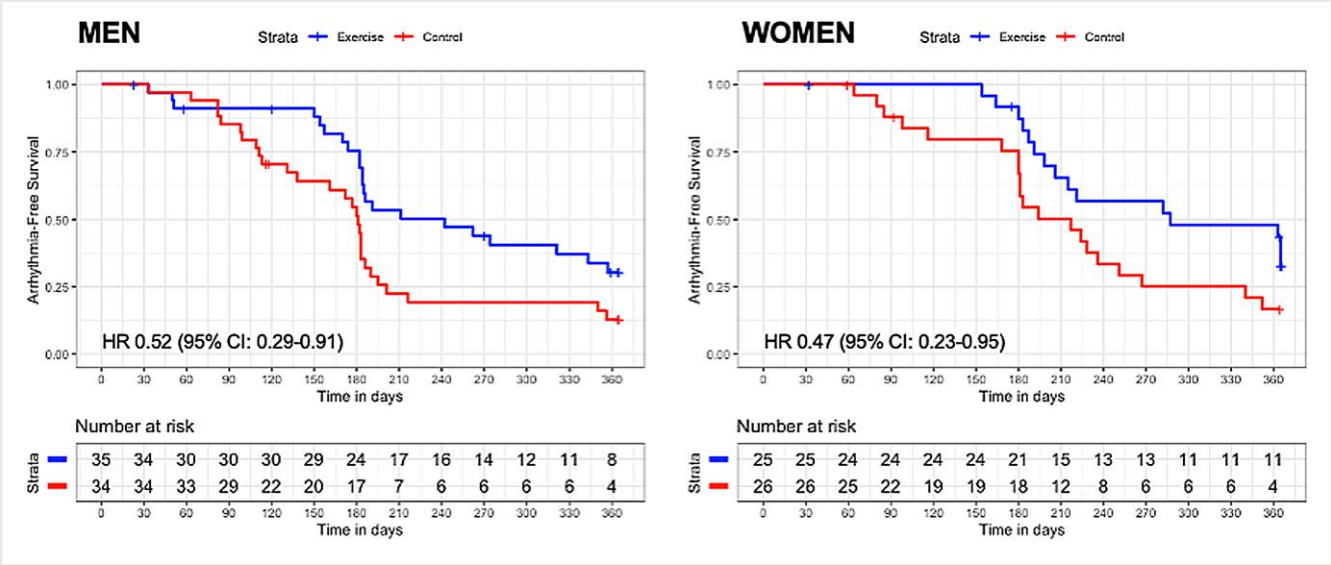

Figure 2 Arrhythmia freedom, off anti-arrhythmic therapy and without ablation, within men (left) and women (right). CI, confidence interval; HR, hazard ratio.

men (mean difference 1.9 mL/kg/min, 95% CI: 0.2 to 3.5) tended to be higher than for women (mean difference 1.3 mL/kg/min, 95% CI: −0.2 to 2.7). Similarly, between-group differences suggested that exercise benefits were sustained at 12 months for men (mean difference 2.6 mL/kg/min, 95% CI: 0.4 to 4.8) but less for women (mean difference 0.7 mL/kg/min, 95% CI: −1.1 to 2.5; *Figure 4*).

Sex differences in echocardiographic measures and risk factors

At baseline, men had higher left atrial (LA) volumes and LV mass when indexed to body size (*Table 1*). Systolic and diastolic LV functions were similar between men and women. There were no statistically significant differences in LA size, LV size, or function between groups for either men or women during follow-up. At baseline, body mass and systolic blood pressure were comparable between sexes, with higher diastolic blood pressure in men compared with women. At the final follow-up (see Supplementary material online, *Table S3*), there were no between-group differences in body mass at 6 months. However, at 12 months, body mass was higher in the exercise group amongst women (mean difference 2.9 kg, 95% CI: 0.1–5.8). Systolic blood pressure was comparable between both groups in both men and women at each time point. In men, diastolic blood pressure was lower in the exercise group at 6 (mean difference −4.4 mmHg, 95% CI: −8.3 to −0.5) but not 12 months. There were no between-group differences in diastolic blood pressure in women.

