The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeartRFA trial protocol

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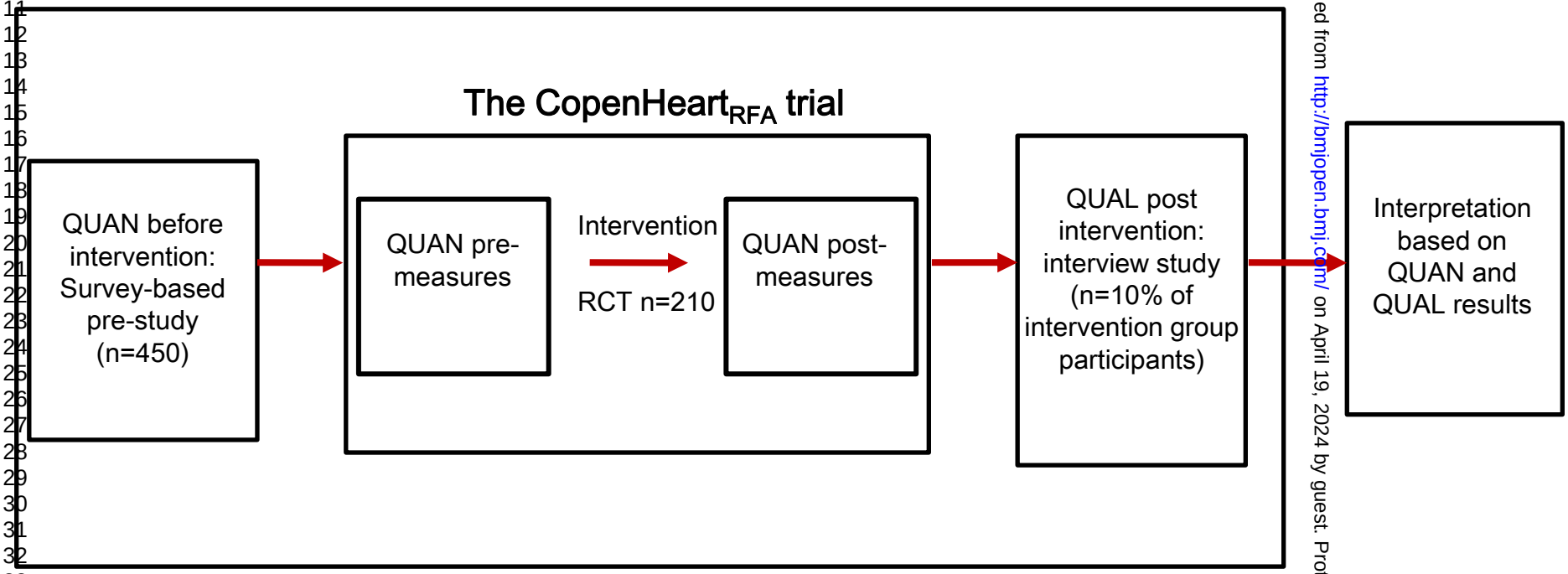
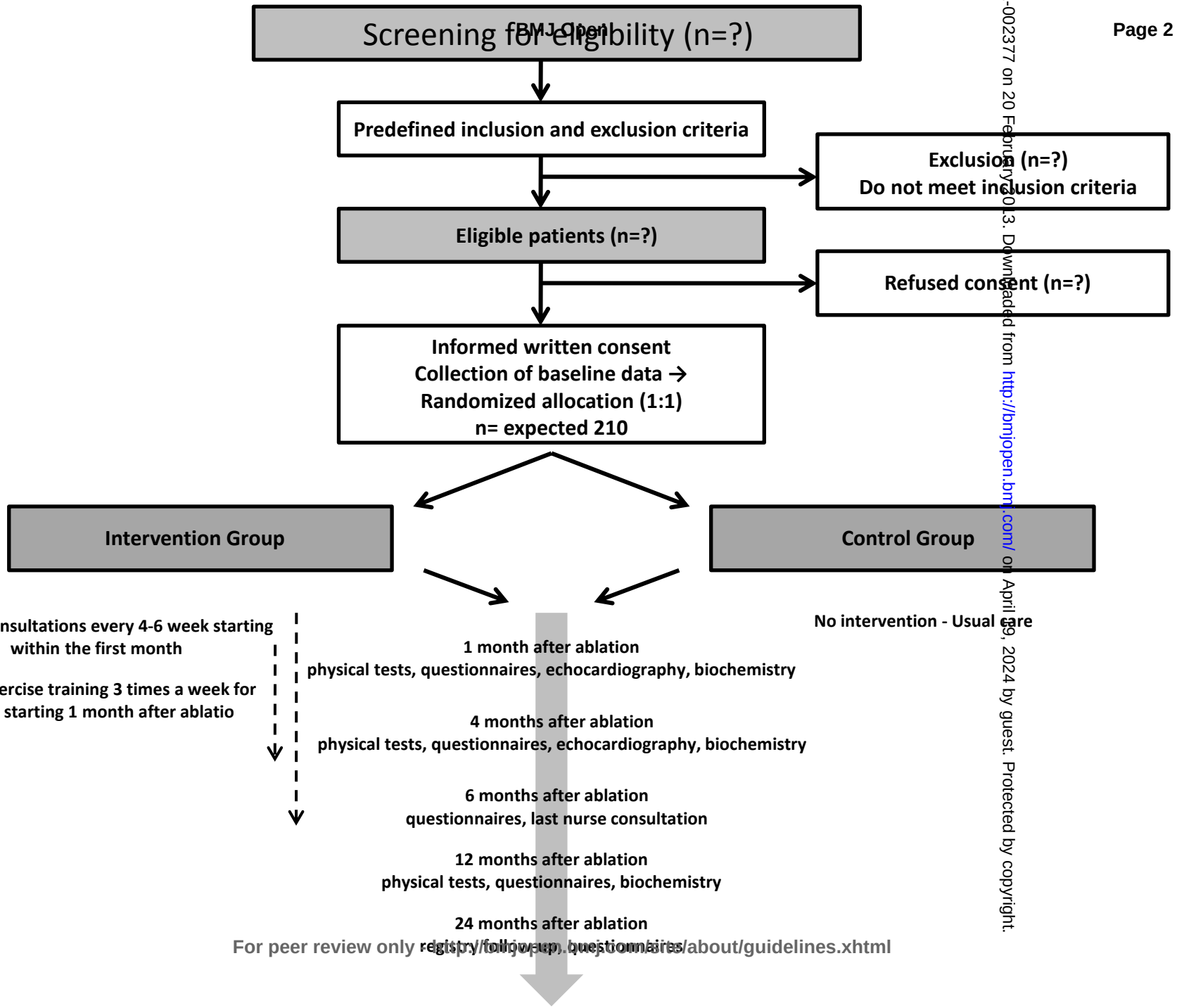


Figure 1. The CopenHeart$_{RFA}$ trial. Mixed methods research design. Embedded Experimental Model. QUAN= quantitative data, QUAL= qualitative data



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-7
	2b	Specific objectives or hypotheses	7 +9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11-17
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	17-21
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	20-21
	7b	When applicable, explanation of any interim analyses and stopping guidelines	23-24
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10-11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10-11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	11 + 21

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	21-23
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	24-25
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	27-28
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	28
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			25-26
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	29

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeart$_{RFA}$ trial protocol

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Keywords: atrial fibrillation, cardiac rehabilitation, physical exercise, psycho-education

Article summary

Article focus

- The CopenHeart$_{RFA}$ trial is a randomised clinical trial investigating the effects of comprehensive cardiac rehabilitation versus usual care for patients treated for atrial fibrillation (AF) with ablation.
- The hypothesis is that comprehensive cardiac rehabilitation improves physical capacity and mental health.
- Using a mixed methods approach, a broad range of outcome measures are collected to evaluate the intervention.

Key messages

- AF affects 1-2% of the population. Patients with AF experience diminished quality of life and are afraid to do physical exercise after treatment with ablation.
- No studies exploring the effects of rehabilitation of patients treated for AF with ablation have been published.
- This trial is the first to examine physical functioning and to test a comprehensive rehabilitation programme on a large population of patients treated for AF with ablation.

CopenHeart$_{RFA}$ will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for AF with ablation.

Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials with central randomisation, multi-centre participation, blinded assessment and analysis.
- We are aware of the day to day variation that can appear when carrying out ergospirometry, in testing and that the performance can depend on the individual tester. Accordingly, we will interpret the findings conservatively.

Abstract

Introduction

Atrial fibrillation affects almost 2% of the population in the Western world. To preserve sinus rhythm, ablation is undertaken in symptomatic patients. Observational studies show that patients with atrial fibrillation often report low quality of life and are less prone to be physically active due to fear of triggering fibrillation. Small trials indicates that exercise training has a positive effect on exercise capacity and mental health, and both patients with recurrent atrial fibrillation and in sinus rhythm may benefit from rehabilitation in managing life after ablation. No randomised trials have been published on cardiac rehabilitation for atrial fibrillation patients treated with ablation that includes exercise and psycho-educational components.

Aim

To test the effects of an integrated cardiac rehabilitation programme versus treatment as usual for patients with atrial fibrillation treated with ablation.

Methods and analysis design

The trial is a multicentre parallel arm design with 1:1 randomisation to the intervention and control group with blinded outcome assessment. 210 patients treated for atrial fibrillation with radiofrequency ablation will be included. The intervention consists of a rehabilitation programme including four psycho-educative consultations with a specially trained nurse and 12 weeks of individualised exercise training, plus the standard medical follow-up. Patients in the control group will receive the standard medical follow-up. The primary outcome measure is exercise capacity measured by VO_2 peak. The secondary outcome measure is self-rated mental health measured by the Short Form 36 questionnaire. Post intervention, qualitative interviews will be conducted in 10% of the intervention group.

Ethics and dissemination

The protocol is approved by the regional research ethics committee (number. H-1-2011-135), the Danish Data Protection Agency (reg. nr. 2007-58-0015) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may possibly impact on rehabilitation guidelines.

Registration: Clinicaltrials.gov identifier: NCT01523145

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and affects 2% of the population in the Western world.[1-3] Typical symptoms are palpitations, dyspnoea, fatigue, dizziness, and syncope. Patients' symptoms and the length of periods in AF are highly variable both for the individual and between patients.[4-6] AF is associated with increased risk of stroke, other thromboembolic events, and heart failure.[6-8] Hospitalisations due to AF account for one third of all admissions for cardiac arrhythmias.[8] As the prevalence of AF increases with age, the incidence of AF is increasing due to an ageing population.[2, 9, 10] After 40 years of age, the lifetime risk of developing AF is 25%. [11] The annual cost of AF is high in comparison with other diseases.[12] Therefore, AF has become an economic burden and this will continue to increase over the coming decades.[13] Thus, AF has now become a health, social and economic challenge in the Western world.[14]

Primary treatment goals for individuals with AF are re-establishing and maintaining sinus rhythm, decreasing AF symptoms, and prevention of complications. In accordance with current national and international guidelines, radiofrequency ablation (RFA) is often undertaken in symptomatic patients. RFA is an invasive treatment, intended to cure AF and has a success rate of 77% versus 52% for antiarrhythmic medication.[15] In Denmark, around 600 RFAs are conducted annually at two heart centres.

A cohort study of 655 patients from a randomised trial found that AF symptoms are a negative predictor for patients' physical capacity,[16] and in the presence of AF, patients do fewer physical activities.[17] Smaller observational studies and a randomised trial investigating the effect of exercise

training on AF patients found increased exercise capacity and a decreased resting heart rate after training.[18-20]

Previous studies show significantly impaired quality of life in patients with AF compared to healthy controls measured by the questionnaire Short Form 36 (SF-36). The general health component (± standard deviation) was 54±21 in AF patients compared to 78±17 in healthy controls.[21] A qualitative study demonstrated that educational help after AF treatment is lacking, even though symptoms of distress and lack of self-management regarding symptoms like palpitations, dyspnoea, and fatigue are common.[22] Furthermore, small observational studies indicate a positive effect of exercise training on patients with AF in terms of mental health and physical activity (15% increase of VO_2).[18, 19] However, these findings need confirmation in larger randomised clinical trials.

Secondary prevention initiatives including cardiac rehabilitation are recommended by the European Society of Cardiology (ESC).[23] Although evidence of its efficacy is strong, general cardiac rehabilitation is still poorly implemented and often only on selected populations thus the development of full comprehensive preventive programmes, according to the ESC recommendations is warranted.[24] Studies exploring the effects of rehabilitation of patients treated for AF are lacking. As there is no evidence of its efficacy, the rehabilitation provided is presumably often suboptimal or totally lacking. Lessons, however, might be learned from rehabilitation studies in patients with related cardiac conditions. The positive effects of cardiac rehabilitation have been well documented, particularly in patients with coronary heart disease and heart failure, where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way,[25, 26] as well as improve quality of life.[27] More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve

replacement surgery [28] and an increase in peak VO_2 of 2.3±2.2 (SD) ml/kg per minute in the intervention group compared with −0.3±2.1 (SD) ml/kg per minute in the control group, as well as a significant change in quality of life in older patients with heart failure.[29] Traditional cardiac rehabilitation has focused on physical training and standardized programmes, but studies indicate that individualized content and supervised exercise components are key design characteristics for improving outcomes.[30] In addition to exercise training, there is evidence to support interventions that include patient education, which in patients with coronary heart disease has been shown to improve health related quality of life and decrease healthcare costs, [31] and psychological support, which has been shown to improve psychological symptoms in patients with coronary heart disease, such as depression and anxiety.[32] Evidence on the efficacy of comprehensive interventions for patients treated for AF, however, is needed.

Interventions designed to cover both physical and psychological problems may provide the best method for optimising functioning and enhancing quality of life.[33] We have not been able to identify randomised trials or observational studies in patients who have undergone RFA for AF that offer both psycho-educational intervention and physical training. Therefore, the CopenHeart$_{RFA}$ trial was undertaken with the aim of testing a rehabilitation programme consisting of physical exercise and a psycho-educational intervention versus treatment as usual for RFA treated AF patients.

Methods

Design

Major parts of the method section and trial design in this paper are similar to two other randomised clinical trials, CopenHeart$_{VR}$ and CopenHeart$_{IE}$, and therefore sections from this paper will be copied in these trial protocols (Sibilitz KL et al. *Effect of integrated cardiac rehabilitation versus treatment as usual for patients with isolated heart valve surgery: The randomised CopenHeart*

valvular trial protocol. drafted October 2012; and Rasmussen TB et al. *A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for infective endocarditis – the CopenHeart$_{IE}$.* Accepted for publication, BMJ Open, October 2012).

