Cardiac rehabilitation versus usual care for patients treated with catheter ablation for atrial fibrillation: Results of the randomized CopenHeart$_{RFA}$ trial

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Background To assess the effects of comprehensive cardiac rehabilitation compared with usual care on physical activity and mental health for patients treated with catheter ablation for atrial fibrillation.

Methods The patients were randomized 1:1 stratified by paroxysmal or persistent atrial fibrillation and sex to cardiac rehabilitation consisting of 12 weeks physical exercise and four psycho-educational consultations plus usual care (cardiac rehabilitation group) versus usual care. The primary outcome was VO_2 peak. The secondary outcome was self-rated mental health measured by the Short Form-36 questionnaire. Exploratory outcomes were collected.

Results 210 patients were included (mean age: 59 years, 74% men), 72% had paroxysmal atrial fibrillation prior to ablation. Compared with usual care, the cardiac rehabilitation group had a beneficial effect on VO_2 peak at four months (24.3 mL kg^{-1} min^{-1} versus 20.7 mL kg^{-1} min^{-1}, p of main effect = 0.003, p of interaction between time and intervention = 0.020). No significant difference between groups on Short Form-36 was found (53.8 versus 51.9 points, P = .20). Two serious adverse events (atrial fibrillation in relation to physical exercise and death unrelated to rehabilitation) occurred in the cardiac rehabilitation group versus one in the usual care group (death unrelated to intervention) (P = .56). In the cardiac rehabilitation group 16 patients versus 7 in the usual care group reported non-serious adverse events (P = .047).

Conclusion Comprehensive cardiac rehabilitation had a positive effect on physical capacity compared with usual care, but not on mental health. Cardiac rehabilitation caused more non-serious adverse events. (Am Heart J 2016;181:120-9.)

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Cardiac rehabilitation has a beneficial effect on patients with ischemic heart disease, reducing hospital re-admissions and mortality in a cost-effective way as well as improving health-related quality of life (HRQoL). In patients with heart failure, rehabilitation reduces hospital readmissions and improves HRQoL.[1] Atrial fibrillation (AF) is the most common sustained arrhythmia and affects 2% of the population in the Western world. Hospitalization due to AF accounts for one third of admissions for cardiac arrhythmias.[2] Patients with AF have decreased physical capacity compared to the general population.[3] Catheter ablation is an invasive therapy to eliminate symptoms and the number of patients treated with it has increased rapidly in recent years.[2,4] Following ablation, HRQoL has been shown to increase[5,6] but decreased physical capacity often remains. Moreover, a qualitative study shows that lack of post treatment education and distress regarding palpitations, dyspnea, and fatigue are common.[7] AF recurrence

after ablation happens for up to 30% of the patients, causing distress and anxiety.[4,7]

Three randomized clinical trials exploring the effects of exercise training on physical capacity in patients with permanent AF have been published.[8-10] A meta-analysis found a statistically significant effect of exercise training on physical capacity (standardized mean difference 1.23, 95% CI 0.83 to 1.63; $P < .00001$; $I^2 = 0\%$; 3 trials; 118 participants).[11] According to the GRADE system[12] the overall quality of evidence in the three trials was considered low and no randomized trials including patients treated with catheter ablation were identified.[11] Such patients require special attention to improve physical capacity and restore HRQoL. Therefore, the aim of this randomized clinical trial was to investigate the effects of the addition of a comprehensive rehabilitation programme to usual care versus usual care alone on physical capacity and mental health in AF patients treated with ablation.

Patients and methods

The design and methods of the trial have previously been described in a design paper.[13] The trial was approved by the local ethics committee (number H-1-2011-135) and the Danish Data Protection Agency (reg. nr. 2007-58-0015). It was registered at ClinicalTrials.gov (NCT01523145), and complied with the Declaration of Helsinki and the ICMJE Recommendations for the Protection of Research Participants.[14]

Trial participants, setting, and recruitment

Consecutive patients planned for treatment with radiofrequency catheter ablation (RFA) for AF were screened for inclusion. Patients ≥18 years of age, Danish speaking, and providing oral and written informed consent were eligible for participation. Patients excluded were: those unable to understand trial instructions, pregnant or breastfeeding, reduced ability to follow the planned programme due to other physical illness, engaged in intense physical exercise or sports at a competitive level several times a week prior to RFA, and those who did not wish to participate, or were enrolled in a clinical trial that prohibited participation in additional trials.