Discussion

The results of this sub-analysis of the ACTIVE-AF study provide important insights into the efficacy of exercise training amongst men and women with symptomatic, non-permanent AF. Specifically, we demonstrate the following clinically relevant findings:

(1) Despite differences in patient characteristics at enrolment, men and women randomized to exercise intervention had a reduction in recurrent AF over the 12-month follow-up.
(2) Amongst women, those randomized to exercise had lower AF symptom severity at the 12-month follow-up. In contrast, we did not observe between-group differences in symptom severity between men randomized to exercise and control groups.
(3) By the 12-month follow-up, men randomized to exercise displayed higher cardiorespiratory fitness than control group patients. In contrast, we did not observe between-group differences amongst women.

Amongst patients with AF, there are frequently reported differences between men and women in risk factor profiles, pathophysiology, symptoms, access to therapy, and treatment outcomes.[2,3,22–24] The ACTIVE-AF study reported the efficacy of exercise intervention for the reduction of AF recurrence and symptom severity amongst patients with symptomatic paroxysmal or persistent AF, lending further evidence in favour of lifestyle modification and risk factor reduction as the first pillar of AF management.[5] However, there is a paucity of data regarding the reported between-sex differences that influence outcomes from lifestyle intervention. The novel finding from our study is that despite more frequent AF recurrences in men compared with women overall, the effect of exercise on AF recurrence was similar between sexes. This finding reinforces the need for consideration of exercise prescription amongst patients with symptomatic AF, regardless of sex. Although further prospective studies within women with AF are warranted, this finding addresses an important clinical knowledge gap.

Exercise training is associated with a reduction in symptom severity amongst patients with AF. In this *post hoc* analysis, our study demonstrated a reduced AF symptom severity at 12 months for women in the exercise arm compared with the control arm, although there was no evidence for reduced symptom severity with exercise training amongst men. Previous multicentre registries have shown persistently worse symptom scores amongst women despite ongoing treatment.[2] Therefore, the observation that exercise intervention provides significant benefits within women is notable and supports exercise recommendation to close the gap in symptoms between men and women. Although we did not find evidence for a reduction in AF symptom severity amongst men in the ACTIVE-AF study, we cannot rule out the