The CopenHeart$_{RFA}$ trial is a multi-centre, multidisciplinary randomised clinical superiority trial. Secondary, qualitative data are also collected and the two methods are integrated by applying a mixed method embedded experimental design (Figure 1).[34, 35] Quantitative methods are applied, with specified quantitative pre- and post-measures to evaluate the effect of the experimental intervention. Alongside quantitative measurements, qualitative data will be collected. The premise of mixed methods research is that the use of qualitative and quantitative approaches in combination provides a better understanding of the research problems than either approach alone, because different types of questions require different types of data and that mixed methods research provides strengths that offset the weaknesses of both qualitative and quantitative research.[34] The methods are integrated by applying a mixed method embedded experimental design and include qualitative data to develop the intervention and to examine the process of the intervention and the results of the trial (see Figure 1).[34, 35] The rationale for this approach is that the quantitative findings provide a general understanding of the research problem through statistical results while qualitative findings refine and explain the results by exploring participants' views in greater detail. Evaluation using qualitative research methods is increasingly promoted in evidence-based rehabilitation.[36-39] Qualitative research alongside randomised controlled trials can contribute in several ways to the development and evaluation of complex healthcare interventions and may be particularly useful in evaluating interventions that involve social and behavioural processes that are difficult to explore or capture using quantitative methods alone.[40] As patient participation is paramount for the efficacy of the rehabilitation,[41] we find it highly valuable to include the patients' perspective in the

development and evaluation of the intervention. This paper presents the study protocol for the CopenHeart$_{RFA}$ randomised clinical trial. The complementary studies are briefly described in a separate section.

The trial is described in accordance with the current SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[42] Results will be reported following the CONSORT (CONsolidated Standards Of Reporting Trials) guidelines for non-pharmacological interventions.[43]

Trial hypotheses

The primary hypothesis is that the rehabilitation program increases physical capacity among AF patients treated with RFA after 4 months measured by VO_2 peak, which is expected to be 20% more than in the control group receiving standard treatment alone. The estimate of 20% is based on findings from pilot studies including patients with permanent AF which found an increase of 15% in VO_2 peak. We therefore expect a VO_2 peak in the intervention group of 18 ml/kg/min and of 15 ml/kg/min in the control group, corresponding to a difference of 20% (3 ml/kg/min).[44]

The secondary hypothesis is that the rehabilitation programme increases quality of life and self-rated mental health among AF patients treated with RFA after 6 months by 3 points on the Medical Outcome Study Short Form 36 (SF-36) questionnaire mental component scale, compared with control participants receiving standard treatment.[19]

Exploratory hypotheses are that the experimental intervention decreases AF recurrence; improves self-rated health and sleep-quality; reduces early retirement from work, use of health care services and mortality, and is cost efficient.

Trial participants

Consecutive patients hospitalised for AF and treated with RFA at two heart centres in Denmark (Gentofte Hospital and Rigshospitalet, Copenhagen University Hospital) will be screened for inclusion and approached for trial participation (Figure 2). Regardless of RFA outcome, both patients with recurrent AF and patients in sinus rhythm after the ablation will be included in the trial. Patients 18 years of age or older, Danish speaking, and providing verbal and written informed consent will be eligible for participation. Patients unable to understand trial instructions, pregnant or breastfeeding, with reduced ability to follow the planned programme due to other physical illness, who prior to RFA have been doing intense physical exercise or sports at competitive level several times a week, or do not wish to participate, and patients already enrolled in clinical trials that prohibit participation in additional trials are excluded.

Trial procedure, randomisation, and follow-up

Patients will be approached for participation during their hospitalisation for RFA. Information will be given by a nurse or physician from the research team, who will obtain informed written consent after the RFA procedure. A brief oral introduction is initially given together with written information describing the trial and implications for the patient in detail. The patient is given ample time to read the information and if necessary involve a relative in the decision making. The enrolling nurse or physician will return after the RFA or call the patient to answer any questions the patient or their relative might have. The patient should subsequently be able to provide informed consent or reject participation. After the informed consent form is signed, baseline data will be collected including the baseline questionnaire package, demographic variables, and clinical characteristics (Table 2). Then the Copenhagen Trial Unit (http://www.ctu.dk/) is contacted for central randomisation of the participant. Randomisation is conducted according to a computer-

generated allocation sequence with a varying block size kept unknown to the investigators. Participants are randomised 1:1 to the experimental intervention group or the control group and stratified according to sex and type of AF (persistent or paroxysmal). Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. For both groups, the follow-up assessment will take place at 1 month, 4 months, 6 months, and 12 months post-discharge, and a register-based follow-up assessment will be conducted at 24 months (Table 2). In case of complications to the RFA after enrolment in the trial, the patients will be handled individually (e.g., arrhythmia or inguinal haematoma).

The patients answer questionnaires independently of the researchers, and before randomisation. All questionnaires are distributed electronically, thus data management is handled independently from the researchers that interpret data. All data are stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group.

Personal information about potential and enrolled patients will be collected electronically and shared in a database only accessible to those within the project group responsible for patient recruitment, in order to protect confidentiality before, during and after the trial.

Due to the nature of rehabilitation, the intervention group is not blinded for the patients or the investigators, but the outcome assessment of the primary outcome, the statistical analyses, and drawing of conclusions will be conducted blinded for the allocated intervention group.

The experimental intervention group

Patients in the experimental intervention group will follow the integrated cardiac rehabilitation programme consisting of a psycho-educational component and an exercise training component

alongside standard treatment (described below). The patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

The physical exercise training component

The intervention has been developed and partly tested in a clinical rehabilitation trial, the COPE-ICD trial [45] , which included patients with an implantable cardioverter defibrillator. We here observed a significant impact of the intervention on peak VO_2, physical capacity and self-assessed mental health. The intervention has been modified for patients treated for atrial fibrillation with ablation as described below. The CopenHeart physical exercise intervention meets European [24]and Danish guidelines [46]for physical exercise in patients with heart disease, and complies with The National Danish Board of Health recommendations for physical exercise in daily living for heart patients.[47]

The physical exercise starts one month after the ablation and after the first ergospirometry test and comprises the following three elements:

Individually planned physical exercise by specially trained physiotherapists. Integrating detailed information concerning AF symptoms and RFA, co-morbidity, hospitalisation, activities of daily living, and level of physical activity prior to RFA, a specially trained physiotherapist conducts a patient telephone consultation up to 30 minutes. The consultation is based on initial testing of the patient including a cardiopulmonary exercise test, a 6 minutes walking test and a 'sit and stand' test, described in the outcome section. For all patients, a rehabilitation plan is prepared as an individual training diary, and all patients are instructed in the use of a heart rate monitor (Polar Watch provided by Rigshospitalet). The heart rate monitor and diary is essential to ensure CopenHeart training protocol compliance and they are returned for data collection at the end of the exercise training intervention.

Intensive exercise training programme. Physical exercise is initiated at Rigshospitalet four weeks after RFA to ensure optimal rest and healing. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q- or T-wave altering, atrial fibrillation, and ventricular arrhythmias and training intensity level are monitored.

After 1-3 exercise training sessions at Rigshospitalet, the patient continues the programme at a local CopenHeart certified training facility supervised by physiotherapists or as supervised home-based training. Supervised home-based exercise training has shown similar results to hospital-based exercise training [31]and has been confirmed in a Danish setting.[48]

The physical exercise training continues for 12 weeks, comprising three sessions weekly of 60 minutes, in total, 36 sessions. The training protocol consists of cardiovascular training and strength exercises to improve endurance and muscular strength.

An exercise session consists of 10 minutes warm up, 20 minutes bicycling, 20 minutes strength, and a 10 minutes stretching and cool-down period. . Using the results from the cardiopulmonary exercise test performed prior to the initial training session, in combination with the Borg scale measuring subjective exhaustion, the aerobic exercise is performed with gradually increasing intensity throughout the exercise intervention period, corresponding to 13 to 17 on the Borg Scale and 50% to 80% of the maximum heart rate. The anaerobic resistance training is initiated at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1 RM for the lower body, with an increasing work load during the training sessions. To achieve cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the training session

is initiated and terminated with a warm up and a cool down period to gradually increase and decrease training intensity and heart rate. This cardiovascular adjustment has been proven to reduce the risk of ischemia and arrhythmia in relation to exercise training.[49, 50] Training is predominantly performed in the upright position to reduce left ventricle preload (diastolic volume) and the risk of ischemia and arrhythmias due to heart failure.[50]

Sustained moderate physical exercise daily. Participants are instructed to perform moderate physical exercise at least 30 minutes a day during the intervention period, e.g., bicycling, walking, gardening, jogging or recreational sports. Participants are encouraged to continue with moderate physical exercise throughout life.

The psycho-educational component

The aim of the psycho-educational intervention is to provide emotional support and improve coping skills and illness appraisal in order for the patient to respond appropriately to physical and psychological symptoms. Education and information about the disease prepare the patient for expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care nurses with specific training will perform the psycho-educational intervention. Some of the most commonly reported concerns of patients treated for AF with RFA, such as recurrent AF, and concerns about being able to manage a working life are outlined in a guide which nurses use to address when and if relevant (see Table 1). Information given will also be based on national guidelines and standard treatment of patients treated for AF. The consultations focus on managing life after AF treated with RFA by establishing a joint approach to disease management and coping strategies, taking a holistic view. The psycho-educational intervention is inspired by R.R. Parse's Human Becoming Practice Methodologies' three dimensions.[51] These are interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss events and possibilities and

3) move along with envisioned possibilities. According to this theory, there are three ways of changing health: creative imaging, that is to see, hear and feel what a situation might be like if lived in a different way, affirming personal patterns and value priorities, and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the view held of something. The nurse is present in the process through discussions, silent immersion and reflection. The human becoming practice methodology was chosen to apply a holistic patient approach, focusing on the coping and transformation process of the individual person. Furthermore, the method is already extensively used in the outpatient heart clinics at the heart centre at Rigshospitalet, such as for patients with inherited heart diseases and adults with congenital heart disease and is documented in the COPE-ICD trial.[45, 52] The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one month after discharge, and then once every four to six weeks, with a total of four consultations. Consultations can be done by telephone, in accordance with the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

Table1. Guide to the psycho-educative consultation.

Number visit	**1**	**2**	**3**	**4**
Ask the patient how he/she has been since the ablation. What has happened since last time he/she was here?	X	X	X	X
Invite the patient to talk about his/her thoughts and questions.	X	X	X	X
Ask about the time leading up to RFA and his/her AF history. Experiences before, under and	X			

after the hospitalization and RFA.	
Talk about how it is to have had/ have AF and been through RFA, how that have affected the patient's life. Is there something he/she avoids or feel like he/she cannot do anymore? This in relation to family relations, friends and free time/ leisure activities.	X
Make sure that the patient has started the physical training and talk about how it is going. Are training appointments booked?	X X X
Talk about if the patient has changed his/her feelings or thoughts of the body and its functions.	X
Talk about recognition of symptoms, how the patient is feeling about recurrence of AF and opinions about future AF treatment. Worries about recurrence of AF, strategies of prevention.	X X (X) (X)
Information/recommendations in relation to the subjects/problems discussed.	X X X X

Intervention deviations

Both components of the intervention will be supervised regularly by the primary investigator to ensure protocol compliance. Modification of the allocated intervention due to surgery complications, rehospitalisation or emerging co-morbidities (e.g. recurrent AF, musculoskeletal problems) will be individually assessed, and the time of the primary outcome assessment at four

months (described in section below) will be corrected in accordance with changes in the intervention.

Control group: treatment as usual

Patients in the control group will follow standard treatment for patients treated for AF with RFA including 3-6 months follow-up with a physician and a 12 months follow-up with a nurse. Furthermore, patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

Outcomes and data collection

Data will be collected to evaluate the effect and meaning of the intervention. The primary and secondary outcomes reflect the primary modifiable factors of the intervention. Since almost no evidence exists for rehabilitation programmes for patients treated for AF with RFA, data on a number of outcomes will be collected for exploratory analyses.

Primary outcome

Physical capacity measured by peak VO_2 according to a standardised protocol developed in accordance with guidelines [53, 54] 1, 4 and 12 months after randomisation (Table 1).

Physical capacity is measured by peak VO_2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Schweiz). The test is performed according to current guidelines for ergospirometry testing, and by ergometer bicycle, simultaneously monitoring heart-rhythm, blood pressure, electrocardiogram (ECG), and measuring gas-exchange during workload and in the following recovery period. The average test duration is 10-15 minutes including pre- and post- test phase without work load. Before each session calibration is performed to address changes in room

temperature, humidity and air oxygen content. A standardised ramp-protocol is used with initial work load of 25 or 50 watts, increasing gradually by 12.5 watts every minute until peak exhaustion. Peak exhaustion is evaluated by a respiratory exchange ratio (RER) ≥ T 1.10 or subjective exhaustion of the patient. In order to equally encourage the patients, independent of the tester, a standardised guide has been developed. During the test period, clinical manifestations, ECG abnormalities (ST depression, ST elevation, Q- and T-wave changes, supraventricular or ventricular arrhythmias), blood pressure response, and several physiological variables are observed and documented. The test will be performed by either a cardiac care nurse or a physician. For safety reasons preset criteria for initiation and/or termination of the test have been defined.

Secondary outcome

Self-rated mental health is measured by the SF-36 questionnaire, [55-57] mental component score, after 1 month, 4 months, 6 months and 12 months (Table 2).

Exploratory outcomes

Long-term follow-up: Register data regarding mortality, causes of death, hospitalisation/re-hospitalisation, emergency room visits, outpatient visits, health care costs, visits to the general practitioner, medication use, employment status and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess long term effects of the intervention (Table 2). Danish recording keeping for the data mentioned above functions well, with only a small percentage of lost data. [58] Consequently the method is well suited as an outcome measure in small patient populations. Data will be extracted from the Danish National Patient Register, the Danish National Health Service Register, the Danish National Prescription Registry,

the Danish National Causes of Death Register and records of transfer payments and labour market affiliation.[59-62]

6 minutes walking test: The maximum walking distance (in meters) within 6 minutes is measured, using standardized instructions,[63] while subjective exhaustion with regard to fatigue and dyspnoea using the Borg scale [64] is registered.

Sit and stand test: The maximum amount of times a patient can sit and rise from a normal chair within 30 seconds is recorded. Subjective exhaustion is measured using the Borg exhaustion scale.[64]

Biochemical screening: Potassium, sodium, haemoglobin and creatinine. 1 EDTA plasma heparin tube will be frozen (80°) for further analyses (pro-BNP, BNP, copeptin).

Other exploratory outcomes: AF recurrence, self-rated health and sleep-quality, retirement from work, use of health care services, mortality and cost efficiency (Table 2).