While hospitalized patientes were approached by a trial investigator or trial nurse before the ablation with both oral and written information about the trial. After ablation patients were contacted again and written consent was obtained by all participants prior to inclusion.

The setting was two Danish university hospitals: Rigshospitalet and Gentofte Hospital.

Randomization and masking

To ensure allocation concealment, patients were centrally randomized 1:1 to comprehensive cardiac rehabilitation plus usual care (cardiac rehabilitation group) versus usual care (usual care group) using a computer-generated allocation sequence with a varying block size of 6, 8, and 12. Allocation was stratified according to paroxysmal or persistent AF and sex.[2]

In rehabilitation trials it is not possible to completely mask patients and interventional personnel. However, outcome assessment including ergospirometry testing, data management, and analyses were undertaken by research staff masked to group allocation.

Cardiac rehabilitation group

Patients in the experimental cardiac rehabilitation group followed a comprehensive programme consisting of exercise training and psycho-educational consultations plus usual care (see below).

Physical exercise program. The aim of the program was to improve exercise capacity. The program was developed in collaboration between European rehabilitation experts including doctors, physiotherapists and nurses. The exercise program was based on evidence of cardiac rehabilitation for patients with ischemic heart disease and heart failure.[15] The program was initiated one month after the ablation. We offered three weekly exercise sessions for 12 weeks. All patients followed an individualized exercise protocol which matched different needs. The program was initiated with one mandatory training session at the hospital using t-shirts with wireless integrated electrocardiogram electrodes (Corus-Fit Cardio and Corus Exercise Assistant, V.2.0.16, Finland). We offered the continuing physical exercise program in three locations according to the patient's preference: (1) supervised training at hospital; (2) local trial-protocol-certified, supervised facility; or (3) home-based training with contact to a physiotherapist when needed. The training program consisted of graduated cardiovascular training based on intensity prescription using the Borg 15-point scale[16] and strength exercises altered stepwise during training sessions. Training intensity was progressively increased during the 12 weeks. To monitor the training, individual training diaries and heart rate monitors were used (Polar Watch, Polar HR RS 400 monitors, Polar Electro, Finland).

Psycho-educational consultations. The aim of the consultations was to provide emotional support and improve coping skills and illness appraisal in order to enable patients to respond appropriately to physical and psychological symptoms. Education and information about AF prepared the patients for expected symptoms and a consultation guide was developed to ensure that certain areas were discussed, e.g., the ablation and fear of AF recurrence. The psycho-educational consultations were inspired by RR Parse's Human Becoming Practice Methodologies theory.[17] Furthermore, the consultations complied with recommendations on the use of patient education and psychosocial support in secondary prevention.[18,19] Two cardiac care nurses were trained in the theory and conducted the consultations, a physician

could be contacted if needed. The first of the four consultations was approximately 1 month after discharge and was repeated once every 5–7 weeks up till 6 months after ablation. Consultations were performed face-to-face or by telephone.

Usual care group

The usual care group followed usual care for patients treated for AF with RFA, which includes a 3–6 month follow-up consultation with a physician at the treating hospital and no further rehabilitation or after-care. Usual care was the same on both included hospitals. As long-term follow up is still in progress patients are contacted at 12 and 24 months for outcome assessments. Data from months 12 and 24 will be reported elsewhere.

Outcome evaluation

Both groups underwent outcome assessments at 1, 4, and 6 months post-randomization.

Primary outcome: physical capacity (Vo_2 peak)

Physical capacity was measured according to a standardized protocol developed in accordance with guidelines after 1 and 4 months[20] using peak Vo_2 (ergospirometry testing (CPET) (Ergo-Spiro CS-200, Schiller, Switzerland)). Vo_2 peak was defined as the highest Vo_2 measured during the test found by a respiratory exchange ratio (RER) ≥T 1.10 or subjective exhaustion of the patient. A standardized ramp-protocol was used with an initial work load of 25 or 50 watts, increasing gradually by 12.5 watts every minute until peak exhaustion. A standardized guide was developed to encourage the patients equally.

