Cardiac Rehabilitation for Patients Treated for Atrial Fibrillation With Ablation Has Long-Term Effects
12-and 24-Month Follow-up Results From the Randomized CopenHeartRFA Trial

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Cardiac rehabilitation for patients treated for atrial fibrillation with ablation has long-term effects: 12 and 24 month follow-up results from the randomized CopenHeartRFA trial

Abstract:

Objective: To assess outcomes at 12 and 24 months following participation in a multidisciplinary cardiac rehabilitation program plus usual care compared with usual care alone for patients treated for atrial fibrillation with catheter ablation.

Design: Long-term follow-up on the randomized CopenHeartRFA trial.

Setting: Patients were enrolled and outcome assessed at the hospital and the intervention were carried out at the hospital or at local rehabilitation centers.

Participants: Patients treated for atrial fibrillation with catheter ablation included in the CopenHeartRFA trial.

Interventions: A six months cardiac rehabilitation program consisting of physical exercise and psycho-educational consultations plus usual care or usual care alone.

Main outcome Measures: Physical capacity was measured by peak oxygen uptake (VO2 peak) at 12 months and patient-reported outcomes on perceived health, anxiety and depression were collected at by validated questionnaires at 12 and 24 months. Information on hospital admissions and mortality was collected through national registers up to 24 months.

Results: Mean VO2 peak was higher at 12 months in the cardiac rehabilitation group (cardiac rehabilitation group: 25.82 ml/kg/min vs. usual care group, 22.43 ml/kg/min, p=0.003). A lower proportion of patients had high levels of anxiety at 24 months in the cardiac rehabilitation group compared to usual care (12% vs 24%, p=0.004). There was no difference in mortality or hospital admissions at 24 months between groups.

Conclusions: This long-term follow-up of a comprehensive multidisciplinary cardiac rehabilitation program for patients treated for atrial fibrillation with catheter ablation found sustained improvements with respect to physical capacity and anxiety compared to usual care but no difference on mortality or hospital admission.
Keywords: Atrial Fibrillation, Cardiac Rehabilitation, Patient Readmission, Patient Reported Outcome Measures, Quality of Life.

Abbreviations

AF: Atrial Fibrillation
AFEQT: The Specific Atrial Fibrillation Effect on Quality of life questionnaire
CPET: Cardiopulmonary exercise testing
DNPR: Danish National Patient Register
ESC: European Society of Cardiology
HADS-A: The Hospital Anxiety and Depression Scale – Anxiety
HADS-D: The Hospital Anxiety and Depression Scale - Depression
HRQoL: Health-related quality of life
MCS: Mental Component Scale
PCS: Physical Component Scale
RFA: Radiofrequency catheter ablation
SF-36: Short Form-36 questionnaire
VO₂ peak: Peak oxygen uptake
INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 2% of the adult population in the western world (1,2). The arrhythmia may give rise to symptoms such as palpitations, dyspnea, fatigue, dizziness, and rarely syncope and the disease is associated with decreased exercise capacity, and poor health-related quality of life (HRQoL) (1−4). Patients with AF have increased risk of mortality, severe stroke and heart failure (1). The prevalence of AF is increasing mainly due to an ageing population and the increased number of individuals living with chronic heart diseases (1,5). Consequently AF treatments aim to maintain or re-establish sinus rhythm, reduce symptoms and improve HRQoL (1,3). Radiofrequency catheter ablation (RFA) is seen as an effective treatment to reduce recurrent AF with a success rate of around 70% among patients with paroxysmal or persistent AF (1).

Prospective studies (6 to 36 months follow-up) show that HRQoL and exercise capacity increases after ablation (6–8). Cochrane systematic reviews demonstrate that exercise-based cardiac rehabilitation compared to usual care improves HRQoL for patients with ischemic heart disease (6 to 12 years follow-up) and heart failure (6 to 10 years follow-up) (9). Our Cochrane review (10) in patients with AF found a positive effect on short-term (8-24 weeks) exercise capacity following cardiac rehabilitation and limited data regarding the impact on mortality or hospitalization in available studies (10).