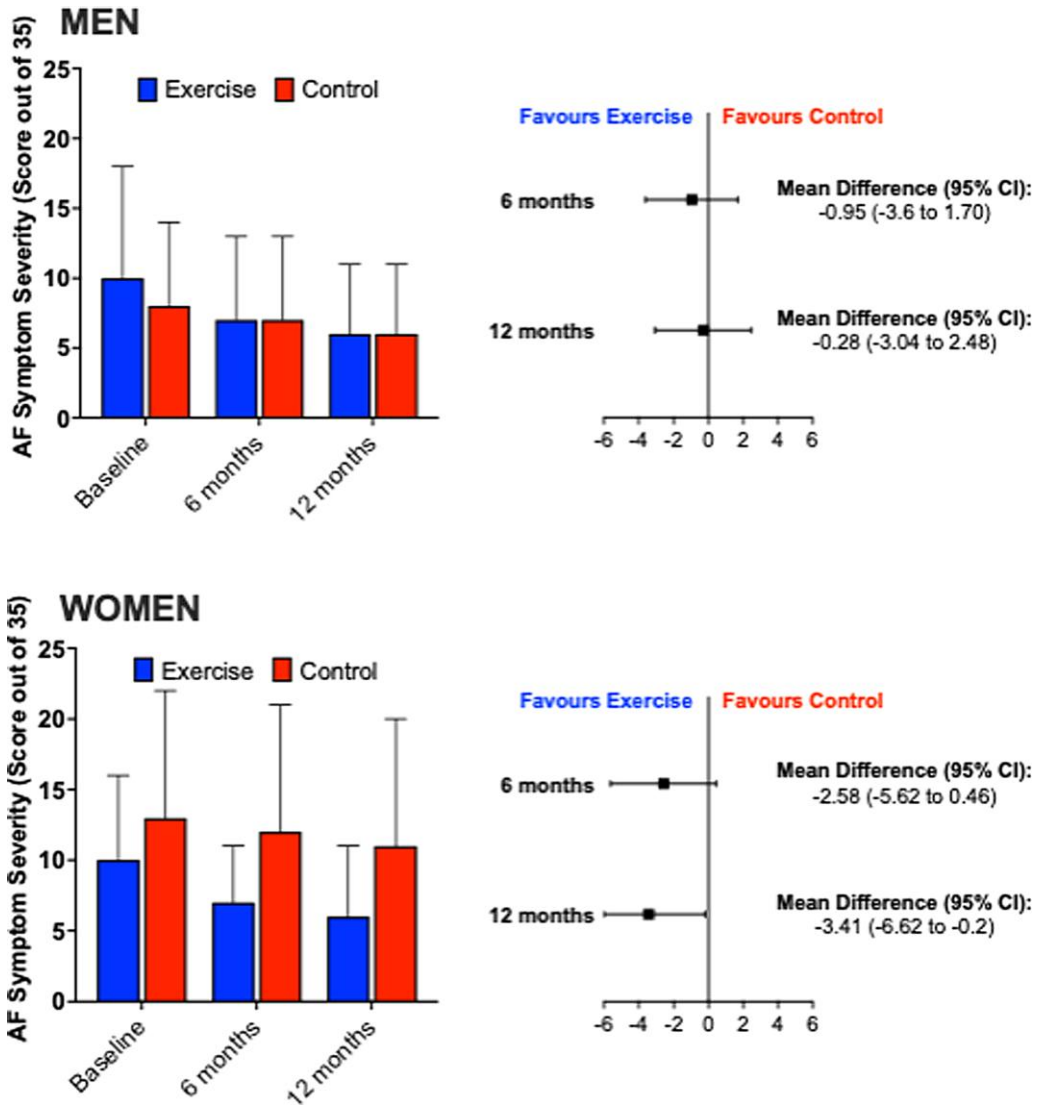

Figure 3 Atrial fibrillation symptom severity at 6 and 12 months, within men (top left) and women (bottom left). The mean difference between groups (adjusted for baseline measures) is shown in men (top right) and women (bottom right). AF, atrial fibrillation; CI, confidence interval.

potential for a type II error given that this *post hoc* analysis was not specifically powered to detect subtle differences in symptom profiles within each sex. Nonetheless, we maintain that exercise recommendation in men with AF is justified for the prevention of recurrent AF and its subsequent progression.

Women in the ACTIVE-AF study had lower VO_{2peak} at enrolment compared with men. Sex differences in aerobic capacity are largely the consequence of reduced cardiac volumes and increased LV stiffness, coupled with differences in blood volume and oxygen-carrying capacity amongst women. However, it is also possible that prior physical activity habits may influence the difference observed here. Interestingly, exercise training resulted in more sustained improvements in VO_{2peak} for men compared with women. Although the mechanisms for this difference are not immediately clear, previous studies have shown a blunted cardiovascular response to training amongst women.[25] In our study, we did not demonstrate any difference between exercise and control groups within either sex for echocardiographic assessment of LA size, LV dimensions, or cardiac function. An interesting observation from this analysis is the absence of any observed change in VO_{2peak} despite improved symptom severity and reduced AF recurrence amongst women. We have previously reported discordance between VO_{2peak} and self-reported symptoms amongst patients with AF.[26] Collectively, these findings suggest that improvements in exercise tolerance may not directly translate into changes in symptom profiles amongst patients with AF.

The beneficial effects of exercise were observed in the absence of a significant reduction in modifiable risk factors or favourable cardiac remodelling. This suggests that the benefits of exercise may be independent of reduced body mass and blood pressure. Interestingly, we observed a modest increase in body mass amongst women in the exercise group compared with the control group. Previous studies have shown an increase in lean mass with aerobic exercise training, which