Due to pitfalls in testing (such as calibration errors, flow errors, mask leakage), 48 (25%) test results had to be estimated, with no overrepresentation in either randomization group, using the following estimation equation: Vo_2 = 10.8 × (watt max/weight) + 3.5. The estimation was masked to allocation group and was validated on all patients' measurements, and compared with non-estimated values. In general the equation underestimated the Vo_2 peak.

Secondary outcome: mental health

Self-rated mental health was measured by the Short-Form 36 (SF-36) questionnaire[21] Mental Component Score (MCS), after 1, 4, and 6 months.

Safety

Ergospirometry testing was performed by specially trained personnel. Criteria for early termination of a test were formulated[13] and interim analysis performed.

Serious adverse events and non-serious adverse events

Deaths at 6 months were registered by patients' records. All serious adverse events associated with the physical exercise or ergospirometry testing were evaluated by a trial physician. Self-reported non-serious adverse events were registered by a patient reported questionnaire at 6 months. Resting echocardiogram was analyzed after end of intervention.

Statistical analysis

The analyzes were performed as intention-to-treat analysis with two-sided tests and significance level = 0.05 using SAS 9.3, SAS Enterprise Guide 5.1 and IBM SPSS.

On the basis of our primary outcome, Vo_2 peak, a difference between the cardiac rehabilitation and usual care groups of 3.0 mL kg^{-1} min^{-1} with a common standard deviation (SD) of 6.0 mL kg^{-1} min^{-1} in the usual care group was considered clinically relevant. With a power of 95% and a p value of less than 0.05, 105 patients in each group (210 in total) were needed.

All regression analyzes of continuous quantities were performed using proc. mixed (SAS 9.3) which applies the direct maximum likelihood method. When the outcome was measured twice, the repeated measures option was used with an unstructured covariance matrix. When it was measured thrice a choice was made among the unstructured, the compound symmetric, or the power function correlation structure based on the Bayesian information criterion and visual inspection of the estimated correlation matrices. Analyzes of longitudinal binary outcomes was conducted using proc. glimmix. The European Heart Rate Association (EHRA) score was analyzed using a non-parametric test (Mann-Whitney) comparing the distributions at each point in time.

All analyzes were adjusted for the protocol specified stratification variables (type of AF and sex), and (if included by design) the baseline value of the outcome.

To adjust the *P* values for multiplicity in the analysis of the primary and secondary outcome, parallel gate keeping was used.[22] A sensitivity analysis was carried out for the significant primary outcome to assess the potential impact of values missing not at random.[13] To evaluate the clinical effect size of the primary outcome, Cohen's *d* was calculated.