Table 2. Exploratory quantities subjected to post-hoc analysis

Quantity	Time of measure (months)	Type of quantity
Demographic		
Sex	BL	Binary (M/F)
Age, height, weight,	BL, 1,4,12	Continuous
Marital, occupational, educational status	BL	Categorical
Clinical		
NYHA- classification	BL, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COPD), co-morbidities, hypertension, dyslipidaemia, smoking	BL	Binary (Y/N)
Medication	BL, 1, 4, 12	Binary (Y/N)
AF specific data:		
Type of atrial fibrillation	BL	Categorical
Number of ablations	BL, 1,4,12	Binary (Y/N)
Atrial fibrillation symptoms	BL, 1,4,12	Continuous
CHA_2DS_2VASc score	BL, 1,4, 12	Continuous
The European Heart Rhythm Association symptom score	BL, 1,4, 12	Continuous

Paraclinical and imaging		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid status, ProBNP)	BL, 1, 4, 12	Continuous
Electrocardiogram	BL, 4, 12	Continuous
Physical function		
6 minute walking test [63]	BL, 1, 4, 12	Continuous
Sit to stand test [65]	1, 4, 12	Continuous
EVO recording	1,4,12	Categorical
Questionnaires		
Physical activity level [66]	BL, 1, 4, 6, 12, 24	Binary (Y/N)
SF-36 [67] HADS [68], QoL-CV [69]	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health [70]	BL	Continuous
Rehabilitation [71]	12	Continuous
HeartQoL R [72], EQ-5D [73]	BL, 6, 12, 24	Continuous
IPAQ [74]	1, 4, 12, 24	Continuous
MFI-20 [75]	BL, 1, 4, 12	Continuous
PSQI [76]	1, 6	Continuous
AFEQT[77]	BL, 1,4,12,24	Continuous

AFEQT, Atrial Fibrillation Effect on Quality-of-life; BL, baseline; CHA_2DS_2VASc, score for Atrial Fibrillation Stroke Risk; EQ-5D, EuroQoL; HADS, Hospital Anxiety and Depression Scale; HeartQoL R, Heart-Related Quality of Life; IPAQ, International Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL-CV, Quality of Life - Cardiac Version; SF-36, Short Form 36.

Sample size calculation for the primary outcome

We are performing a randomised trial where the continuous variable VO_2 peak is the primary outcome. The control and the intervention group are independent and the ratio of patients in the intervention group to the patients in the control group is 1:1. A previous trial of patients with permanent AF found that VO_2 peak was normally distributed with a standard deviation of 3.8 ml/kg/min.[44] As the CopenHeart$_{RFA}$ trial has a more varied patient population who have all been treated for AF with RFA, which means that the majority of the patients will have sinus rhythm and

the rest will have AF, the patients are not directly comparable with the patients in the previous trial, and we assume a standard deviation of 6 ml/kg/min to be more relevant. We consider a 0.5 standard deviation to be the minimal relevant difference, equivalent to 3 ml/kg/min. Therefore, if the true difference between the intervention group and control group is 3 ml/kg/min and the standard deviation is 6 ml/kg/min in the control group, 105 patients in the intervention group and 105 in the control group (a total of 210 patients) are needed to reject the null hypothesis, stating that the mean in the intervention group and the control group is the same, with a power of 95%. The type I error probability associated with this test of this null hypothesis is 5%.

Power calculation for the secondary outcome

The secondary outcome measure is the continuous variable mental component, SF 36. If the true difference between the intervention and control group is 7 points, and the standard deviation in the control group is 18 points. [21] We will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability of (power) 0.80. The type I error probability associated with this test of this null hypothesis is 5%.

Statistical analyses

Data will be pseudo-anonymised and analysed blinded by a trial-independent statistician using intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous outcome measures.[78] Using MMRM ensures that missing data values (in case of the primary and secondary outcome) will not create bias as long as the values are missing at random. Two-sided tests are performed. The level of significance is set at 5%. With regard to multiplicity, gate keeping will be used to adjust the observed P values for primary and secondary outcomes.[79] Both unadjusted and adjusted P values will be reported.

For the primary and secondary outcomes, sensitivity analysis will be conducted to assess the potential impact of values missing not at random. For each intervention group (A and B) some quantities (imputing quantities) are computed to be used to impute missing values in a group (A or B) as follows. A comparison between group A and group B where missing values in group A are imputed using imputing quantities obtained from group A and missing values from group B are imputed using imputing quantities obtained from group B is referred to as a best case analysis. If missing values in group A are imputed using imputing quantities obtained from group B and vice versa the comparison is called a worst case analysis. The imputing quantities for the primary outcome are the group mean at T1 (X1-bar), the group mean at T4 (X4-bar), the group mean at T6 (X6-bar), the mean difference between the value measured at T4 and that measured at T1 (delta 1), and the mean difference between the value measured at T6 and that measured at T4 (delta-2). Table 3 explains how the quantities are used to impute missing values in a group (either the same group or the other intervention group). If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that of the corresponding parameter calculated using complete case data it is replaced by the latter SE when the P value is calculated (Table 3).

Long-term register-based outcomes will be analysed by two different models: non-negative count outcomes (e.g., number of contacts with hospital or number of visits to general practitioners) will be analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and time-to-event data (e.g., cause-specific mortality and leaving the labor market) will be analysed with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-economic outcomes, competing risks due to mortality will be considered if a large proportion of patients die during follow-up.

Exploratory data will be analysed using appropriate statistical methods according to the type of data (see Table 2). SPSS version 17.0 and SAS version 9.3 will be used.

Table 3. Statistical analysis

Observed pattern in group B at 1, 4, and 6 months	Imputed value in group B at 1 month	Imputed value in group B at 4 month	Imputed value in group B at 6 months
mis[A], mis, mis	X1-bar[B]	X4-bar[C]	X6-bar[D]
mis, mis, Y3[E]	Y3 – (delta1[F] + delta2[G])[H]	Y3 – delta2	
mis, Y2, mis	Y2 – delta1		Y2 + delta2
Y1, mis, mis		Y1 + delta1	Y1 + delta1 + delta2
Y1, Y2, mis			Y2 + delta2
Y1, mis, Y3		(Y1 + delta1 + Y3 - delta2)/2	
mis, Y2, Y3	Y2 – delta1		

Table to explain the use of imputing quantities derived from observed values in a group (group A) to impute missing values in a group (group B). mis=missing value, X1=value at month 1, X4=value at month 4, X6=value at month 6.
[A]The value at 4 months is missing in group B, [B]Mean of values observed in group A at time 1 month. [C]Mean of values observed in group A at time 4 months. [D]Mean of values observed in group A at time 6 months. [E]Observed value in group B at time 6 months. [F]The mean of difference between values observed at time 4 months and value observed at time 1 month in group A, [G]The mean of difference between value observed at time 6 months and value observed at time 4 months in group A, [H]If an imputed value is 0 it is set equal to 0.

Interim analysis and Data Monitoring Safety Committee (DMSC)

The DMSC works independently from the funder and has no competing interests, and consists of two clinicians and a statistician. The committee is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. In line with the terms of the Data Monitoring

and Safety Committee charter, one formal interim analysis meeting will be held to review data relating to treatment efficacy, participant safety, and quality of trial conduct. The three members of the Data Monitoring and Safety Committee will meet when the 12 week follow-up data of about 50% of the trial participants have been obtained. Any serious adverse events will be registered as part of the data collection and the overall number of adverse events will be reported at the meeting.

Complementary studies

The Surveysbased study. The post-discharge status of the patients treated with RFA will be explored through a national survey. The standardised questionnaires SF-36,[67] Hospital Anxiety and Depression Scale (HADS), [68] EuroQoL-EQ-5D, [69, 70] Heart Related Quality of Life (HeartQoL R), [71] International Physical Activity Questionnaire (IPAQ), [72, 73] and a questionnaire developed by the Danish Heart Foundation on the extent and quality of rehabilitation offered will be sent to patients having undergone treatment for RFA, 6-12 months post-discharge. The instruments are all validated and have good reliability and responsiveness.[68, 72, 74, 75, 80, 81] The data will provide knowledge on patients' self-rated health, quality of life, anxiety and depression, economic situation and the extent and quality of the rehabilitation currently received. Patients were identified through the National Patient Register [59] and questionnaires were sent out to 608 patients. We anticipate 25% will decline participation, leaving an estimated 456 questionnaire respondents. Data will be anonymised and analysed by relevant descriptive statistical methods.

Qualitative post intervention study

After the intervention, 10% of the participants from the intervention group will be strategically chosen for an interview in order to explore the experiences and processes behind the potential effects of the intervention. The qualitative study will explore patient experiences of participating in the CopenHeart$_{RFA}$ programme and investigate which components were meaningful.

To achieve maximum variation, qualified interviewees are chosen on the basis of sex, AF type, and current heart rhythm.[82] The analysis will be inspired by Ricoeur's theory of interpretation consisting of three levels: naive reading, structured analysis and critical interpretation and discussion.[83]

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-utility of cardiac rehabilitation compared with treatment as usual in the study population. The economic evaluation will compare the costs to quality adjusted life years (QALY) and take a societal perspective, as recommended nationally. QALYs and costs will be assessed at the end of the intervention, 6 months from randomisation, and later after 24 months from randomisation using register-based follow up.

QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[84, 85] The estimated calculations will be valued using Danish preference weights.[86] Information on costs will only include costs that are expected to differ between the intervention and usual care group.[73] Costs included in the evaluation are health costs associated with the rehabilitation programme, other health care costs (health care utilization besides rehabilitation), patient costs and costs of productivity losses. Information on costs will be collected by a mixture of activity-based costing, surveys, patient diary and by the use of public records. Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER). Sensitivity analysis will be conducted to express uncertainty in the estimates.[87] The reporting of the ICER is presented using Bayesian methods, including bootstrapping and presented as cost-effectiveness acceptability curves.[88]

Ethics

The inclusion started December 2011 and is approved by the Regional Ethics Committee (number H-1-2011-135) and the Danish Data Protection Agency (no. 2007-58-0015). All eligible patients

will be informed about the trial verbally and in writing, and the patients are included after informed consent has been obtained. All data will be handled confidentially and patients ensured anonymity. The trial complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01523145). An independent international safety committee monitors the trial. All serious and adverse events will be registered and reported in accordance with the safety charter.

Not providing rehabilitation to the control group can be ethically justified as current national and international guidelines give no specific recommendations on cardiac rehabilitation for patients treated for AF with RFA. The scope and quality of rehabilitation offered to this population is unknown, but suspicions are that generally no rehabilitation is offered in Denmark. The only way patients can get supervised exercise training is if they voluntarily enrol in a programme e.g. through non-profit organisations. The survey based complementary study, described previously in this paper, will hopefully provide more insight into this. In screening patients for participation, the enrolling nurse or physician will exclude those with a compelling rehabilitation need. Furthermore, patients are informed of the study design before giving their consent, and are free to decline participation.

Discussion

Due to the difference in the three patient groups that are included in the overall CopenHeart trial, patients treated for infective endocarditis, heart valve surgery and patients treated for AF with RFA, the intervention and outcome measures differ slightly, most importantly in the case of the psycho-educational intervention, which is longer for patients treated for infective endocarditis and heart valve surgery, because of the complexity of the diseases and the longer hospitalisation. Biochemical markers are similarly chosen differently to address the various co-morbidities of the three diseases and some disease specific questionnaires are chosen to capture the specific disease relevant issues.

To our knowledge no previous randomised clinical trials or observational studies have been conducted focusing on integrated cardiac rehabilitation for AF patients treated with RFA, so therefore it is not known what effect, if any, rehabilitation has on these patients. However, in the light of evidence from other groups of patients with heart disease a positive effect can be expected.[23, 89, 90]

This trial is different from previous trials because we apply a comprehensive coronary rehabilitation intervention which consists of both a physical training component and a psycho-educational component. This combination is hypothesised to strengthen the patient both physically and mentally even if the patient has AF. Also we use mixed methods, which has its strengths in both using qualitative and quantitative research design.[34]

The major strengths of this randomised clinical trial are that it includes consecutive patients with a reasonable number of inclusion and exclusion criteria securing external validity for the results. The trial employs central, stratified randomisation which secures against selection bias.[91-93] The primary outcome is assessed blinded to intervention and so are all statistical analyses, which should reduce detection and interpretation bias.[91-93] The long-term outcomes are based on data taken from public registry data, which are also likely not to include biased reporting of outcomes.

The secondary outcomes of self-rated mental health are by nature subjective and are likely to be biased.[91-93] The patients answer questionnaires independently of the researchers. Data management is handled independently from the researchers that interpret data. All questionnaires are distributed electronically. All data entry is stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart Group.

Trial limitations include the fact that it is known from previous rehabilitation trials [33] that patients in the control group have a tendency to do physical training due to the focus on the subject in the recruitment process. We will be aware of that when we recruit and not focus on giving extensive information about the exercise programme, or encourage patients to do physical training before knowing what group they are randomised to. Any difference between patients completing the intervention and those not completing (drop-outs) will be carefully discussed when evaluating the intervention, results and the suitability for implementation. The trial is designed with multiple statistical comparisons so results will be interpreted with caution. Further limitations of the trial and methods used are similar to those of other trials including physical exercise and physical testing, namely time-of-day, and day-to-day variation using exercise testing.[94] To ensure standard testing of all physical exercise tests in the trial, standardised instructions for patients have been developed as described in the methods section. Conversely, the trial population will be representative for the true RFA population, meaning that some patients will have AF and some sinus rhythm while exercising and testing, and this will facilitate implementation of The CopenHeart$_{RFA}$ trial rehabilitation programme in daily clinical practice.

The challenge with the set-up is that patients come from considerable distances and therefore some will decline participation. Also, due to the nature of rehabilitation trials, the patients have to meet at the hospital frequently, especially when randomised to the experimental intervention group.

The trial will, to our knowledge, be the largest trial conducted dealing with rehabilitation AF ablation recipients. If a positive effect of integrated rehabilitation is found, it may have an impact on the rehabilitation offered to patients treated for AF with RFA at international level. The trial is expected to identify an intervention which can improve health and quality of life for the patients,

and subsequently reduce healthcare utilization and costs, as well as mortality.

Publication policy

The results of the trial will be published in appropriate peer-reviewed journals regardless of the outcome. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors.

The outcome data will be analysed and published in the short term of 4 and 6 months and the long term of 24 months. Due to the comprehensiveness of the outcome measures further post hoc analysis will be published in separate papers. Economic and long term follow up will be reported as data becomes accessible.

Timetable

Recruitment started in December 2011 in one heart centre and in July 2012 in the other participating heart centre and is planned to finish in December 2013. To achieve adequate participant enrolment, patients in doubt are contacted after hospital discharge by phone. The inclusion rate is closely monitored every week.

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Authors' contributions

SKB and ADZ in collaboration with SSR, JLH, MP, LCT, PW and CG designed the trial. SSR in collaboration with SKB, ADZ, TBR, KLS, JHS, CG, LCT, SD, JLH and SD drafted the manuscript. All revised the manuscript critically. All authors have given their final approval of the version to be published.

Competing interests

None.

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The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeartRFA trial protocol

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The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeart$_{RFA}$ trial protocol

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Article summary

Article focus

- The CopenHeart$_{RFA}$ trial is a randomised clinical trial investigating the effects of comprehensive cardiac rehabilitation versus usual care for patients treated for atrial fibrillation (AF) with ablation.
- The hypothesis is that comprehensive cardiac rehabilitation improves physical capacity and mental health.
- Using a mixed methods approach, a broad range of outcome measures are collected to evaluate the intervention.