The CopenHeartRFA trial (11) was a multidisciplinary randomized trial designed to examine the impact of cardiac rehabilitation in AF patients treated with catheter ablation. A total of 210 patients were randomized to either cardiac rehabilitation plus usual care or to usual care alone. A positive effect on the primary outcome defined as exercise capacity measured by peak oxygen uptake (VO₂ peak) on cardiopulmonary exercise testing at 4 months (cardiac rehabilitation group: 24.3 mL/kg/min versus usual care: 20.7 mL/kg/min, p=0.003) and no effect (cardiac rehabilitation group: 53.8 points vs. usual care: 51.9 points p=0.20) on perceived mental health measured by the Mental Component Scale (MCS) on the Short Form-36 questionnaire (SF-36), at 6 months were found (12).

The objective of this study was to report the 12 and 24 month follow-up results of the CopenHeartRFA trial on the outcomes of exercise capacity, perceived health, HRQoL, anxiety and depressive symptoms, mortality, and hospital admission.
METHODS

We conducted the CopenHeartRFA randomized clinical trial to investigate the effects of a comprehensive cardiac rehabilitation program. The design, methods and intervention of the trial are described in detail in the published protocol (11) and the primary results have been published (12).

The follow-up data reported in this study were collected at 12 and 24 months after inclusion. In the following the CopenHeartRFA trial is briefly outlined.

Participants

Consecutive patients from two Danish university hospitals treated with ablation for AF were screened for inclusion. Inclusion criteria were: ≥18 years of age, Danish speaking, and providing signed informed consent.

Exclusion criteria: those unable to understand trial instructions, pregnant or breastfeeding, reduced ability to follow the planned program due to other physical illness, engaged in intense physical exercise or sports at a competitive level, patients who did not wish to participate, or were enrolled in a clinical trial that prohibited participation in additional trials. Patients were approached by one of the research team while in hospital for ablation. After oral and written information, the consent was signed and returned, patients took the time they needed and involved relatives before consent was signed if wanted.

Intervention

Patients were randomized 1:1 to comprehensive cardiac rehabilitation plus usual care vs. usual care stratified by age and type of AF.

The intervention consisted of physical exercise and Psycho-educational consultations. A 12 weeks physical exercise program aimed at increasing exercise capacity. The program was initiated with one mandatory training session at the hospital by trial physical therapists. The following program was offered at a local trial-protocol-certified supervised hospital; the municipality where the patient lived; or home-based training. The training program consisted of graduated cardiovascular training based on intensity prescription using the Borg 15-point scale (13) and strength exercises altered stepwise during training sessions. The psycho-educational consultations had the aim of providing emotional support and improve coping skills and illness appraisal to
enable the patients to respond appropriately to physical and psychological symptoms. Education and information about AF prepared the patients for expected symptoms. The psycho-educational consultations were inspired by R.R. Parse’s Human Becoming Practice Methodology (14,15) and complied with recommendations on the use of patient education and psychosocial support in secondary prevention (16,17). Patients were offered four consultations face-to-face or by telephone over 6 months with a nurse. At the end of the intervention no systematic information about further physical exercise or mental well-being were given to the patients to ensure adherence to the intervention after the trial was over.

**Data collection**

In the short-term trial a sample size calculation was performed. The primary outcome was exercise capacity measured at four months and the secondary outcome were mental health measured at six months. The follow-up data reported in this study were collected 12 and 24 months after inclusion. At 12 months patients were invited to perform a physical exercise test at the hospital. All patients who had an email address and accepted participation received the electronic questionnaire at home. Others had a paper version mailed to their home address.

**Exercise capacity testing**

Exercise capacity was measured by VO₂ peak determined by cardiopulmonary exercise testing (CPET) on an ergometer bicycle (Ergo-Spiro CS-200, Schiller, Switzerland) following standardized guidelines (18). A standardized ramp-protocol was used starting with a workload of 25 or 50 watts depending on the patient’s prior fitness level, increasing gradually by 12.5 watts per minute until peak exhaustion occurred. Peak exhaustion was when subjective exhaustion of the patient was reached. Encouragement of the patient followed a standardized guide developed for this trial. During the test period electrocardiogram abnormalities (ST depression, ST elevation, Q- and T-wave changes, supraventricular or ventricular arrhythmias) and blood pressure were observed and documented. VO₂ peak was defined as the peak VO₂ reached during the test. Blinded research assistants performed the tests. For initiation and/or termination of the test, safety criteria were defined prior to the trial beginning.
When CPET was carried out, problems with VO₂ flow measuring or non-plausible measured VO₂ values did occur, therefore some tests had to be estimated, using the following equation: \( \text{VO}_2 = 10.8 \times \left( \frac{\text{Watt max}}{\text{weight}} \right) + 3.5 \) (19).