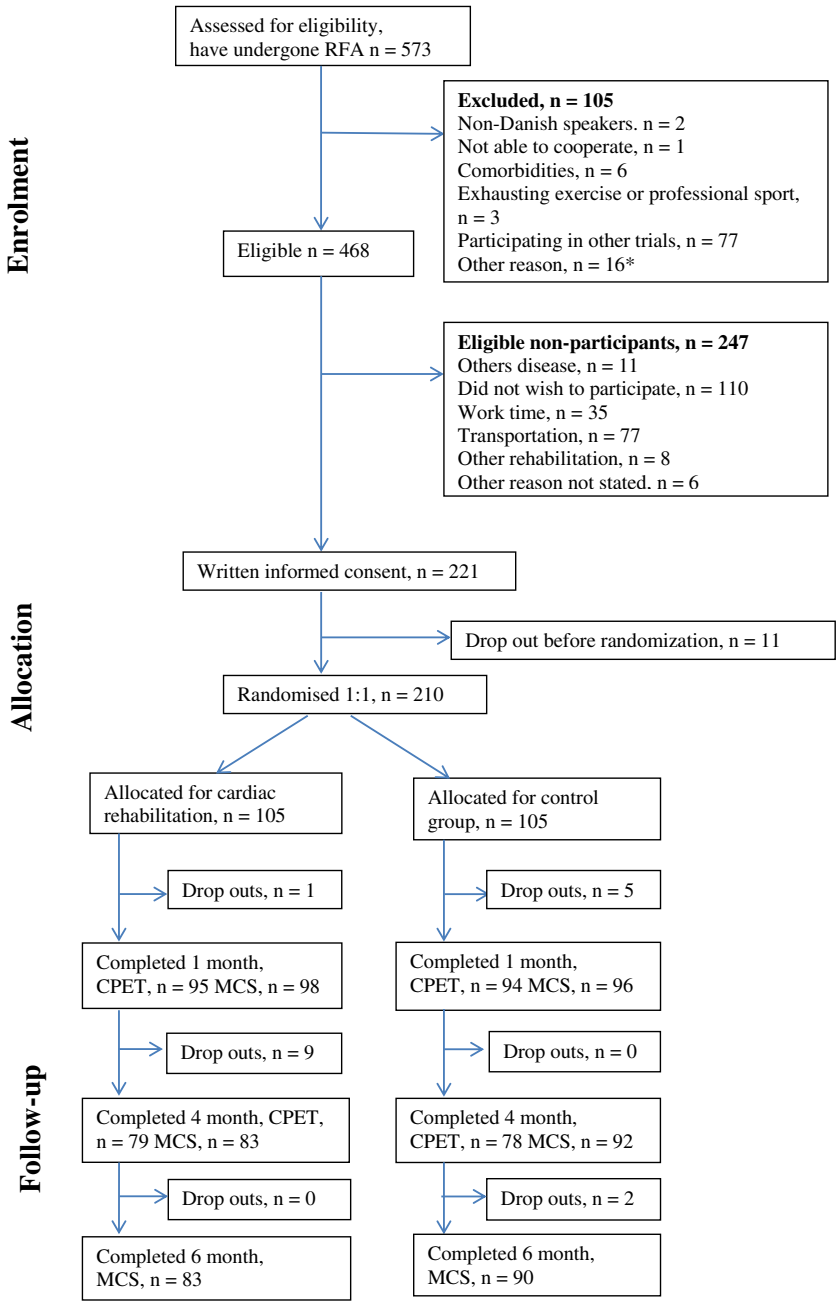
Adherence

Per-protocol levels of adherence of at least 75% of the exercise sessions evaluated by training diaries and polar registrations (≥27 sessions)[23] and at least ≥75% psycho-educational consultations (≥3 consultations) were defined as sufficient. Data were analyzed using two-sided *t*-tests and Mann-Whitney tests with a level of significance set at 5%.

Adverse events

Differences between cardiac rehabilitation versus usual care were assessed using the χ^2 test.

Figure



Flowchart. *For example, other arrhythmia, not possible to contact the patient.

Self-rated physical exercise level

Differences between cardiac rehabilitation versus usual care were assessed by the International Physical Activity Questionnaire and were analyzed using the Student *t* test.

Results

Between December 2011 and December 2013, we screened 573 patients undergoing RFA treatment. 221 consented (Figure). 11 patients dropped out before randomization, 8 withdrew their consent because of,

e.g., long travel time or comorbidity, and 3 were lost to follow-up (Figure). Patients declining participation compared to those that consented were more often patients with persistent AF, but did not differ regarding sex or distance to the hospital. Accordingly, 210 patients were randomized (105 per group). Throughout the trial, a number of patients withdrew their consent (eg, 1 patient in the cardiac rehabilitation group and 5 patients in the usual care group between allocation and 1 month follow-up) and a number of patients did not complete the outcome assessments (eg, 9 patients in the cardiac rehabilitation group did not do the CPET and 6 patients did not complete the MSC between allocation and 1 month follow-up).

Baseline

The cardiac rehabilitation and usual care groups were well matched at baseline (Table I). Seventy-four per cent were men, mean age 59 years, and mainly presenting with paroxysmal atrial fibrillation (74%). 57% had an EHRA score 1–2. Dominating symptoms of AF were palpitation, dizziness, dyspnoea, and fatigue.

Primary outcome

Physical capacity measured by V_{O_2} peak increased significantly in the rehabilitation group compared with the usual care group (P of main effect = 0.003 (see Table II)). In addition a significant interaction between intervention and time (P = .020) indicate an additional effect of cardiac rehabilitation as a function of time. The estimated mean square of V_{O_2} peak value at 1 month in the cardiac rehabilitation group was 22.1 mL kg^{-1} min^{-1} versus 20.1 mL kg^{-1} min^{-1} in the usual care group (p of difference = 0.036). At 4 months, the corresponding values were 24.3 mL kg^{-1} min^{-1} versus 20.7 mL kg^{-1} min^{-1} (p of difference = 0.0004). This between group difference corresponded to a Cohen's d of 0.50, i.e., a medium clinical effect of the cardiac rehabilitation program.