Key messages

- AF affects 1-2% of the population. Patients with AF experience diminished quality of life and are afraid to do physical exercise after treatment with ablation.
- No studies exploring the effects of rehabilitation of patients treated for AF with ablation have been published.
- This trial is the first to examine physical functioning and to test a comprehensive rehabilitation programme on a large population of patients treated for AF with ablation.

CopenHeart$_{RFA}$ will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for AF with ablation.

Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials with central randomisation, multi-centre participation, blinded assessment and analysis.
- We are aware of the day to day variation that can appear when carrying out ergospirometry, in testing and that the performance can depend on the individual tester. Accordingly, we will interpret the findings conservatively.

Abstract

Introduction

Atrial fibrillation affects almost 2% of the population in the Western world. To preserve sinus rhythm, ablation is undertaken in symptomatic patients. Observational studies show that patients with atrial fibrillation often report low quality of life and are less prone to be physically active due to fear of triggering fibrillation. Small trials indicates that exercise training has a positive effect on exercise capacity and mental health, and both patients with recurrent atrial fibrillation and in sinus rhythm may benefit from rehabilitation in managing life after ablation. No randomised trials have been published on cardiac rehabilitation for atrial fibrillation patients treated with ablation that includes exercise and psycho-educational components.

Aim

To test the effects of an integrated cardiac rehabilitation programme versus treatment as usual for patients with atrial fibrillation treated with ablation.

Methods and analysis design

The trial is a multicentre parallel arm design with 1:1 randomisation to the intervention and control group with blinded outcome assessment. 210 patients treated for atrial fibrillation with radiofrequency ablation will be included. The intervention consists of a rehabilitation programme including four psycho-educative consultations with a specially trained nurse and 12 weeks of individualised exercise training, plus the standard medical follow-up. Patients in the control group will receive the standard medical follow-up. The primary outcome measure is exercise capacity measured by VO_2 peak. The secondary outcome measure is self-rated mental health measured by the Short Form 36 questionnaire. Post intervention, qualitative interviews will be conducted in 10% of the intervention group.

Ethics and dissemination

The protocol is approved by the regional research ethics committee (number. H-1-2011-135), the Danish Data Protection Agency (reg. nr. 2007-58-0015) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may possibly impact on rehabilitation guidelines.

Registration: Clinicaltrials.gov identifier: NCT01523145

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and affects 2% of the population in the Western world.[1-3] Typical symptoms are palpitations, dyspnoea, fatigue, dizziness, and syncope. Patients' symptoms and the length of periods in AF are highly variable both for the individual and between patients.[4-6] AF is associated with increased risk of stroke, other thromboembolic events, and heart failure.[6-8] Hospitalisations due to AF account for one third of all admissions for cardiac arrhythmias.[8] As the prevalence of AF increases with age, the incidence of AF is increasing due to an ageing population.[2, 9, 10] After 40 years of age, the lifetime risk of developing AF is 25%. [11] The annual cost of AF is high in comparison with other diseases.[12] Therefore, AF has become an economic burden and this will continue to increase over the coming decades.[13] Thus, AF has now become a health, social and economic challenge in the Western world.[14]

Primary treatment goals for individuals with AF are re-establishing and maintaining sinus rhythm, decreasing AF symptoms, and prevention of complications. In accordance with current national and international guidelines, radiofrequency ablation (RFA) is often undertaken in symptomatic patients. RFA is an invasive treatment, intended to cure AF and has a success rate of 77% versus 52% for antiarrhythmic medication.[15] In Denmark, around 600 RFAs are conducted annually at two heart centres.

A cohort study of 655 patients from a randomised trial found that AF symptoms are a negative predictor for patients' physical capacity,[16] and in the presence of AF, patients do fewer physical activities.[17] Smaller observational studies and a randomised trial investigating the effect of exercise

training on AF patients found increased exercise capacity and a decreased resting heart rate after training.[18-20]

Previous studies show significantly impaired quality of life in patients with AF compared to healthy controls measured by the questionnaire Short Form 36 (SF-36). The general health component (± standard deviation) was 54±21 in AF patients compared to 78±17 in healthy controls.[21] A qualitative study demonstrated that educational help after AF treatment is lacking, even though symptoms of distress and lack of self-management regarding symptoms like palpitations, dyspnoea, and fatigue are common.[22] Furthermore, small observational studies indicate a positive effect of exercise training on patients with AF in terms of mental health and physical activity (15% increase of VO_2).[18, 19] However, these findings need confirmation in larger randomised clinical trials.

Secondary prevention initiatives including cardiac rehabilitation are recommended by the European Society of Cardiology (ESC).[23] Studies exploring the effects of rehabilitation for patients treated for AF are lacking. As there is no evidence of its efficacy, rehabilitation is not systematically provided in Denmark and most often patients treated for AF with RFA are not offered any rehabilitation at all. The evidence for general cardiac rehabilitation is strong, but it is found that it is poorly implemented and only selected patient groups are offered full comprehensive cardiac rehabilitation programmes, even though ESC recommends such programmes.[24] Research has mainly been conducted within patients with coronary heart disease and heart failure, where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way,[25, 26] as well as improve quality of life.[27] More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery [28] and an increase in peak VO_2 of 2.3±2.2 (SD) ml/kg per minute in the intervention group

compared with −0.3±2.1 (SD) ml/kg per minute in the control group, as well as a significant change in quality of life in older patients with heart failure.[29]

.. Traditional cardiac rehabilitation has focused on physical training and standardized programmes, but studies now indicate that individualized content and supervised exercise components can improving outcomes.[30] In addition to exercise training, there is evidence to support interventions that include patient education, which in patients with coronary heart disease has shown to improve health related quality of life and decrease healthcare costs, [31] and psychological support, which has been shown to improve psychological symptoms , such as depression and anxiety.[32] Interventions designed to cover both physical and psychological problems may provide the best method for optimising functioning and enhancing quality of life.[33] We have not been able to identify randomised trials or observational studies in patients who have undergone RFA for AF that offer both psycho-educational intervention and physical training. Therefore, the CopenHeart$_{RFA}$ trial was undertaken with the aim of testing a rehabilitation programme consisting of physical exercise and a psycho-educational intervention versus treatment as usual for RFA treated AF patients.

Methods

Design

Major parts of the method section and trial design in this paper are similar to two other randomised clinical trials, CopenHeart$_{VR}$ and CopenHeart$_{IE}$, and therefore sections from this paper will be copied in these trial protocols (Sibilitz KL et al. *Effect of integrated cardiac rehabilitation versus treatment as usual for patients with isolated heart valve surgery: The randomised CopenHeart valvular trial protocol.* drafted October 2012; and Rasmussen TB et al. *A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for infective endocarditis – the CopenHeart$_{IE}$.* Accepted for publication, BMJ Open, October 2012).

The CopenHeart$_{RFA}$ trial is a multi-centre, multidisciplinary randomised clinical superiority trial. Secondary, qualitative data are also collected and the two methods are integrated by applying a mixed method embedded experimental design (Figure 1).[34, 35] Quantitative methods are applied, with specified quantitative pre- and post-measures to evaluate the effect of the experimental intervention. Alongside quantitative measurements, qualitative data will be collected. The premise of mixed methods research is that the use of qualitative and quantitative approaches in combination provides a better understanding of the research problems than either approach alone, because different types of questions require different types of data and that mixed methods research provides strengths that offset the weaknesses of both qualitative and quantitative research.[34] The methods are integrated by applying a mixed method embedded experimental design and include qualitative data to develop the intervention and to examine the process of the intervention and the results of the trial (see Figure 1).[34, 35] The rationale for this approach is that the quantitative findings provide a general understanding of the research problem through statistical results while qualitative findings refine and explain the results by exploring participants' views in greater detail and will be presented by themes of patient thoughts or concerns about the intervention. Evaluation using qualitative research methods is increasingly promoted in evidence-based rehabilitation.[36-39] Qualitative research alongside randomised controlled trials can contribute in several ways to the development and evaluation of complex healthcare interventions and may be particularly useful in evaluating interventions that involve social and behavioural processes that are difficult to explore or capture using quantitative methods alone.[40] As patient participation is paramount for the efficacy of the rehabilitation,[41] we find it highly valuable to include the patients' perspective in the development and evaluation of the intervention. This paper presents the study protocol for the CopenHeart$_{RFA}$

randomised clinical trial. The complementary studies, including the qualitative part of the trial are briefly described in a separate section.

The trial is described in accordance with the current SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[42] Results will be reported following the CONSORT (CONsolidated Standards Of Reporting Trials) guidelines for non-pharmacological interventions.[43]

Trial hypotheses

The primary hypothesis is that the rehabilitation program increases physical capacity among AF patients treated with RFA after 4 months measured by VO_2 peak, which is expected to be 20% more than in the control group receiving standard treatment alone. The estimate of 20% is based on findings from pilot studies including patients with permanent AF which found an increase of 15% in VO_2 peak. We therefore expect a VO_2 peak in the intervention group of 18 ml/kg/min and of 15 ml/kg/min in the control group, corresponding to a difference of 20% (3 ml/kg/min).[44]

The secondary hypothesis is that the rehabilitation programme increases quality of life and self-rated mental health among AF patients treated with RFA after 6 months by 3 points on the Medical Outcome Study Short Form 36 (SF-36) questionnaire mental component scale, compared with control participants receiving standard treatment.[19]

Exploratory hypotheses are that the experimental intervention decreases AF recurrence; improves self-rated health and sleep-quality; reduces early retirement from work, use of health care services and mortality, and is cost efficient.

Trial participants

Consecutive patients hospitalised for AF and treated with RFA at two heart centres in Denmark (Gentofte Hospital and Rigshospitalet, Copenhagen University Hospital) will be screened for inclusion and approached for trial participation (Figure 2). Regardless of RFA outcome, both patients with recurrent AF and patients in sinus rhythm after the ablation will be included in the trial. Patients 18 years of age or older, Danish speaking, and providing verbal and written informed consent will be eligible for participation. Patients unable to understand trial instructions, pregnant or breastfeeding, with reduced ability to follow the planned programme due to other physical illness, who prior to RFA have been doing intense physical exercise or sports at competitive level several times a week, or do not wish to participate, and patients already enrolled in clinical trials that prohibit participation in additional trials are excluded.

Trial procedure, randomisation, and follow-up

Patients will be approached for participation during their hospitalisation for RFA. Information will be given by a nurse or physician from the research team, who will obtain informed written consent after the RFA procedure. A brief oral introduction is initially given together with written information describing the trial and implications for the patient in detail. The patient is given ample time to read the information and if necessary involve a relative in the decision making. The enrolling nurse or physician will return after the RFA or call the patient to answer any questions the patient or their relative might have. The patient should subsequently be able to provide informed consent or reject participation. After the informed consent form is signed, baseline data will be collected including the baseline questionnaire package, demographic variables, and clinical characteristics (Table 2). Then the Copenhagen Trial Unit (http://www.ctu.dk/) is contacted for

central randomisation of the participant. Randomisation is conducted according to a computer-generated allocation sequence with a varying block size kept unknown to the investigators. Participants are randomised 1:1 to the experimental intervention group or the control group and stratified according to sex and type of AF (persistent or paroxysmal). Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. For both groups, the follow-up assessment will take place at 1 month, 4 months, 6 months, and 12 months post-discharge, and a register-based follow-up assessment will be conducted at 24 months (Table 2). In case of complications to the RFA after enrolment in the trial, the patients will be handled individually (e.g., arrhythmia or inguinal haematoma).

The patients answer questionnaires independently of the researchers, and before randomisation. All questionnaires are distributed electronically, thus data management is handled independently from the researchers that interpret data. All data are stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group.

Personal information about potential and enrolled patients will be collected electronically and shared in a database only accessible to those within the project group responsible for patient recruitment, in order to protect confidentiality before, during and after the trial.

Due to the nature of rehabilitation, the intervention group is not blinded for the patients or the investigators, but the outcome assessment of the primary outcome, the statistical analyses, and drawing of conclusions will be conducted blinded for the allocated intervention group.

The experimental intervention group

Patients in the experimental intervention group will follow the integrated cardiac rehabilitation programme consisting of a psycho-educational component and an exercise training component

alongside standard treatment (described below). The patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

The physical exercise training component

The intervention has been developed and partly tested in a clinical rehabilitation trial, the COPE-ICD trial [45] , which included patients with an implantable cardioverter defibrillator. We here observed a significant impact of the intervention on peak VO_2, physical capacity and self-assessed mental health. The intervention has been modified for patients treated for atrial fibrillation with ablation as described below. The CopenHeart physical exercise intervention meets European [24]and Danish guidelines [46]for physical exercise in patients with heart disease, and complies with The National Danish Board of Health recommendations for physical exercise in daily living for heart patients.[47]

The physical exercise starts one month after the ablation and after the first ergospirometry test and comprises the following three elements:

Individually planned physical exercise by specially trained physiotherapists. Integrating detailed information concerning AF symptoms and RFA, co-morbidity, hospitalisation, activities of daily living, and level of physical activity prior to RFA, a specially trained physiotherapist conducts a patient telephone consultation up to 30 minutes. The consultation is based on initial testing of the patient including a cardiopulmonary exercise test, a 6 minutes walking test and a 'sit and stand' test, described in the outcome section. For all patients, a rehabilitation plan is prepared as an individual training diary, and all patients are instructed in the use of a heart rate monitor (Polar Watch provided by Rigshospitalet). The heart rate monitor and diary is essential to ensure CopenHeart training protocol compliance and they are returned for data collection at the end of the exercise training intervention.

Intensive exercise training programme. Physical exercise is initiated at Rigshospitalet four weeks after RFA to ensure optimal rest and healing. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q- or T-wave altering, atrial fibrillation, and ventricular arrhythmias and training intensity level are monitored.

After 1-3 exercise training sessions at Rigshospitalet, the patient continues the programme at a local CopenHeart certified training facility supervised by physiotherapists or as supervised home-based training. Supervised home-based exercise training has shown similar results to hospital-based exercise training [31]and has been confirmed in a Danish setting.[48]

The physical exercise training continues for 12 weeks, comprising three sessions weekly of 60 minutes, in total, 36 sessions. The training protocol consists of cardiovascular training and strength exercises to improve endurance and muscular strength.

An exercise session consists of 10 minutes warm up, 20 minutes bicycling, 20 minutes strength, and a 10 minutes stretching and cool-down period. . Using the results from the cardiopulmonary exercise test performed prior to the initial training session, in combination with the Borg scale measuring subjective exhaustion, the aerobic exercise is performed with gradually increasing intensity throughout the exercise intervention period, corresponding to 13 to 17 on the Borg Scale and 50% to 80% of the maximum heart rate. The anaerobic resistance training is initiated at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1 RM for the lower body, with an increasing work load during the training sessions. To achieve cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the training session

is initiated and terminated with a warm up and a cool down period to gradually increase and decrease training intensity and heart rate. This cardiovascular adjustment has been proven to reduce the risk of ischemia and arrhythmia in relation to exercise training.[49, 50] Training is predominantly performed in the upright position to reduce left ventricle preload (diastolic volume) and the risk of ischemia and arrhythmias due to heart failure.[50]

Sustained moderate physical exercise daily. Participants are instructed to perform moderate physical exercise at least 30 minutes a day during the intervention period, e.g., bicycling, walking, gardening, jogging or recreational sports. Participants are encouraged to continue with moderate physical exercise throughout life.