In addition to the CPET a six-minute walking test and a sit to stand test were carried out.

*Patient-reported outcomes*

Patients completed questionnaires at baseline, 1 month, 4 months, 6 months, 12 months, and 24 months to obtain information about:

**Perceived health** – *Short-Form-36 (SF-36)* is a generic measure of self-reported health. The reliability of SF-36 is considered high. The scale consists of 36 items, including the measurement of the following eight health attributes: physical functioning, physical roles, bodily pain, general health, vitality, social functioning, emotional roles and mental health. The score ranges from 0 to 100 with higher scores indicating better perceived health, and two summary scales; a physical component scale (PCS) and a mental component scale (MCS). Reliability statistics have exceeded (Cronbach’s alpha) a minimum of 0.90 for PCS and MCS (20) showing a high internal consistency (21).

**Anxiety and depression** – *The Hospital Anxiety and Depression Scale (HADS)*. In clinical practice HADS is a commonly used tool to identify patients with symptoms of clinically relevant symptoms of anxiety and/or depression (21). The instrument is extensively validated and is now recommended for use in cardiac patients (22). HADS is a 14 item questionnaire with two sub-scales, an anxiety scale (HADS-A) and a depression scale (HADS-D). Each scale includes seven items rated on a 4 point scale from 0-3. A cut off score of 8 was used since scores of 0 to 7 for either sub-scales are regarded as normal and scores of 8 and above indicate the presence of a mood disorder. The Cronbach’s alpha exceeds 0.83 and 0.82 for HADS-A and HADS-D, respectively (23).
Disease specific health – The Specific Atrial Fibrillation Effect on Quality of life (AFEQT) questionnaire (24) is developed and validated for patients with AF and is used in various clinical settings. AFEQT consists of 20-items distributed on a seven-step Likert scale measuring four domains: symptoms related to AF, daily activities, concern about treatment and treatment satisfaction. Symptoms, daily activities, and concern about treatment constitutes a global score. Raw scores within each domain is calculated into a 0 – 100 score. Low scores indicate the most serious symptoms and limitations (24,25).

Registry data
Information on all-cause mortality and hospital admission were obtained using the Danish Civil Registration System (26) and the Danish National Patient Registry (27). Both registers are nationwide with none lost to follow-up. Data were collected two years (730 days) after randomization date. Hospital admissions were divided into elective and acute admissions, admissions due to atrial fibrillation (ICD-10, I48) and emergency room contacts (patients with AF are often seen in the emergency room for direct current conversion if needed).

Ethics
This 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.

Statistical analysis
All analyses were undertaken according to the principle of intention-to-treat and results reported according to the CONSORT guidelines (28). We undertook a mixed effects repeated measures regression analysis (using the command ‘xtmixed’) comparing primary, secondary, and exploratory outcomes between cardiac rehabilitation and usual care groups at all follow-up points reporting the p-value for between group differences and the p-value for the interaction between group difference and time. All models included adjustment for stratification variables (type of AF and sex). In addition, we undertook a post-hoc analysis of VO₂ where we categorized participants according to
whether they achieved a minimally important clinical increase in peak VO₂ of 3 ml/kg/min (11) between 1
month and either 4 or 12 months follow-up. Proportions of patients achieving this minimally important clinical
increase between groups were compared using logistic regression (with adjustment as above).
Time to first hospital admission and mortality was analyzed using Kaplan–Meier survival plots. Differences in
admissions and mortality were tested with chi²-tests and mean number of admissions were tested using t-tests.
All analyses were undertaken using STATA v.14 with two-sided tests and statistical significance achieved level
at p ≤ 0.05.

RESULTS
Baseline characteristics of participants are reported in a prior publication (12) and is presented in an
Supplementary File. A total of 210 patients ablated for AF were included. Most were men (74%), mean age was
59 years, and the majority of patients were categorized as having paroxysmal atrial fibrillation (74%). The
dominating symptoms patients reported were palpitations, dyspnea, dizziness, and fatigue.
In total, 210 patients were included (105 in the cardiac rehabilitation group and 105 in the usual care group).
This study reports long term follow-up results and it was observed that at 12 months 67 patients in the cardiac
rehabilitation group and 72 in the usual care group completed the exercise capacity testing. At 24 months 78
patients (74.3%) in the cardiac rehabilitation group and 81 patients (77.1%) in the usual care group completed
the MCS (Figure 1).