The sensitivity analyzes on the primary outcome V_{O_2} peak at 4 months showed that in the worst-case scenario, the p-value of the main effect of group allocation remained significant (P = .008), however, interaction between groups and time was not significant (P = .12).[13]

Secondary outcome

The self-reported SF-36 MCS did not demonstrate significant difference between the intervention and control group (53.8 points vs. 51.9 points, P = .20) (Table III). However there was a short lasting effect (P = .023) of the intervention after 4 months that was not present at 6 months (see Table III).

Serious adverse events and non-serious adverse events

Two deaths were registered; one in each group and both assessed as unrelated to the cardiac rehabilitation by trial physicians (Table IV). One serious adverse event was assessed as related to the cardiac rehabilitation when a patient was hospitalized due to AF during exercise training. In the cardiac rehabilitation group, 16/105 (15%) versus 7/105 (7%) in the usual care group reported non-serious adverse events (P = .047). These were mainly related to the musculoskeletal system. AF symptoms were reported by 3 patients in the cardiac rehabilitation group and 3 patients in the usual care group (see Table IV). Resting echocardiogram analyzes showed no difference between the groups at 1 and 4 months (P = .755).

Adherence

Among the 105 patients in the cardiac rehabilitation group, 51% adhered to the physical exercise program, 84% to the psycho-educational consultations, and 44%

Table I. Demographic and physical profile at baseline

	Cardiac rehabilitation (n = 105)	Usual care (n = 105)
Male sex, n (%)	74 (70)	77 (73)
Age years mean (±SD)	60 (±9)	59 (±12.25)
Body mass index mean (±SD) (kg/m^2)	27 (±4)	28 (±5.62)
Current smoking, n (%)	2 (2)	3 (3)
Type of AF		
Paroxysmal, n (%)	76 (72)	76 (72)
Persistent, n (%)	29 (28)	29 (28)
History of concomitant diseases		
Hypertension, n (%)	30 (29)	31 (30)
Diabetes mellitus, n (%)	4 (4)	5 (5)
Ischemic heart disease, n (%)	0	0
Palpitations, n (%)	68 (65)	53 (50)
Angina, n (%)	19 (18)	16 (15)
Dyspnoea, n (%)	62 (59)	64 (61)
Dizziness, n (%)	34 (32)	28 (27)
Fatigue, n (%)	45 (43)	57 (54)
Syncope, n (%)	2 (2)	3 (3)
Treatment		
Previous ablation, n (%)	41 (39)	49 (47)
Previous cardioversions, n (%)	49 (47)	54 (51)
Previous medical AF treatment, n (%)	100 (95)	100 (95)
Beta-blocker, n (%)	55 (52)	56 (53)
Calcium channel blocker, n (%)	22 (21)	28 (27)
Amiodarone, n (%)	20 (19)	12 (11)
ACE-inhibitor, n (%)	14 (13)	18 (17)
Digoxin, n (%)	11 (10)	7 (7)
Warfarin, n (%)	92 (88)	94 (90)
Dabigatran, n (%)	3 (3)	3 (3)
Statin, n (%)	28 (27)	37 (35)
EHRA score		
EHRA 1-2, n (%)	60 (57)	60 (57)
EHRA 3-4, n (%)	45 (43)	45 (43)
EHRA (Median)	(2)	(2)
CHA_2DS_2VASc score		
0, n (%)	30 (29)	37 (35)
≥1, n (%)	75 (71)	68 (65)

CHA_2DS_2VASc score, score of AF stroke risk; EHRA, European Heart Rhythm Association.