The psycho-educational component

The aim of the psycho-educational intervention is to provide emotional support and improve coping skills and illness appraisal in order for the patient to respond appropriately to physical and psychological symptoms. Education and information about the disease prepare the patient for expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care nurses with specific training will perform the psycho-educational intervention. Some of the most commonly reported concerns of patients treated for AF with RFA, such as recurrent AF, and concerns about being able to manage a working life are outlined in a guide which nurses use to address when and if relevant (see Table 1). Information given will also be based on national guidelines and standard treatment of patients treated for AF. The consultations focus on managing life after AF treated with RFA by establishing a joint approach to disease management and coping strategies, taking a holistic view. The psycho-educational intervention is inspired by R.R. Parse's Human Becoming Practice Methodologies' three dimensions.[51] These are interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss events and possibilities and

3) move along with envisioned possibilities. According to this theory, there are three ways of changing health: creative imaging, that is to see, hear and feel what a situation might be like if lived in a different way, affirming personal patterns and value priorities, and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the view held of something. The nurse is present in the process through discussions, silent immersion and reflection. The human becoming practice methodology was chosen to apply a holistic patient approach, focusing on the coping and transformation process of the individual person. Furthermore, the method is already extensively used in the outpatient heart clinics at the heart centre at Rigshospitalet, such as for patients with inherited heart diseases and adults with congenital heart disease and is documented in the COPE-ICD trial.[45, 52] The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one month after discharge, and then once every four to six weeks, with a total of four consultations. Consultations can be done by telephone, in accordance with the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

Table1. Guide to the psycho-educative consultation.

Number visit	**1**	**2**	**3**	**4**
Ask the patient how he/she has been since the ablation. What has happened since last time he/she was here?	X	X	X	X
Invite the patient to talk about his/her thoughts and questions.	X	X	X	X
Ask about the time leading up to RFA and his/her AF history. Experiences before, under and	X			

after the hospitalization and RFA.	
Talk about how it is to have had/ have AF and been through RFA, how that have affected the patient's life. Is there something he/she avoids or feel like he/she cannot do anymore? This in relation to family relations, friends and free time/ leisure activities.	X
Make sure that the patient has started the physical training and talk about how it is going. Are training appointments booked?	X X X
Talk about if the patient has changed his/her feelings or thoughts of the body and its functions.	X
Talk about recognition of symptoms, how the patient is feeling about recurrence of AF and opinions about future AF treatment. Worries about recurrence of AF, strategies of prevention.	X X (X) (X)
Information/recommendations in relation to the subjects/problems discussed.	X X X X

Intervention deviations

Both components of the intervention will be supervised regularly by the primary investigator to ensure protocol compliance. Modification of the allocated intervention due to surgery complications, rehospitalisation or emerging co-morbidities (e.g. recurrent AF, musculoskeletal problems) will be individually assessed, and the time of the primary outcome assessment at four

months (described in section below) will be corrected in accordance with changes in the intervention.

Control group: treatment as usual

Patients in the control group will follow standard treatment for patients treated for AF with RFA including 3-6 months follow-up with a physician and a 12 months follow-up with a nurse. Furthermore, patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

Outcomes and data collection

Data will be collected to evaluate the effect and meaning of the intervention. The primary and secondary outcomes reflect the primary modifiable factors of the intervention. Since this is a complex intervention with two main components, an exercise component and a psycho-educational component, this is reflected in the primary and secondary outcome. The intervention has been tested in ICD patients (unpublished data in the COPE-ICD trail, available on request) and the intervention reflects well in the chosen measures that have found to be sensitive to changes based on the intervention. Since almost no evidence exists for rehabilitation programmes for patients treated for AF with RFA, data on a number of outcomes will be collected for exploratory analyses.

Primary outcome

Physical capacity measured by peak VO_2 according to a standardised protocol developed in accordance with guidelines [53, 54] 1, 4 and 12 months after randomisation (Table 1).

Physical capacity is measured by peak VO_2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Schweiz). This is chosen as a primary outcome since this is standard in exercise based

rehabilitation trails. The test is performed according to current guidelines for ergospirometry testing, and by ergometer bicycle, simultaneously monitoring heart-rhythm, blood pressure, electrocardiogram (ECG), and measuring gas-exchange during workload and in the following recovery period. The average test duration is 10-15 minutes including pre- and post- test phase without work load. Before each session calibration is performed to address changes in room temperature, humidity and air oxygen content. A standardised ramp-protocol is used with initial work load of 25 or 50 watts, increasing gradually by 12.5 watts every minute until peak exhaustion. Peak exhaustion is evaluated by a respiratory exchange ratio (RER) ≥ T 1.10 or subjective exhaustion of the patient. In order to equally encourage the patients, independent of the tester, a standardised guide has been developed. During the test period, clinical manifestations, ECG abnormalities (ST depression, ST elevation, Q- and T-wave changes, supraventricular or ventricular arrhythmias), blood pressure response, and several physiological variables are observed and documented. The test will be performed by either a cardiac care nurse or a physician. For safety reasons preset criteria for initiation and/or termination of the test have been defined.

Secondary outcome

Self-rated mental health is measured by the SF-36 questionnaire, [55-57] mental component score, after 1 month, 4 months, 6 months and 12 months (Table 2).

Exploratory outcomes

Long-term follow-up: Register data regarding mortality, causes of death, hospitalisation/re-hospitalisation, emergency room visits, outpatient visits, health care costs, visits to the general practitioner, medication use, employment status and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess long term effects of

the intervention (Table 2). Danish recording keeping for the data mentioned above functions well, with only a small percentage of lost data. [58] Consequently the method is well suited as an outcome measure in small patient populations. Data will be extracted from the Danish National Patient Register, the Danish National Health Service Register, the Danish National Prescription Registry, the Danish National Causes of Death Register and records of transfer payments and labour market affiliation.[59-62]

6 minutes walking test: The maximum walking distance (in meters) within 6 minutes is measured, using standardized instructions,[63] while subjective exhaustion with regard to fatigue and dyspnoea using the Borg scale [64] is registered.

Sit and stand test: The maximum amount of times a patient can sit and rise from a normal chair within 30 seconds is recorded. Subjective exhaustion is measured using the Borg exhaustion scale.[64]

Biochemical screening: Potassium, sodium, haemoglobin and creatinine. 1 EDTA plasma heparin tube will be frozen (80°) for further analyses (pro-BNP, BNP, copeptin).

Other exploratory outcomes: AF recurrence, self-rated health and sleep-quality, retirement from work, use of health care services, mortality and cost efficiency (Table 2).

Table 2. Exploratory quantities subjected to post-hoc analysis

Quantity	Time of measure (months)	Type of quantity
Demographic		
Sex	BL	Binary (M/F)
Age, height, weight,	BL, 1,4,12	Continuous
Marital, occupational, educational status	BL	Categorical
Clinical		
NYHA- classification	BL, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COPD), co-morbidities, hypertension, dyslipidaemia, smoking	BL	Binary (Y/N)
Medication	BL, 1, 4, 12	Binary (Y/N)

AF specific data:		
Type of atrial fibrillation	BL	Categorical
Number of ablations	BL, 1,4,12	Binary (Y/N)
Atrial fibrillation symptoms	BL, 1,4,12	Continuous
CHA_2DS_2VASc score	BL, 1,4, 12	Continuous
The European Heart Rhythm Association symptom score	BL, 1,4, 12	Continuous
Paraclinical and imaging		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid status, ProBNP)	BL, 1, 4, 12	Continuous
Electrocardiogram	BL, 4, 12	Continuous
Physical function		
6 minute walking test [63]	BL, 1, 4, 12	Continuous
Sit to stand test [65]	1, 4, 12	Continuous
EVO recording	1,4,12	Categorical
Questionnaires		
Physical activity level [66]	BL, 1, 4, 6, 12, 24	Binary (Y/N)
SF-36 [67] HADS [68], QoL-CV [69]	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health [70]	BL	Continuous
Rehabilitation [71]	12	Continuous
HeartQoL R [72], EQ-5D [73]	BL, 6, 12, 24	Continuous
IPAQ [74]	1, 4, 12, 24	Continuous
MFI-20 [75]	BL, 1, 4, 12	Continuous
PSQI [76]	1, 6	Continuous
AFEQT[77]	BL, 1,4,12,24	Continuous

AFEQT, Atrial Fibrillation Effect on Quality-of-life; BL, baseline; CHA_2DS_2VASc, score for Atrial Fibrillation Stroke Risk; EQ-5D, EuroQoL; HADS, Hospital Anxiety and Depression Scale; HeartQoL R, Heart-Related Quality of Life; IPAQ, International Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL-CV, Quality of Life - Cardiac Version; SF-36, Short Form 36.

Sample size calculation for the primary outcome

We are performing a randomised trial where the continuous variable VO_2 peak is the primary outcome. The control and the intervention group are independent and the ratio of patients in the

intervention group to the patients in the control group is 1:1. A previous trial of patients with permanent AF found that VO_2 peak was normally distributed with a standard deviation of 3.8 ml/kg/min.[44] As the CopenHeart$_{RFA}$ trial has a more varied patient population who have all been treated for AF with RFA, which means that the majority of the patients will have sinus rhythm and the rest will have AF, the patients are not directly comparable with the patients in the previous trial, and we assume a standard deviation of 6 ml/kg/min to be more relevant. We consider a 0.5 standard deviation to be the minimal relevant difference, equivalent to 3 ml/kg/min. Therefore, if the true difference between the intervention group and control group is 3 ml/kg/min and the standard deviation is 6 ml/kg/min in the control group, 105 patients in the intervention group and 105 in the control group (a total of 210 patients) are needed to reject the null hypothesis, stating that the mean in the intervention group and the control group is the same, with a power of 95%. The type I error probability associated with this test of this null hypothesis is 5%.

Power calculation for the secondary outcome

The secondary outcome measure is the continuous variable mental component, SF 36. If the true difference between the intervention and control group is 7 points, and the standard deviation in the control group is 18 points, [21] we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability of (power) 0.80. The type I error probability associated with this test of this null hypothesis is 5%.

Statistical analyses

Data will be pseudo-anonymised and analysed blinded by a trial-independent statistician using intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous outcome measures.[78] Using MMRM ensures that missing data values (in case of the primary and

secondary outcome) will not create bias as long as the values are missing at random. Two-sided tests are performed. The level of significance is set at 5%. With regard to multiplicity, gate keeping will be used to adjust the observed P values for primary and secondary outcomes.[79] Both unadjusted and adjusted P values will be reported.

For the primary and secondary outcomes, sensitivity analysis will be conducted to assess the potential impact of values missing not at random. For each intervention group (A and B) some quantities (imputing quantities) are computed to be used to impute missing values in a group (A or B) as follows. A comparison between group A and group B where missing values in group A are imputed using imputing quantities obtained from group A and missing values from group B are imputed using imputing quantities obtained from group B is referred to as a best case analysis. If missing values in group A are imputed using imputing quantities obtained from group B and vice versa the comparison is called a worst case analysis. The imputing quantities for the primary outcome are the group mean at T1 (X1-bar), the group mean at T4 (X4-bar), the group mean at T6 (X6-bar), the mean difference between the value measured at T4 and that measured at T1 (delta 1), and the mean difference between the value measured at T6 and that measured at T4 (delta-2). Table 3 explains how the quantities are used to impute missing values in a group (either the same group or the other intervention group). If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that of the corresponding parameter calculated using complete case data it is replaced by the latter SE when the P value is calculated (Table 3).

Long-term register-based outcomes will be analysed by two different models: non-negative count outcomes (e.g., number of contacts with hospital or number of visits to general practitioners) will be analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and time-to-event data (e.g., cause-specific mortality and leaving the labor market) will be analysed

with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-economic outcomes, competing risks due to mortality will be considered if a large proportion of patients die during follow-up.

Exploratory data will be analysed using appropriate statistical methods according to the type of data (see Table 2). SPSS version 17.0 and SAS version 9.3 will be used.

Table 3. Statistical analysis

Observed pattern in group B at 1, 4, and 6 months	Imputed value in group B at 1 month	Imputed value in group B at 4 month	Imputed value in group B at 6 months
mis[A], mis, mis	X1-bar[B]	X4-bar[C]	X6-bar[D]
mis, mis, Y3[E]	Y3 – (delta1[F] + delta2[G])[H]	Y3 – delta2	
mis, Y2, mis	Y2 – delta1		Y2 + delta2
Y1, mis, mis		Y1 + delta1	Y1 + delta1 + delta2
Y1, Y2, mis			Y2 + delta2
Y1, mis, Y3		(Y1 + delta1 + Y3 - delta2)/2	
mis, Y2, Y3	Y2 – delta1		

Table to explain the use of imputing quantities derived from observed values in a group (group A) to impute missing values in a group (group B). mis=missing value, X1=value at month 1, X4=value at month 4, X6=value at month 6.
[A]The value at 4 months is missing in group B, [B]Mean of values observed in group A at time 1 month. [C]Mean of values observed in group A at time 4 months. [D]Mean of values observed in group A at time 6 months. [E]Observed value in group B at time 6 months. [F]The mean of difference between values observed at time 4 months and value observed at time 1 month in group A, [G]The mean of difference between value observed at time 6 months and value observed at time 4 months in group A, [H]If an imputed value is 0 it is set equal to 0.

Interim analysis and Data Monitoring Safety Committee (DMSC)

The DMSC works independently from the funder and has no competing interests, and consists of two clinicians and a statistician. The committee is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. In line with the terms of the Data Monitoring and Safety Committee charter, one formal interim analysis meeting will be held to review data relating to treatment efficacy, participant safety, and quality of trial conduct. The three members of the Data Monitoring and Safety Committee will meet when the 12 week follow-up data of about 50% of the trial participants have been obtained. Any serious adverse events will be registered as part of the data collection and the overall number of adverse events will be reported at the meeting.

Complementary studies

The Surveysbased study. The post-discharge status of the patients treated with RFA will be explored through a national survey. The standardised questionnaires SF-36,[67] Hospital Anxiety and Depression Scale (HADS), [68] EuroQoL-EQ-5D, [69, 70] Heart Related Quality of Life (HeartQoL R), [71] International Physical Activity Questionnaire (IPAQ), [72, 73] and a questionnaire developed by the Danish Heart Foundation on the extent and quality of rehabilitation offered will be sent to patients having undergone treatment for RFA, 6-12 months post-discharge. The instruments are all validated and have good reliability and responsiveness.[68, 72, 74, 75, 80, 81] The data will provide knowledge on patients' self-rated health, quality of life, anxiety and depression, economic situation and the extent and quality of the rehabilitation currently received. Patients were identified through the National Patient Register [59] and questionnaires were sent out to 608 patients. We anticipate 25% will decline participation, leaving an estimated 456 questionnaire respondents. Data will be anonymised and analysed by relevant descriptive statistical methods.