Exercise capacity outcomes
Mean exercise capacity measured by VO₂ peak at 12 months was higher in the cardiac rehabilitation group
(25.82 ml/kg/min) compared to the usual care group (22.43 ml/kg/min) (The p-value of the main effect of
cardiac rehabilitation p=0.003 and the p-value of interaction between intervention and time were p=0.10).
Additional physical exploratory outcomes also demonstrated statistically significant effects over time in favor
of the rehabilitation group (Table 1), including max power (p=0.002), six-minute walking test (p=0.002) and sit
to stand test (p=0.005). In total 9 patients tests were estimated using the estimation equation: VO₂ = 10.8 ×
(watt max/weight) + 3.5 due to pitfalls in testing like mask leakage or calibration errors.
**Patient-reported outcomes**

No statistically significant differences between groups were found for the mental or physical component summary scales on SF-36, nor in any of the eight subscales except for the subscale General Health (p of interaction between intervention and time = 0.02) (Table 2).

No statistically significant differences between groups were found for the four domains of AFEQT or AFEQT-global (Table 2). Over time the AFEQT-global (p of interaction between intervention and time= 0.04) and AFEQT-treatment (P of interaction between intervention and time=0.03) showed a significant effect in favor of the rehabilitation group.

HADS-A showed a significant difference over time (p=0.004) in favor of the cardiac rehabilitation group. For the rehabilitation group the mean value decreased from baseline (5.81 points) to 24 months (3.90 points), while the mean score in the usual care group increased slightly from baseline (4.47 points) to 24 months (4.73 points).

For clinical symptoms of anxiety defined as score of 8 and above on HADS-A, a decrease from 33.7% at baseline to 12.8% at 24 months was observed in the rehabilitation group, and a decrease from 28.6% at baseline to 23.8% at 24 months in the usual care group.

**Mortality and readmission**

During the follow-up period two patients died, one in the cardiac rehabilitation group and one in the usual care group. In total 131 patients were admitted during the two years period (cardiac rehabilitation group: n=71, 68%, usual care group: n=60, 57%, p=0.12). The number of admissions registered in the cardiac rehabilitation group were n=327 compared with the usual care group n=247 (p=0.51). The cardiac rehabilitation group did, in general, have a higher admission rate and a higher number of emergency room contacts during follow-up compared with the usual care group, but none of these findings were statistically significant (Table 3 and Figure 2).

**DISCUSSION**
This reports the long-term follow-up outcomes for patients treated with ablation for AF following participation in the CopenHeartRFA comprehensive multidisciplinary cardiac rehabilitation program. The main findings included favorable effects for patients in the cardiac rehabilitation group in relation to: exercise capacity after one year; anxiety scores after two years with scores decreasing in the cardiac rehabilitation group and increasing in the usual care group; in additional AF specific perceived health scores; and no between group differences in mortality or hospital admissions within two years after inclusion in the trial. The average improvement with cardiac rehabilitation compared to control at 12-months in both exercise capacity (VO2peak increase of 3.4 ml/kg/min) and anxiety (HADS-A reduction of 0.8 units) are both clinical meaningful (29,30).

To our knowledge there are no trials that include a physical exercise component for patients diagnosed with AF that have longer exercise capacity follow-up than 20 weeks (31). A sub-study to the HF-ACTION trial (32) included 382 patients with AF and chronic heart failure and tested a supervised aerobic exercise training program (12 weeks, 3 sessions per week), followed by home-based exercise training for an additional 2 years had a mean 2.6 years follow-up (33). No difference was found on the composite endpoint hospital admission and mortality between groups (HR, 1.15; 95% CI 0.98 to 1.35; p =0.09) (33). That result is in line with our results, since we also find no difference between groups on mortality and hospitalization.

Mean VO2 peak was lower at baseline in the HF-ACTION trial (mean=13.4 ml/kg/min (SD: 10.7, 16.3)) (33) compared to baseline VO2 peak in our study (cardiac rehabilitation group: mean 24.0 ml/kg/min versus usual care: mean 21.9 ml/kg/min). The reason for the difference is most likely that patients in the HF-ACTION trial had heart failure and AF, where the patients in our study had undergone ablation for AF, which means that some patients were in sinus rhythm and some in AF. The likely mechanisms behind the effect of physical exercise for patients with AF are that physical exercise decreases the heart rate at rest and while exercising and increases exercise capacity in general (10,34,35). Since a significant difference on exercise capacity (cardiac rehabilitation group: 25.82 ml/kg/min vs. usual care group 22.43 ml/kg/min, p=0.003) is found in our study at 12 months follow-up the positive effects of physical activity are likely present.