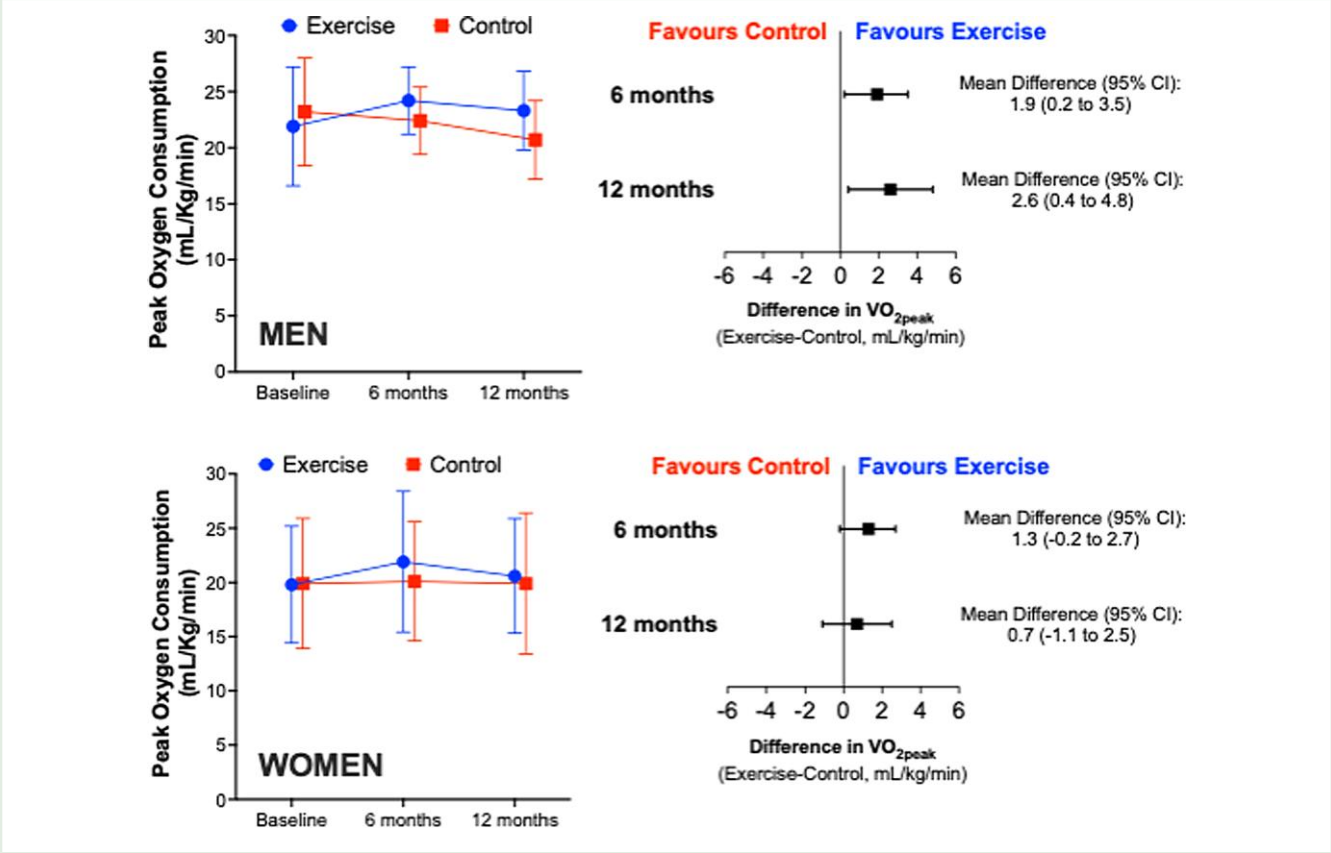

Figure 4 Peak oxygen consumption at 6 and 12 months, within men (top left) and women (bottom left). The mean difference between groups (adjusted for baseline measures) is shown in men (top right) and women (bottom right). CI, confidence interval; VO_{2peak}, peak oxygen consumption.

Table 2 Atrial fibrillation symptom scores at baseline and 6 and 12 months. Between-group differences are presented after adjustment for baseline scores