Table II. Physical test results of the primary outcome and exploratory outcomes of physical tests; estimated means at 1 and 4 months

	Cardiac rehabilitation		Usual care		*P* of main effect of cardiac rehabilitation	*P* of interaction between cardiac rehabilitation and time
	Month 1	Month 4	Month 1	Month 4		
Ergospirometry test						
Log(Vo_2-peak)* (mL kg^{-1} min^{-1}) *mean*	3.095 (22)	3.189 (24)	3.002 (20)	3.030 (21)	0.003	0.020
Log(Max power) (watt) *mean*	4.903 (135)	5.049 (156)	4.880 (132)	4.935 (139)	0.018	0.0003
Blood Pressure max (mm Hg) *mean*	203	208	198	202	0·19	0·83
6 minute walk test						
6MWT (meters) *mean*	548	592	559	576	0.88	0.02
Sit to stand test						
Log(sit to stand) (numbers) *mean*	2.6 (13.3)	2.8 (16.0)	2.7 (14.3)	2.7 (15.5)	0.6	0.004
EHRA score (the raw *mean* value)	2.00	1.79	2.23	1.81	na	na

Results of mixed model analyses of exercise data. Test of main effect of cardiac rehabilitation and of interaction between intervention and time.
6MWT, 6 minutes walking test; *EHRA*, European Heart Rhythm Association.
* Some variables were skewed and therefore log-transformed. In these instances the estimated means were back-transformed to the original scale using exp. The back-transformed numbers are presented in the parentheses.

adhered to both. At 4 months, those training ≥75% compared with those training <75% had 28.01 mL kg^{-1} min^{-1} compared to 25.12 mL kg^{-1} min^{-1} (P = .41). The main reason for patients not adhering to the training program was that the intervention was time consuming.

The patients in the cardiac rehabilitation group chose to do the physical-exercise program in the following locations; hospital (52.7%), municipality (44.4%), home-based (69.4%). 84% of the 105 patients attended at least 3 consultations with a nurse, 51% of the consultations were personal while 49% were telephone consultations.

Level of physical exercise in the usual care group

The patients in the usual care group did less physical exercise per week (3396 metabolic equivalents [METs]) compared to the patients in the cardiac rehabilitation group (4239 METs) however the difference was not significant (P = .066) measured by the International Physical Activity Questionnaire.

Discussion

To our knowledge this is the first randomized clinical trial that investigates the effect of comprehensive cardiac rehabilitation in AF patients treated with catheter ablation. The program comprised a physical exercise and psycho-educational component. In the cardiac rehabilitation group the primary outcome increased significantly compared with usual care, which indicates a short term effect on physical capacity after 4 months. No significant effect on the secondary outcome was noted after 6 months.

Despite that the usual care group was relatively physically active and no significant difference in METS was found between the cardiac rehabilitation and usual care group a statistically significant difference in favor of the cardiac rehabilitation group was found in physical capacity.

The finding of an effect on physical capacity is important since physical capacity is an independent predictor of cardiovascular events and all-cause mortality.[24,25] Moreover, associations between physical capacity, physical functional level, and mental functional level have been shown.[18] Physical capacity is a main clinical outcome of cardiac rehabilitation, independent of diagnosis.[1] The difference of 3.6 mL kg^{-1} min^{-1} (approximately 1 MET) found in our trial is probably clinically relevant, since large cohort studies show that for every 1 MET increase in physical capacity the mortality rate decreases for men by 17%[24] and for women by 14%.[25] Thus, if the demonstrated difference between the groups persists over time, one may speculate that the cardiac rehabilitation could also affect mortality. However, physical capacity is a surrogate for more patient relevant outcomes and needs validation in larger randomized clinical trials.[26]

The findings of physical capacity improvement following exercise-based intervention in patients with AF is in accordance with findings of two reviews.[27,28] Previous randomized trials[8-10] were smaller than this trial, and not based on formal sample size calculations. They may therefore be subject to bias leading to an overestimation of the effect of intervention.

In the CopenHeartRFA exercise capacity measured by Vo_2 peak was chosen as the primary outcome since this is recommended by experts in the field as the most reliable measuring tool, because it is easy and cheap to obtain.[8-10]

There could be a number of reasons for the lack of a between group difference in MCS at 6 months. Firstly, a large number of patients in both groups had higher MCS after 6 months following ablation, leaving little room for further improvement. The psycho-educational

Table III. Patient reported secondary and exploratory outcomes before and after cardiac rehabilitation and a comparison of the effect between the cardiac rehabilitation in the cardiac rehabilitation group to that of the cardiac rehabilitation in the usual care group