Qualitative post intervention study

After the intervention, 10% of the participants from the intervention group will be strategically chosen for an interview in order to explore the experiences and processes behind the potential effects of the intervention. The qualitative study will explore patient experiences of participating in the CopenHeart$_{RFA}$ programme and investigate which components were meaningful.

To achieve maximum variation, qualified interviewees are chosen on the basis of sex, AF type, and current heart rhythm.[82] The analysis will be inspired by Ricoeur's theory of interpretation consisting of three levels: naive reading, structured analysis and critical interpretation and discussion.[83]

The results will be presented in themes based on patient experience and evaluation of the intervention. As an example we will look for explanations for the results in physical capacity and mental health as described by the patients. We are using mixed method to explore all aspects of the intervention, but the qualitative findings are seen as a complementary study to the primary randomised clinical trial.

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-utility of cardiac rehabilitation compared with treatment as usual in the study population. The economic evaluation will compare the costs to quality adjusted life years (QALY) and take a societal perspective, as recommended nationally. QALYs and costs will be assessed at the end of the intervention, 6 months from randomisation, and later after 24 months from randomisation using register-based follow up.

QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[84, 85] The estimated calculations will be valued using Danish preference weights.[86] Information on costs will only include costs that are expected to differ

between the intervention and usual care group.[73] Costs included in the evaluation are health costs associated with the rehabilitation programme, other health care costs (health care utilization besides rehabilitation), patient costs and costs of productivity losses. Information on costs will be collected by a mixture of activity-based costing, surveys, patient diary and by the use of public records. Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER). Sensitivity analysis will be conducted to express uncertainty in the estimates.[87] The reporting of the ICER is presented using Bayesian methods, including bootstrapping and presented as cost-effectiveness acceptability curves.[88]

Ethics

The inclusion started December 2011 and is approved by the Regional Ethics Committee (number H-1-2011-135) and the Danish Data Protection Agency (no. 2007-58-0015). All eligible patients will be informed about the trial verbally and in writing, and the patients are included after informed consent has been obtained. All data will be handled confidentially and patients ensured anonymity. The trial complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01523145). An independent international safety committee monitors the trial. All serious and adverse events will be registered and reported in accordance with the safety charter.

Not providing rehabilitation to the control group can be ethically justified as current national and international guidelines give no specific recommendations on cardiac rehabilitation for patients treated for AF with RFA. The scope and quality of rehabilitation offered to this population is unknown, but suspicions are that generally no rehabilitation is offered in Denmark. The only way patients can get supervised exercise training is if they voluntarily enrol in a programme e.g. through non-profit organisations. The survey based complementary study, described previously in this paper, will hopefully provide more insight into this. In screening patients for participation, the

enrolling nurse or physician will exclude those with a compelling rehabilitation need. Furthermore, patients are informed of the study design before giving their consent, and are free to decline participation.

Discussion

Due to the difference in the three patient groups that are included in the overall CopenHeart trial, patients treated for infective endocarditis, heart valve surgery and patients treated for AF with RFA, the intervention and outcome measures differ slightly, most importantly in the case of the psycho-educational intervention, which is longer for patients treated for infective endocarditis and heart valve surgery, because of the complexity of the diseases and the longer hospitalisation. Biochemical markers are similarly chosen differently to address the various co-morbidities of the three diseases and some disease specific questionnaires are chosen to capture the specific disease relevant issues.

To our knowledge no previous randomised clinical trials or observational studies have been conducted focusing on integrated cardiac rehabilitation for AF patients treated with RFA, so therefore it is not known what effect, if any, rehabilitation has on these patients. However, in the light of evidence from other groups of patients with heart disease a positive effect can be expected.[23, 89, 90]

This trial is different from previous trials because we apply a comprehensive rehabilitation intervention which consists of both a physical training component and a psycho-educational component. This combination is hypothesised to strengthen the patient both physically and mentally even if the patient has AF. Also we use mixed methods, which has its strengths in both using qualitative and quantitative research design.[34]

The major strengths of this randomised clinical trial are that it includes consecutive patients with a reasonable number of inclusion and exclusion criteria securing external validity for the results. The trial employs central, stratified randomisation which secures against selection bias.[91-93] The primary outcome is assessed blinded to intervention and so are all statistical analyses, which should reduce detection and interpretation bias.[91-93] The long-term outcomes are based on data taken from public registry data, which are also likely not to include biased reporting of outcomes.

The secondary outcomes of self-rated mental health are by nature subjective and are likely to be biased.[91-93] The patients answer questionnaires independently of the researchers. Data management is handled independently from the researchers that interpret data. All questionnaires are distributed electronically. All data entry is stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart Group.

Trial limitations include the fact that it is known from previous rehabilitation trials [33] that patients in the control group have a tendency to do physical training due to the focus on the subject in the recruitment process. We will be aware of that when we recruit and not focus on giving extensive information about the exercise programme, or encourage patients to do physical training before knowing what group they are randomised to. Any difference between patients completing the intervention and those not completing (drop-outs) will be carefully discussed when evaluating the intervention, results and the suitability for implementation. The trial is designed with multiple statistical comparisons so results will be interpreted with caution. Further limitations of the trial and methods used are similar to those of other trials including physical exercise and physical testing, namely time-of-day, and day-to-day variation using exercise testing.[94] To ensure standard testing of all physical exercise tests in the trial, standardised instructions for patients have been developed as

described in the methods section. Conversely, the trial population will be representative for the true RFA population, meaning that some patients will have AF and some sinus rhythm while exercising and testing, and this will facilitate implementation of The CopenHeart$_{RFA}$ trial rehabilitation programme in daily clinical practice. We are aware that patients treated with RFA are a highly selected group of patients with paroxysmal or persistent AF, and they are properly more likely to participate and complete a rehabilitation programme, compared to patients with e.g. permanent AF since patients with permanent AF often are older and suffer from co-morbidity [4]. Therefore we do not expect to generalize the results to all AF patients.

The challenge with the set-up is that patients come from considerable distances and therefore some will decline participation. Also, due to the nature of rehabilitation trials, the patients have to meet at the hospital frequently, especially when randomised to the experimental intervention group.

The trial will, to our knowledge, be the largest trial conducted dealing with rehabilitation AF ablation recipients. If a positive effect of integrated rehabilitation is found, it may have an impact on the rehabilitation offered to patients treated for AF with RFA at international level. The trial is expected to identify an intervention which can improve health and quality of life for the patients, and subsequently reduce healthcare utilization and costs, as well as mortality.

Publication policy

The results of the trial will be published in appropriate peer-reviewed journals regardless of the outcome. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors.

The outcome data will be analysed and published in the short term of 4 and 6 months and the long term of 24 months. Due to the comprehensiveness of the outcome measures further post hoc analysis will be published in separate papers. Economic and long term follow up will be reported as data becomes accessible.

Timetable

Recruitment started in December 2011 in one heart centre and in July 2012 in the other participating heart centre and is planned to finish in December 2013. To achieve adequate participant enrolment, patients in doubt are contacted after hospital discharge by phone. The inclusion rate is closely monitored every week.

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Authors' contributions

SKB and ADZ in collaboration with SSR, JLH, MP, LCT, PW and CG designed the trial. SSR in collaboration with SKB, ADZ, TBR, KLS, JHS, CG, LCT, SD, JLH and SD drafted the manuscript. All revised the manuscript critically. All authors have given their final approval of the version to be published.

Competing interests

None.

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The effect of integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised CopenHeart$_{RFA}$ trial protocol

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Article summary

Article focus

- The CopenHeart$_{RFA}$ trial is a randomised clinical trial investigating the effects of comprehensive cardiac rehabilitation versus usual care for patients treated for atrial fibrillation (AF) with ablation.
- The hypothesis is that comprehensive cardiac rehabilitation improves physical capacity and mental health.
- Using a mixed methods approach, a broad range of outcome measures are collected to evaluate the intervention.

Key messages

- AF affects 1-2% of the population. Patients with AF experience diminished quality of life and are afraid to do physical exercise after treatment with ablation.
- No studies exploring the effects of rehabilitation of patients treated for AF with ablation have been published.
- This trial is the first to examine physical functioning and to test a comprehensive rehabilitation programme on a large population of patients treated for AF with ablation.

CopenHeart$_{RFA}$ will provide much needed evidence and insight on the post-discharge status and rehabilitation needs of patients treated for AF with ablation.

Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trials with central randomisation, multi-centre participation, blinded assessment and analysis.
- We are aware of the day to day variation that can appear when carrying out ergospirometry, in testing and that the performance can depend on the individual tester. Accordingly, we will interpret the findings conservatively.

Abstract

Introduction

Atrial fibrillation affects almost 2% of the population in the Western world. To preserve sinus rhythm, ablation is undertaken in symptomatic patients. Observational studies show that patients with atrial fibrillation often report low quality of life and are less prone to be physically active due to fear of triggering fibrillation. Small trials indicates that exercise training has a positive effect on exercise capacity and mental health, and both patients with recurrent atrial fibrillation and in sinus rhythm may benefit from rehabilitation in managing life after ablation. No randomised trials have been published on cardiac rehabilitation for atrial fibrillation patients treated with ablation that includes exercise and psycho-educational components.

Aim

To test the effects of an integrated cardiac rehabilitation programme versus treatment as usual for patients with atrial fibrillation treated with ablation.

Methods and analysis design

The trial is a multicentre parallel arm design with 1:1 randomisation to the intervention and control group with blinded outcome assessment. 210 patients treated for atrial fibrillation with radiofrequency ablation will be included. The intervention consists of a rehabilitation programme including four psycho-educative consultations with a specially trained nurse and 12 weeks of individualised exercise training, plus the standard medical follow-up. Patients in the control group will receive the standard medical follow-up. The primary outcome measure is exercise capacity measured by VO_2 peak. The secondary outcome measure is self-rated mental health measured by the Short Form 36 questionnaire. Post intervention, qualitative interviews will be conducted in 10% of the intervention group.

Ethics and dissemination

The protocol is approved by the regional research ethics committee (number. H-1-2011-135), the Danish Data Protection Agency (reg. nr. 2007-58-0015) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may possibly impact on rehabilitation guidelines.

Registration: Clinicaltrials.gov identifier: NCT01523145

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and affects 2% of the population in the Western world.[1-3] Typical symptoms are palpitations, dyspnoea, fatigue, dizziness, and syncope. Patients' symptoms and the length of periods in AF are highly variable both for the individual and between patients.[4-6] AF is associated with increased risk of stroke, other thromboembolic events, and heart failure.[6-8] Hospitalisations due to AF account for one third of all admissions for cardiac arrhythmias.[8] As the prevalence of AF increases with age, the incidence of AF is increasing due to an ageing population.[2, 9, 10] After 40 years of age, the lifetime risk of developing AF is 25%. [11] The annual cost of AF is high in comparison with other diseases.[12] Therefore, AF has become an economic burden and this will continue to increase over the coming decades.[13] Thus, AF has now become a health, social and economic challenge in the Western world. [14]

Primary treatment goals for individuals with AF are re-establishing and maintaining sinus rhythm, decreasing AF symptoms, and prevention of complications. In accordance with current national and international guidelines, radiofrequency ablation (RFA) is often undertaken in symptomatic patients. RFA is an invasive treatment, intended to cure AF and has a success rate of 77% versus 52% for antiarrhythmic medication.[15] In Denmark, around 600 RFAs are conducted annually at two heart centres.

A cohort study of 655 patients from a randomised trial found that AF symptoms are a negative predictor for patients' physical capacity,[16] and in the presence of AF, patients do fewer physical activities.[17] Smaller observational studies and a randomised trial investigating the effect of exercise

training on AF patients found increased exercise capacity and a decreased resting heart rate after training.[18-20]

Previous studies show significantly impaired quality of life in patients with AF compared to healthy controls measured by the questionnaire Short Form 36 (SF-36). The general health component (± standard deviation) was 54±21 in AF patients compared to 78±17 in healthy controls.[21] A qualitative study demonstrated that educational help after AF treatment is lacking, even though symptoms of distress and lack of self-management regarding symptoms like palpitations, dyspnoea, and fatigue are common.[22] Furthermore, small observational studies indicate a positive effect of exercise training on patients with AF in terms of mental health and physical activity (15% increase of VO_2).[18, 19] However, these findings need confirmation in larger randomised clinical trials.

Secondary prevention initiatives including cardiac rehabilitation are recommended by the European Society of Cardiology (ESC).[23] Studies exploring the effects of rehabilitation for patients treated for AF are lacking. As there is no evidence of its efficacy, rehabilitation is not systematically provided in Denmark and most often patients treated for AF with RFA are not offered any rehabilitation at all. The evidence for general cardiac rehabilitation is strong, but it is found that it is poorly implemented and only selected patient groups are offered full comprehensive cardiac rehabilitation programmes, even though ESC recommends such programmes.[24] Research has mainly been conducted within patients with coronary heart disease and heart failure, where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way,[25, 26] as well as improve quality of life.[27] More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery [28] and an increase in peak VO_2 of 2.3±2.2 (SD) ml/kg per minute in the intervention group

compared with −0.3±2.1 (SD) ml/kg per minute in the control group, as well as a significant change in quality of life in older patients with heart failure.[29]

~~Although evidence of its efficacy is strong, general cardiac rehabilitation is still poorly implemented and often only on selected populations thus the development of full comprehensive preventive programmes, according to the ESC recommendations is warranted.~~[24] ~~Studies exploring the effects of rehabilitation of patients treated for AF are lacking. As there is no evidence of its efficacy, the rehabilitation provided is presumably often suboptimal or totally lacking. Lessons, however, might be learned from rehabilitation studies in patients with related cardiac conditions. The positive effects of cardiac rehabilitation have been well documented, particularly in patients with coronary heart disease and heart failure, where rehabilitation has been proven to reduce hospital re-admissions and mortality in a cost-effective way,~~[25, 26] ~~as well as improve quality of life.~~[27] ~~More specifically, studies on the effect of exercise training have demonstrated an increase in exercise capacity of up to 38% in patients after valve replacement surgery~~[28] ~~and an increase in peak VO_2 of 2.3±2.2 (SD) ml/kg per minute in the intervention group compared with −0.3±2.1 (SD) ml/kg per minute in the control group, as well as a significant change in quality of life in older patients with heart failure.~~[29] Traditional cardiac rehabilitation has focused on physical training and standardized programmes, but studies now indicate that individualized content and supervised exercise components can ~~are key design characteristics for~~ improving outcomes.[30] In addition to exercise training, there is evidence to support interventions that include patient education, which in patients with coronary heart disease has ~~been~~ shown to improve health related quality of life and decrease healthcare costs, [31] and psychological support, which has been shown to improve psychological symptoms ~~in patients with coronary heart disease~~, such as depression and anxiety.[32] ~~Evidence on the efficacy of comprehensive interventions for patients treated for AF, however, is needed.~~

Interventions designed to cover both physical and psychological problems may provide the best method for optimising functioning and enhancing quality of life.[33] We have not been able to identify randomised trials or observational studies in patients who have undergone RFA for AF that offer both psycho-educational intervention and physical training. Therefore, the CopenHeart$_{RFA}$ trial was undertaken with the aim of testing a rehabilitation programme consisting of physical exercise and a psycho-educational intervention versus treatment as usual for RFA treated AF patients.