Wood and colleges have explored life after ablation for AF with six months follow-up (36). They found that patients reported lower anxiety scores on questionnaires six months after ablation compared to baseline (mean
The authors discussed that anxiety could be related to a patient’s not feeling their recovery was normal and that more in-depth information about expectations after ablation may decrease anxiety symptoms (36). A difference of 11 points was found in favor of the rehabilitation group in this study measured on HADS-A, which could support the discussion by Wood and colleagues. The negative impact of anxiety on patients with AF include physiological factors that stimulate the autonomic nervous system that then release the production of catecholamines, increase the blood pressure, decrease the plasma volume, contractions of the coronary atria, thrombocyte activity, coagulation and inflammation. As a consequence, the patient may be at increased risk of thrombogenesis, arrhythmia, decreased heart rate variability, increased myocardial oxygen need and subsequent myocardial ischemia, and decreased left ventricular contractile function (37). In addition, patients who are anxious, often practice an unhealthy lifestyle including; smoking, excessive alcohol consumption, unhealthy dietary habits, poor sleep quality and physical inactivity (38–41).

The long-term evidence for participating in cardiac rehabilitation for patients with heart failure or ischemic heart disease has been identified with a follow-up period of 6-120 months, including 98,093 patients (42). The rehabilitation programs included physical exercise and some trials had an additional psychological- and educational component. Positive outcomes in terms of reduced hospital admissions and improved HRQoL were found. However, it is not definitely known whether these favorable outcomes can be applied to patients with AF and therefore cardia rehabilitation is currently not recommended in the European Society of Cardiology AF guidelines (1). Nevertheless, this study of long-term outcomes has shown positive long-term effects in terms of exercise capacity, anxiety and AF related health and patients highlight the positive outcomes and effect that participating in a cardiac rehabilitation program has on their life (43) and, therefore, existing evidence on cardiac rehabilitation for patients with AF should be considered future guidelines.

**Study limitations**

This study was not formally powered to examine the difference in outcomes at long-term follow-up in the CopenHeartRFA trial population. The power calculation for the short term follow-up was calculated from the
primary outcome that were physical capacity measured by VO2 peak and not clinical events, like mortality (11,12). The methods used to gather data could have introduced some bias. We used an ergospirometry bicycle to measure VO2 peak where day-to-day and time-of-the-day variation results can vary, however these variations would presumably have been present in both randomization groups. Data on mental health were collected by questionnaires emailed to patients. Using questionnaires introduce recall bias, since it is relying on patients' memories. Data on mortality and re-admissions were obtained through registers. Data collected in registers can contain inaccuracies, for example, because of lack of registration and incorrect coding for disease or procedures and inaccuracy has been found between clinical databases and registries (44).

Since the patients did not have an implanted loop-recorder we did/do not know which patients were in sinus rhythm and which were in AF and thus we were unable to factor this valuable information into the interpretation of results.

**Conclusion**

In conclusion, this latest report of the CopenHeartRFA trial shows that exercise capacity were slightly higher and anxiety levels were lower in patients with AF treated with ablation following a comprehensive cardiac rehabilitation program at 12-24 months. We found too few events to conclude on all-cause mortality or hospital admissions after 12 and 24 months.

However, further studies are needed in the field of rehabilitation for patients treated for AF. These studies should not only report short-term effects but also include long-term effects on serious adverse events, non-serious adverse events, AF symptoms including permanent heart rhythm recording with a e.g. a loop-recorder and patient reported outcomes.

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**Conflict of interest:**

The authors declare the following conflicts of interest: Dr XXX reports grants, personal fees and other from Medtronic, grants from Gilead, outside the submitted work.
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FIGURE LEGENDS

Figure 1: Flowchart

Figure 2: Admission plots
  • Figure 2a: Total admissions
  • Figure 2b: Elective admissions
  • Figure 2c: Acute admissions
  • Figure 2d: Emergency room visits
  • Figure 2e: Admission with primary or secondary diagnosis of atrial fibrillation