	Cardiac rehabilitation (N = 105)†		Usual care (N = 105)*		Cardiac rehabilitation	Usual care		
Quantity	Mean at baseline	Mean at 6 months	Mean at baseline	Mean at 6 months	6 months - baseline‡	6 months - baseline‡	95% CI	P‡
SF-36 quantities								
Bodily pain index	74.1	84.1	78.2	86.1	9.04	7.34	-7.64 to 5.47	0.74
General health perception	63.1	72.2	65.5	64.2	6.84	-1.61	-13.2 to –3.70	0.001
Mental health index	70.9	82.7	69.1	79.2	9.44	9.12	-5.90 to 5.61	0.96
Physical functioning index	81.4	87.0	80.7	86.8	4.28	4.83	-3.18 to 4.79	0.69
Role emotional index	59.2	83.9	68.3	82.8	21.7	12.7	-19.7 to 4.08	0.20
Role physical index	45.2	71.1	50.5	74.2	24.1	23.3	-14.5 to 13.0	0.92
Social functioning index	75.4	89.0	78.2	87.4	11.9	7.30	-11.6 to 2.01	0.17
Vitality index	51.0	68.8	50.6	64.9	15.4	13.6	-7.37 to 4.83	0.68
Physical Component Scale (PCS)	46.0	49.5	47.0	49.5	3.12	2.39	-2.98 to 1.61	0.56
Mental Component Scale (MCS)	45.7	53.8	46.4	51.9	6.82	4.62	-5.13 to 1.07	0.20
HADS quantities								
HADS-A§	5.21 (22.5%)	3.85 (11.0%)	5.79 (28.2%)	3.80 (7.3%)	-0.94	-1.63	-0.13 to 1.70	0.09(0.11)
HADS-D§	3.32 (8.1%)	2.92 (9.9%)	3.15 (8.7%)	2.36 (8.5%)	0.011	-0.41	-0.46 to 1.13	0.41

SF-36, Short Form 36; *HADS-A*, Hospital Anxiety and Depression Scale–Anxiety; *HADS-D*, Hospital Anxiety and Depression Scale–Depression.
* For 7 quantities 15.1% and for 13 quantities 16% of the delta values (6 months value minus baseline value) were missing.
† For all quantities 21.2% of the delta values (6 months value minus baseline value) were missing.
‡ The two distributions of each "6 months – baseline" quantity were assessed graphically and using tests for skewness and kurtosis. Most distributions were either normal or symmetric with heavy tales, one distribution were significantly skewed, however. The latter were accepted as being normal with reasonable approximation. In any events the *P* value should be considered a data reducing device designed to select promising hypothesis generating outcomes from the rest of the exploratory outcomes.
§ HADS_A and HADS_D were analyzed after transformation to a binary variable (1: if value >8, 0 otherwise). The percent of the values which were >8 are shown in parenthesis. Each binary quantity was analyzed using logistic regression with adjustment by the protocol specified variables (type of atrial fibrillation and sex) and the baseline value.

intervention dose may have been too low, or the intervention was not sufficiently targeted. Furthermore, other psycho-educational interventions might be more suitable, or the patients or some of the patients may not benefit from this type of intervention, recover sufficiently from the ablation treatment, and might not need additional support from health professionals.

This trial found no significant increase in serious adverse events or self-reported AF symptoms in the cardiac rehabilitation group compared with usual care. This is in line with findings of a review, suggesting that performing physical exercise leads to several physical health benefits and seems safe for patients with AF.[27] However, significantly more non-serious adverse events in the cardiac rehabilitation versus usual care were observed. These events were primarily musculoskeletal injuries and pain related to physical exercise performance.

Adherence to cardiac rehabilitation is a challenge and surveys have shown that across several countries only around 30% of eligible patients continue their participation in such programs.[29-31]

We found that the adherence was higher in the psycho-educational consultations (84%) than in the physical exercise program (51%) and that the overall adherence was 44%, which is higher than in previous surveys but leaves room for improvement. Karmali et al demonstrated in a systematic review that three out of eight RCT's (1167 participants) found significant improvements in adherence to cardiac rehabilitation after specific interventions that promoted adherence.[23] The main reason for not adhering to this intervention was that the intervention was very time consuming. We might have achieved higher adherence if we had been more active throughout the trial motivating and supporting the patients in following the programme.