Methods

Design

Major parts of the method section and trial design in this paper are similar to two other randomised clinical trials, CopenHeart$_{VR}$ and CopenHeart$_{IE}$, and therefore sections from this paper will be copied in these trial protocols (Sibilitz KL et al. *Effect of integrated cardiac rehabilitation versus treatment as usual for patients with isolated heart valve surgery: The randomised CopenHeart valvular trial protocol.* drafted October 2012; and Rasmussen TB et al. *A randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients treated for infective endocarditis – the CopenHeart$_{IE}$.* Accepted for publication, BMJ Open, October 2012).

The CopenHeart$_{RFA}$ trial is a multi-centre, multidisciplinary randomised clinical superiority trial. Secondary, qualitative data are also collected and the two methods are integrated by applying a mixed method embedded experimental design (Figure 1).[34, 35] Quantitative methods are applied, with specified quantitative pre- and post-measures to evaluate the effect of the experimental intervention. Alongside quantitative measurements, qualitative data will be collected. The premise of mixed methods research is that the use of qualitative and quantitative approaches in combination

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provides a better understanding of the research problems than either approach alone, because different types of questions require different types of data and that mixed methods research provides strengths that offset the weaknesses of both qualitative and quantitative research.[34] The methods are integrated by applying a mixed method embedded experimental design and include qualitative data to develop the intervention and to examine the process of the intervention and the results of the trial (see Figure 1).[34, 35] The rationale for this approach is that the quantitative findings provide a general understanding of the research problem through statistical results while qualitative findings refine and explain the results by exploring participants' views in greater detail and will be presented by themes of patient thoughts or concerns about the intervention. Evaluation using qualitative research methods is increasingly promoted in evidence-based rehabilitation.[36-39] Qualitative research alongside randomised controlled trials can contribute in several ways to the development and evaluation of complex healthcare interventions and may be particularly useful in evaluating interventions that involve social and behavioural processes that are difficult to explore or capture using quantitative methods alone.[40] As patient participation is paramount for the efficacy of the rehabilitation,[41] we find it highly valuable to include the patients' perspective in the development and evaluation of the intervention. This paper presents the study protocol for the CopenHeart$_{RFA}$ randomised clinical trial. The complementary studies, including the qualitative part of the trial are briefly described in a separate section.

The trial is described in accordance with the current SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials).[42] Results will be reported following the CONSORT (CONsolidated Standards Of Reporting Trials) guidelines for non-pharmacological interventions.[43]

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Trial hypotheses

The primary hypothesis is that the rehabilitation program increases physical capacity among AF patients treated with RFA after 4 months measured by VO_2 peak, which is expected to be 20% more than in the control group receiving standard treatment alone. The estimate of 20% is based on findings from pilot studies including patients with permanent AF which found an increase of 15% in VO_2 peak. We therefore expect a VO_2 peak in the intervention group of 18 ml/kg/min and of 15 ml/kg/min in the control group, corresponding to a difference of 20% (3 ml/kg/min).[44]

The secondary hypothesis is that the rehabilitation programme increases quality of life and self-rated mental health among AF patients treated with RFA after 6 months by 3 points on the Medical Outcome Study Short Form 36 (SF-36) questionnaire mental component scale, compared with control participants receiving standard treatment.[19]

Exploratory hypotheses are that the experimental intervention decreases AF recurrence; improves self-rated health and sleep-quality; reduces early retirement from work, use of health care services and mortality, and is cost efficient.

Trial participants

Consecutive patients hospitalised for AF and treated with RFA at two heart centres in Denmark (Gentofte Hospital and Rigshospitalet, Copenhagen University Hospital) will be screened for inclusion and approached for trial participation (Figure 2). Regardless of RFA outcome, both patients with recurrent AF and patients in sinus rhythm after the ablation will be included in the trial. Patients 18 years of age or older, Danish speaking, and providing verbal and written informed consent will be eligible for participation. Patients unable to understand trial instructions, pregnant or

breastfeeding, with reduced ability to follow the planned programme due to other physical illness, who prior to RFA have been doing intense physical exercise or sports at competitive level several times a week, or do not wish to participate, and patients already enrolled in clinical trials that prohibit participation in additional trials are excluded.

Trial procedure, randomisation, and follow-up

Patients will be approached for participation during their hospitalisation for RFA. Information will be given by a nurse or physician from the research team, who will obtain informed written consent after the RFA procedure. A brief oral introduction is initially given together with written information describing the trial and implications for the patient in detail. The patient is given ample time to read the information and if necessary involve a relative in the decision making. The enrolling nurse or physician will return after the RFA or call the patient to answer any questions the patient or their relative might have. The patient should subsequently be able to provide informed consent or reject participation. After the informed consent form is signed, baseline data will be collected including the baseline questionnaire package, demographic variables, and clinical characteristics (Table 2). Then the Copenhagen Trial Unit (http://www.ctu.dk/) is contacted for central randomisation of the participant. Randomisation is conducted according to a computer-generated allocation sequence with a varying block size kept unknown to the investigators. Participants are randomised 1:1 to the experimental intervention group or the control group and stratified according to sex and type of AF (persistent or paroxysmal). Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. For both groups, the follow-up assessment will take place at 1 month, 4 months, 6 months, and 12 months post-discharge, and a register-based follow-up assessment will be conducted at 24 months (Table 2). In

case of complications to the RFA after enrolment in the trial, the patients will be handled individually (e.g., arrhythmia or inguinal haematoma).

The patients answer questionnaires independently of the researchers, and before randomisation. All questionnaires are distributed electronically, thus data management is handled independently from the researchers that interpret data. All data are stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group.

Personal information about potential and enrolled patients will be collected electronically and shared in a database only accessible to those within the project group responsible for patient recruitment, in order to protect confidentiality before, during and after the trial.

Due to the nature of rehabilitation, the intervention group is not blinded for the patients or the investigators, but the outcome assessment of the primary outcome, the statistical analyses, and drawing of conclusions will be conducted blinded for the allocated intervention group.

The experimental intervention group

Patients in the experimental intervention group will follow the integrated cardiac rehabilitation programme consisting of a psycho-educational component and an exercise training component alongside standard treatment (described below). The patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

The physical exercise training component

The intervention has been developed and partly tested in a clinical rehabilitation trial, the COPE-ICD trial [45] , which included patients with an implantable cardioverter defibrillator. We here observed a significant impact of the intervention on peak VO_2, physical capacity and self-assessed mental health. The intervention has been modified for patients treated for atrial fibrillation with

ablation as described below. The CopenHeart physical exercise intervention meets European [24]and Danish guidelines [46]for physical exercise in patients with heart disease, and complies with The National Danish Board of Health recommendations for physical exercise in daily living for heart patients.[47]

The physical exercise starts one month after the ablation and after the first ergospirometry test and comprises the following three elements:

Individually planned physical exercise by specially trained physiotherapists. Integrating detailed information concerning AF symptoms and RFA, co-morbidity, hospitalisation, activities of daily living, and level of physical activity prior to RFA, a specially trained physiotherapist conducts a patient telephone consultation up to 30 minutes. The consultation is based on initial testing of the patient including a cardiopulmonary exercise test, a 6 minutes walking test and a 'sit and stand' test, described in the outcome section. For all patients, a rehabilitation plan is prepared as an individual training diary, and all patients are instructed in the use of a heart rate monitor (Polar Watch provided by Rigshospitalet). The heart rate monitor and diary is essential to ensure CopenHeart training protocol compliance and they are returned for data collection at the end of the exercise training intervention.

Intensive exercise training programme. Physical exercise is initiated at Rigshospitalet four weeks after RFA to ensure optimal rest and healing. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and Corus Exercise Assistant, CEA, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST-depression, ST-elevation, Q- or T-wave altering, atrial fibrillation, and ventricular arrhythmias and training intensity level are monitored.

After 1-3 exercise training sessions at Rigshospitalet, the patient continues the programme at a local CopenHeart certified training facility supervised by physiotherapists or as supervised home-based training. Supervised home-based exercise training has shown similar results to hospital-based exercise training [31]and has been confirmed in a Danish setting.[48]

The physical exercise training continues for 12 weeks, comprising three sessions weekly of 60 minutes, in total, 36 sessions. The training protocol consists of cardiovascular training and strength exercises to improve endurance and muscular strength.

An exercise session consists of 10 minutes warm up, 20 minutes bicycling, 20 minutes strength, and a 10 minutes stretching and cool-down period. . Using the results from the cardiopulmonary exercise test performed prior to the initial training session, in combination with the Borg scale measuring subjective exhaustion, the aerobic exercise is performed with gradually increasing intensity throughout the exercise intervention period, corresponding to 13 to 17 on the Borg Scale and 50% to 80% of the maximum heart rate. The anaerobic resistance training is initiated at 30% to 40 % of 1 repetition maximum (RM) for the upper body, and 40% to 50 % of 1 RM for the lower body, with an increasing work load during the training sessions. To achieve cardiovascular adjustment and reduce the risk of malignant cardiac arrhythmias and ischemia, the training session is initiated and terminated with a warm up and a cool down period to gradually increase and decrease training intensity and heart rate. This cardiovascular adjustment has been proven to reduce the risk of ischemia and arrhythmia in relation to exercise training.[49, 50] Training is predominantly performed in the upright position to reduce left ventricle preload (diastolic volume) and the risk of ischemia and arrhythmias due to heart failure.[50]

Sustained moderate physical exercise daily. Participants are instructed to perform moderate physical exercise at least 30 minutes a day during the intervention period, e.g., bicycling, walking,

gardening, jogging or recreational sports. Participants are encouraged to continue with moderate physical exercise throughout life.

The psycho-educational component

The aim of the psycho-educational intervention is to provide emotional support and improve coping skills and illness appraisal in order for the patient to respond appropriately to physical and psychological symptoms. Education and information about the disease prepare the patient for expected symptoms and sensations. Dialogue and shared reflection facilitate strategies for coping with symptoms and experiences associated with the condition, e.g., anxiety and fear. Cardiac care nurses with specific training will perform the psycho-educational intervention. Some of the most commonly reported concerns of patients treated for AF with RFA, such as recurrent AF, and concerns about being able to manage a working life are outlined in a guide which nurses use to address when and if relevant (see Table 1). Information given will also be based on national guidelines and standard treatment of patients treated for AF. The consultations focus on managing life after AF treated with RFA by establishing a joint approach to disease management and coping strategies, taking a holistic view. The psycho-educational intervention is inspired by R.R. Parse's Human Becoming Practice Methodologies' three dimensions.[51] These are interpreted as: 1) discuss and give meaning to the past, present and future, 2) explore and discuss events and possibilities and 3) move along with envisioned possibilities. According to this theory, there are three ways of changing health: creative imaging, that is to see, hear and feel what a situation might be like if lived in a different way, affirming personal patterns and value priorities, and shedding light on paradoxes, that is, looking at the incongruence in a situation and changing the view held of something. The nurse is present in the process through discussions, silent immersion and reflection. The human becoming practice methodology was chosen to apply a holistic patient approach, focusing on the coping and transformation process of the individual person. Furthermore, the method is already

extensively used in the outpatient heart clinics at the heart centre at Rigshospitalet, such as for patients with inherited heart diseases and adults with congenital heart disease and is documented in the COPE-ICD trial.[45, 52] The consultations take place in a quiet setting at the out-patient clinic and will last for approximately one hour. The nurse is able to facilitate contact with or seek advice from a physician if needed. The first consultation will be approximately one month after discharge, and then once every four to six weeks, with a total of four consultations. Consultations can be done by telephone, in accordance with the patient's wishes. The primary investigator will attend the consultations regularly to ensure protocol compliance.

Table1. Guide to the psycho-educative consultation.

Number visit	**1**	**2**	**3**	**4**
Ask the patient how he/she has been since the ablation. What has happened since last time he/she was here?	X	X	X	X
Invite the patient to talk about his/her thoughts and questions.	X	X	X	X
Ask about the time leading up to RFA and his/her AF history. Experiences before, under and after the hospitalization and RFA.	X			
Talk about how it is to have had/ have AF and been through RFA, how that have affected the patient's life. Is there something he/she avoids or feel like he/she cannot do anymore? This in relation to family relations, friends and free time/ leisure activities.	X			
Make sure that the patient has started the physical	X	X	X	

training and talk about how it is going. Are training appointments booked?	
Talk about if the patient has changed his/her feelings or thoughts of the body and its functions.	X
Talk about recognition of symptoms, how the patient is feeling about recurrence of AF and opinions about future AF treatment. Worries about recurrence of AF, strategies of prevention.	X X (X) (X)
Information/recommendations in relation to the subjects/problems discussed.	X X X X

Intervention deviations

Both components of the intervention will be supervised regularly by the primary investigator to ensure protocol compliance. Modification of the allocated intervention due to surgery complications, rehospitalisation or emerging co-morbidities (e.g. recurrent AF, musculoskeletal problems) will be individually assessed, and the time of the primary outcome assessment at four months (described in section below) will be corrected in accordance with changes in the intervention.

Control group: treatment as usual

Patients in the control group will follow standard treatment for patients treated for AF with RFA including 3-6 months follow-up with a physician and a 12 months follow-up with a nurse. Furthermore, patients will be contacted at 1, 4, 6 and 12 months for outcome assessment including clinical data collection.

Outcomes and data collection

Data will be collected to evaluate the effect and meaning of the intervention. The primary and secondary outcomes reflect the primary modifiable factors of the intervention. Since this is a complex intervention with two main components, an exercise component and a psycho-educational component, this is reflected in the primary and secondary outcome. The intervention has been tested in ICD patients (unpublished data in the COPE-ICD trail, available on request) and the intervention reflects well in the chosen measures that have found to be sensitive to changes based on the intervention. Since almost no evidence exists for rehabilitation programmes for patients treated for AF with RFA, data on a number of outcomes will be collected for exploratory analyses.

Primary outcome

Physical capacity measured by peak VO_2 according to a standardised protocol developed in accordance with guidelines [53, 54] 1, 4 and 12 months after randomisation (Table 1).