	Group	Baseline	6 months	12 months	Adjusted mean difference at 6 months (95% CI)	Adjusted mean difference at 12 months (95% CI)
Men						
Symptom severity	Exercise	10.2 ± 8.3	6.4 ± 5.6	6.0 ± 5.8	−1.0 (−3.6 to 1.7)	−0.3 (−3.0 to 2.5)
	Control	7.8 ± 6.2	7.3 ± 5.5	6.3 ± 5.8		
Symptom burden	Exercise	15.4 ± 6.8	15.0 ± 5.3	14.4 ± 5.0	−0.9 (−3.4 to 1.6)	−0.3 (2.6 to 2.1)
	Control	15.7 ± 7.3	15.9 ± 5.3	14.7 ± 5.0		
Symptom duration	Exercise	5.3 ± 3.4	5.6 ± 2.5	4.8 ± 2.9	0.1 (−1.1 to 1.3)	−1.2 (−2.5 to 0.2)
	Control	5.7 ± 3.6	5.4 ± 2.5	4.7 ± 2.9		
Symptom frequency	Exercise	4.5 ± 3.5	4.2 ± 2.7	3.6 ± 2.9	−0.5 (−1.8 to 0.8)	−0.4 (−1.8 to 0.9)
	Control	4.4 ± 3.7	4.7 ± 2.7	4.0 ± 2.9		
Women						
Symptom severity	Exercise	9.8 ± 5.4	8.5 ± 5.5	7.1 ± 5.8	−2.6 (−5.6 to 0.5)	−3.4 (−6.6 to −0.2)
	Control	12.8 ± 8.6	11.0 ± 5.6	10.5 ± 5.8		
Symptom burden	Exercise	14.3 ± 4.4	13.3 ± 4.9	12.7 ± 4.3	−3.3 (−6.0 to −0.5)	−3.5 (−5.9 to −1.1)
	Control	16.5 ± 5.0	16.5 ± 4.9	16.2 ± 4.3		
Symptom duration	Exercise	4.8 ± 3.0	4.2 ± 2.5	3.4 ± 2.2	−1.2 (−2.5 to 0.2)	−1.2 (−2.4 to 0.0)
	Control	5.0 ± 2.9	5.4 ± 2.5	4.6 ± 2.2		
Symptom frequency	Exercise	3.7 ± 2.6	4.3 ± 2.0	3.1 ± 2.5	−0.7 (−2.9 to −0.1)	−1.5 (−2.9 to −0.1)
	Control	5.5 ± 3.2	4.9 ± 2.0	4.6 ± 2.5		

may have contributed to this weight gain.[27] We did not assess specific components of body composition, precluding evaluation of whether weight gain in women was promoted by lean or fat mass. However, it should be noted that the extent of weight gain was relatively modest and may not be associated with a parallel increase in specific adipose depots, such as epicardial adipose tissue, which are associated with recurrent AF.[28] All patients in our study were offered risk factor advice from their treating physician in line with current clinical guidelines. The absence of any between-group difference in measured risk factors at follow-up suggests that the extent of risk factor intervention did not differ between groups.

Limitations

We acknowledge several limitations within this study. First, this is a sub-analysis of the ACTIVE-AF study and would require replication in a larger cohort. Our sample size was not specifically powered to detect differences between sexes. This also limited our capacity to perform sensitivity analyses within each sex. As a result, we limited our analyses to the efficacy of exercise training within each sex. We acknowledge that there were statistically significant interactions between sex and group allocation for the outcomes assessed. Therefore, between-group differences in outcomes such as AF symptom severity and VO_{2peak} should be interpreted with caution and will require formal testing in larger, prospective studies. To account for missing follow-up data of the co-primary outcome of AF symptom severity, we performed multiple imputation in the primary study, although this was limited to the imputation of only five databases. The nature of exercise studies limits patient blinding to treatment allocation, which may influence findings in relation to self-reported measures of AF symptoms. We acknowledge that additional clinic visits for patients in the intervention group may have promoted greater medication adherence and awareness of AF management. We did not use continuous rhythm monitoring to detect asymptomatic episodes of AF, which may have differed between study groups and by sex. Furthermore, two-dimensional echocardiography may have been insufficient to detect subtle differences in LA remodelling. Finally, we are unable to extrapolate beyond the 12-month findings to evaluate whether the longer-term benefits of exercise intervention may differ between men and women.

Conclusions

Although there were sex differences upon enrolment in age, AF type, LA size, body mass index, and symptom severity, we found that the benefits of exercise on AF recurrence in the ACTIVE-AF study were comparable between men and women. However, AF symptoms were improved in the exercise group for women, with no differences observed amongst men. This study provides evidence supporting the prescription of exercise for the secondary prevention of AF amongst both men and women.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability

The data underlying this article cannot be shared publicly due to restrictions from the Human Research Ethics Committees of the Central Adelaide Local Health Network and the University of Adelaide. The data will be shared on reasonable request to the corresponding author.

Author contribution

A.D.E. and P.S. oversaw the conception and design of the study. C.V.V., A.D.E., R.M., C.G., R.S.M., M.E.M., and D.H.L. contributed to data acquisition and analysis. C.V.V. and A.D.E. drafted the manuscript. All authors critically revised the manuscript and gave final approval.

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