The patients had the following options for location of their exercise intervention; home-based training, municipal setting, or continuous training at a heart center in a hospital setting. Previous studies have shown that supervised home-based training and center based training are equally beneficial with different training locations.[32]

Psycho-educational consultations were initiated within the first month after the ablation because of considerations of patient's insecurity of AF recurrence within the first three months. For safety reasons related to the femoral vein the physical exercise intervention was started one month after ablation. Observational studies have found that physical exercise can trigger AF symptoms in patients with AF and doing physical exercise has been described by patients with AF to be associated with fear of AF recurrence.[7,33] Therefore, the physical exercise intervention and the first

Table IV. Safety in the CopenHeart$_{RFA}$ trial: adverse and serious adverse events

	Cardiac rehabilitation n = 105 n of events (n of patients)	Usual care n = 105 n of events (n of patients)	Total	*P**
Patients with serious adverse events	2 (2)	1 (1)	3(3)	.56
Serious adverse events				
Deaths at 6 months	1(1)	1(1)	2(2)	
Other serious adverse events at 6 months†	1(1)		1(1)	
Patients with self-reported non-serious adverse events	16(16)	7(7)	23(23)	.047
AF symptoms during physical exercise	2(2)	1(1)	3(3)	
AF symptoms not related to physical exercise	1(1)	2(2)	3(3)	
Musculoskeletal injuries and pain	10(10)	4(4)	14(14)	
Dizziness	1(1)	0	1(1)	
Headache after exercise	1(1)	0	1(1)	
Hypertension	1(1)	0	1(1)	

Death was registered at 6 months; serious adverse events were associated with the cardiac rehabilitation or outcome measurement; non-serious adverse events were captured using a patient-reported questionnaire at 6 months with events due to physical exercise and negative events reported.
*P values were measured by Chi square; differences between the cardiac rehabilitation and usual care group.

training session were performed under supervision by research staff.

This trial has limitations. The primary outcome V_{O_2} peak was obtained using an ergospirometry bicycle whose output exhibits random temporal variations such as variation from day-to-day and time-of-the-day when the test was performed. Furthermore due to malfunctioning in 25% of the measurements the V_{O_2} peak was estimated blinded using the Watt max/weight using a standard formula. However, these conditions were the same for both groups and a convincing effect on maximum watt achievement was found (see Table II). Furthermore, to minimize detection bias, a manual had been developed to guide the personnel when encouraging patients. The results can be generalized to other patients treated for AF with low CHADS-VASc scores similar to this patient population.

The secondary outcome was measured on the SF-36 questionnaire, which is a patient-reported outcome that by nature is subjective relying on patients' memories with the risk of recall and other bias. The questionnaires were electronically distributed and patients completed them without the presence of a researcher. Data management and analysis was conducted by a blinded/masked statistician independently of the researchers who interpreted data.

In conclusion, our results are consistent with three previous randomized clinical trials showing a favorable effect of exercise-based cardiac rehabilitation on physical capacity in individuals with AF.[8-10] Our trial adds to that evidence and provides support for the recommendation of exercise-based rehabilitation for patients treated for AF with ablation, to increase physical capacity. Today, cardiac rehabilitation is not specified in guidelines for patients treated for AF with ablation, whereas follow-up is generally focused on procedure complications and medical treatment.[2,4,34]

Taken together, the short-term beneficial effects of exercise-based cardiac rehabilitation have been demonstrated, but long-term follow-up is warranted. Based on our trial, exercise-based rehabilitation seems safe. However, there were more symptoms and injuries from the musculoskeletal system in the exercise based rehabilitation group. The trial was not designed to study these effects and consequently the results are inconclusive due to the lack of power. In future trials, the focus should be on serious adverse events, non-serious adverse events, and AF symptoms. Additionally, attention should be drawn to designing and testing a psycho-educational intervention successfully reducing fear of AF recurrence and increasing perceived health.

Individual contributions

SSR in collaboration with SKB, ADZ, JHS, CG, JL, PW and JHS designed the trial. SSR, TBR, KLS and TLSM did the trial management, data collection and data management. PW, CG, JL and SSR conducted the statistical analyzes. SSR drafted the manuscript. All revised the manuscript critically. All have given their final approval of the version to be published. All authors meet the criteria in the ICMJE Authorship guidelines.

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