Physical capacity is measured by peak VO_2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Schweiz). This is chosen as a primary outcome since this is standard in exercise based rehabilitation trails. The test is performed according to current guidelines for ergospirometry testing, and by ergometer bicycle, simultaneously monitoring heart-rhythm, blood pressure, electrocardiogram (ECG), and measuring gas-exchange during workload and in the following recovery period. The average test duration is 10-15 minutes including pre- and post- test phase without work load. Before each session calibration is performed to address changes in room temperature, humidity and air oxygen content. A standardised ramp-protocol is used with initial work load of 25 or 50 watts, increasing gradually by 12.5 watts every minute until peak exhaustion. Peak exhaustion is evaluated by a respiratory exchange ratio (RER) ≥ T 1.10 or subjective

exhaustion of the patient. In order to equally encourage the patients, independent of the tester, a standardised guide has been developed. During the test period, clinical manifestations, ECG abnormalities (ST depression, ST elevation, Q- and T-wave changes, supraventricular or ventricular arrhythmias), blood pressure response, and several physiological variables are observed and documented. The test will be performed by either a cardiac care nurse or a physician. For safety reasons preset criteria for initiation and/or termination of the test have been defined.

Secondary outcome

Self-rated mental health is measured by the SF-36 questionnaire, [55-57] mental component score, after 1 month, 4 months, 6 months and 12 months (Table 2).

Exploratory outcomes

Long-term follow-up: Register data regarding mortality, causes of death, hospitalisation/re-hospitalisation, emergency room visits, outpatient visits, health care costs, visits to the general practitioner, medication use, employment status and payment of welfare benefits (sick leave payment and early retirement pension) will be collected at 24 months to assess long term effects of the intervention (Table 2). Danish recording keeping for the data mentioned above functions well, with only a small percentage of lost data. [58] Consequently the method is well suited as an outcome measure in small patient populations. Data will be extracted from the Danish National Patient Register, the Danish National Health Service Register, the Danish National Prescription Registry, the Danish National Causes of Death Register and records of transfer payments and labour market affiliation.[59-62]

6 minutes walking test: The maximum walking distance (in meters) within 6 minutes is measured, using standardized instructions,[63] while subjective exhaustion with regard to fatigue and dyspnoea using the Borg scale [64] is registered.

Sit and stand test: The maximum amount of times a patient can sit and rise from a normal chair within 30 seconds is recorded. Subjective exhaustion is measured using the Borg exhaustion scale.[64]

Biochemical screening: Potassium, sodium, haemoglobin and creatinine. 1 EDTA plasma heparin tube will be frozen (80°) for further analyses (pro-BNP, BNP, copeptin).

Other exploratory outcomes: AF recurrence, self-rated health and sleep-quality, retirement from work, use of health care services, mortality and cost efficiency (Table 2).

Table 2. Exploratory quantities subjected to post-hoc analysis

Quantity	Time of measure (months)	Type of quantity
Demographic		
Sex	BL	Binary (M/F)
Age, height, weight,	BL, 1,4,12	Continuous
Marital, occupational, educational status	BL	Categorical
Clinical		
NYHA- classification	BL, 1, 4, 12	Continuous
Previous heart disease, diabetes mellitus, kidney disease, pulmonary disease (COPD), co-morbidities, hypertension, dyslipidaemia, smoking	BL	Binary (Y/N)
Medication	BL, 1, 4, 12	Binary (Y/N)
AF specific data:		
Type of atrial fibrillation	BL	Categorical
Number of ablations	BL, 1,4,12	Binary (Y/N)
Atrial fibrillation symptoms	BL, 1,4,12	Continuous
CHA_2DS_2VASc score	BL, 1,4, 12	Continuous
The European Heart Rhythm Association symptom score	BL, 1,4, 12	Continuous
Paraclinical and imaging		
Blood work (Haemoglobin, infection-, kidney- liver and selected nutritional parameters, electrolytes, cholesterol- and thyroid	BL, 1, 4, 12	Continuous

status, ProBNP)		
Electrocardiogram	BL, 4, 12	Continuous
Physical function		
6 minute walking test [63]	BL, 1, 4, 12	Continuous
Sit to stand test [65]	1, 4, 12	Continuous
EVO recording	1,4,12	Categorical
Questionnaires		
Physical activity level [66]	BL, 1, 4, 6, 12, 24	Binary (Y/N)
SF-36 [67] HADS [68], QoL-CV [69]	BL, 1, 4, 6, 12, 24	Continuous
Emotions and Health [70]	BL	Continuous
Rehabilitation [71]	12	Continuous
HeartQoL R [72], EQ-5D [73]	BL, 6, 12, 24	Continuous
IPAQ [74]	1, 4, 12, 24	Continuous
MFI-20 [75]	BL, 1, 4, 12	Continuous
PSQI [76]	1, 6	Continuous
AFEQT[77]	BL, 1,4,12,24	Continuous

AFEQT, Atrial Fibrillation Effect on Quality-of-life; BL, baseline; CHA_2DS_2VASc, score for Atrial Fibrillation Stroke Risk; EQ-5D, EuroQoL; HADS, Hospital Anxiety and Depression Scale; HeartQoL R, Heart-Related Quality of Life; IPAQ, International Physical Activity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QoL-CV, Quality of Life - Cardiac Version; SF-36, Short Form 36.

Sample size calculation for the primary outcome

We are performing a randomised trial where the continuous variable VO_2 peak is the primary outcome. The control and the intervention group are independent and the ratio of patients in the intervention group to the patients in the control group is 1:1. A previous trial of patients with permanent AF found that VO_2 peak was normally distributed with a standard deviation of 3.8 ml/kg/min.[44] As the CopenHeart$_{RFA}$ trial has a more varied patient population who have all been treated for AF with RFA, which means that the majority of the patients will have sinus rhythm and the rest will have AF, the patients are not directly comparable with the patients in the previous trial, and we assume a standard deviation of 6 ml/kg/min to be more relevant. We consider a 0.5 standard

deviation to be the minimal relevant difference, equivalent to 3 ml/kg/min. Therefore, if the true difference between the intervention group and control group is 3 ml/kg/min and the standard deviation is 6 ml/kg/min in the control group, 105 patients in the intervention group and 105 in the control group (a total of 210 patients) are needed to reject the null hypothesis, stating that the mean in the intervention group and the control group is the same, with a power of 95%. The type I error probability associated with this test of this null hypothesis is 5%.

Power calculation for the secondary outcome

The secondary outcome measure is the continuous variable mental component, SF 36. If the true difference between the intervention and control group is 7 points, ~~.~~ [21] w~~W~~e will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability of (power) 0.80. The type I error probability associated with this test of this null hypothesis is 5%.

Statistical analyses

Data will be pseudo-anonymised and analysed blinded by a trial-independent statistician using intention-to-treat analyses and a mixed model with repeated measures (MMRM) for continuous outcome measures.[78] Using MMRM ensures that missing data values (in case of the primary and secondary outcome) will not create bias as long as the values are missing at random. Two-sided tests are performed. The level of significance is set at 5%. With regard to multiplicity, gate keeping will be used to adjust the observed P values for primary and secondary outcomes.[79] Both unadjusted and adjusted P values will be reported.

For the primary and secondary outcomes, sensitivity analysis will be conducted to assess the potential impact of values missing not at random. For each intervention group (A and B) some

quantities (imputing quantities) are computed to be used to impute missing values in a group (A or B) as follows. A comparison between group A and group B where missing values in group A are imputed using imputing quantities obtained from group A and missing values from group B are imputed using imputing quantities obtained from group B is referred to as a best case analysis. If missing values in group A are imputed using imputing quantities obtained from group B and vice versa the comparison is called a worst case analysis. The imputing quantities for the primary outcome are the group mean at T1 (X1-bar), the group mean at T4 (X4-bar), the group mean at T6 (X6-bar), the mean difference between the value measured at T4 and that measured at T1 (delta 1), and the mean difference between the value measured at T6 and that measured at T4 (delta-2). Table 3 explains how the quantities are used to impute missing values in a group (either the same group or the other intervention group). If the standard error (SE) of a parameter estimate calculated using imputed data is smaller than that of the corresponding parameter calculated using complete case data it is replaced by the latter SE when the P value is calculated (Table 3).

Long-term register-based outcomes will be analysed by two different models: non-negative count outcomes (e.g., number of contacts with hospital or number of visits to general practitioners) will be analysed by a Poisson model or a zero-inflated Poisson model if the number of zeros are large, and time-to-event data (e.g., cause-specific mortality and leaving the labor market) will be analysed with survival methods (Kaplan-Meier estimator and Cox regression model). Especially for socio-economic outcomes, competing risks due to mortality will be considered if a large proportion of patients die during follow-up.

Exploratory data will be analysed using appropriate statistical methods according to the type of data (see Table 2). SPSS version 17.0 and SAS version 9.3 will be used.

Table 3. Statistical analysis

Observed pattern in group B at 1, 4, and 6 months	Imputed value in group B at 1 month	Imputed value in group B at 4 month	Imputed value in group B at 6 months
mis[A], mis, mis	X1-bar[B]	X4-bar[C]	X6-bar[D]
mis, mis, Y3[E]	Y3 – (delta1[F] + delta2[G])[H]	Y3 – delta2	
mis, Y2, mis	Y2 – delta1		Y2 + delta2
Y1, mis, mis		Y1 + delta1	Y1 + delta1 + delta2
Y1, Y2, mis			Y2 + delta2
Y1, mis, Y3		(Y1 + delta1 + Y3 - delta2)/2	
mis, Y2, Y3	Y2 – delta1		

Table to explain the use of imputing quantities derived from observed values in a group (group A) to impute missing values in a group (group B). mis=missing value, X1=value at month 1, X4=value at month 4, X6=value at month 6.
[A]The value at 4 months is missing in group B, [B]Mean of values observed in group A at time 1 month. [C]Mean of values observed in group A at time 4 months. [D]Mean of values observed in group A at time 6 months. [E]Observed value in group B at time 6 months. [F]The mean of difference between values observed at time 4 months and value observed at time 1 month in group A, [G]The mean of difference between value observed at time 6 months and value observed at time 4 months in group A, [H]If an imputed value is 0 it is set equal to 0.

Interim analysis and Data Monitoring Safety Committee (DMSC)

The DMSC works independently from the funder and has no competing interests, and consists of two clinicians and a statistician. The committee is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. In line with the terms of the Data Monitoring and Safety Committee charter, one formal interim analysis meeting will be held to review data relating to treatment efficacy, participant safety, and quality of trial conduct. The three members of

the Data Monitoring and Safety Committee will meet when the 12 week follow-up data of about 50% of the trial participants have been obtained. Any serious adverse events will be registered as part of the data collection and the overall number of adverse events will be reported at the meeting.

Complementary studies

The Surveysbased study. The post-discharge status of the patients treated with RFA will be explored through a national survey. The standardised questionnaires SF-36,[67] Hospital Anxiety and Depression Scale (HADS), [68] EuroQoL-EQ-5D, [69, 70] Heart Related Quality of Life (HeartQoL R), [71] International Physical Activity Questionnaire (IPAQ), [72, 73] and a questionnaire developed by the Danish Heart Foundation on the extent and quality of rehabilitation offered will be sent to patients having undergone treatment for RFA, 6-12 months post-discharge. The instruments are all validated and have good reliability and responsiveness.[68, 72, 74, 75, 80, 81] The data will provide knowledge on patients' self-rated health, quality of life, anxiety and depression, economic situation and the extent and quality of the rehabilitation currently received. Patients were identified through the National Patient Register [59] and questionnaires were sent out to 608 patients. We anticipate 25% will decline participation, leaving an estimated 456 questionnaire respondents. Data will be anonymised and analysed by relevant descriptive statistical methods.

Qualitative post intervention study

After the intervention, 10% of the participants from the intervention group will be strategically chosen for an interview in order to explore the experiences and processes behind the potential effects of the intervention. The qualitative study will explore patient experiences of participating in the CopenHeart$_{RFA}$ programme and investigate which components were meaningful.

To achieve maximum variation, qualified interviewees are chosen on the basis of sex, AF type, and current heart rhythm.[82] The analysis will be inspired by Ricoeur's theory of interpretation consisting of three levels: naive reading, structured analysis and critical interpretation and discussion.[83] The results will be presented in themes based on patient experience and evaluation of the intervention. As an example we will look for explanations for the results in physical capacity and mental health as described by the patients. We are using mixed method to explore all aspects of the intervention, but the qualitative findings are seen as a complementary study to the primary randomised clinical trial.

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Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-utility of cardiac rehabilitation compared with treatment as usual in the study population. The economic evaluation will compare the costs to quality adjusted life years (QALY) and take a societal perspective, as recommended nationally. QALYs and costs will be assessed at the end of the intervention, 6 months from randomisation, and later after 24 months from randomisation using register-based follow up.

QALYs will be estimated using the self-completed EQ-5D instrument, which is a standardised instrument assessing 5 dimensions of self-reported health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[84, 85] The estimated calculations will be valued using Danish preference weights.[86] Information on costs will only include costs that are expected to differ between the intervention and usual care group.[73] Costs included in the evaluation are health costs associated with the rehabilitation programme, other health care costs (health care utilization besides rehabilitation), patient costs and costs of productivity losses. Information on costs will be collected by a mixture of activity-based costing, surveys, patient diary and by the use of public records. Results from the analysis will be reported as an incremental cost-effectiveness analysis (ICER).

Sensitivity analysis will be conducted to express uncertainty in the estimates.[87] The reporting of the ICER is presented using Bayesian methods, including bootstrapping and presented as cost-effectiveness acceptability curves.[88]

Ethics

The inclusion started December 2011 and is approved by the Regional Ethics Committee (number H-1-2011-135) and the Danish Data Protection Agency (no. 2007-58-0015). All eligible patients will be informed about the trial verbally and in writing, and the patients are included after informed consent has been obtained. All data will be handled confidentially and patients ensured anonymity. The trial complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01523145). An independent international safety committee monitors the trial. All serious and adverse events will be registered and reported in accordance with the safety charter.

Not providing rehabilitation to the control group can be ethically justified as current national and international guidelines give no specific recommendations on cardiac rehabilitation for patients treated for AF with RFA. The scope and quality of rehabilitation offered to this population is unknown, but suspicions are that generally no rehabilitation is offered in Denmark. The only way patients can get supervised exercise training is if they voluntarily enrol in a programme e.g. through non-profit organisations. The survey based complementary study, described previously in this paper, will hopefully provide more insight into this. In screening patients for participation, the enrolling nurse or physician will exclude those with a compelling rehabilitation need. Furthermore, patients are informed of the study design before giving their consent, and are free to decline participation.

Discussion

Due to the difference in the three patient groups that are included in the overall CopenHeart trial, patients treated for infective endocarditis, heart valve surgery and patients treated for AF with RFA, the intervention and outcome measures differ slightly, most importantly in the case of the psycho-educational intervention, which is longer for patients treated for infective endocarditis and heart valve surgery, because of the complexity of the diseases and the longer hospitalisation. Biochemical markers are similarly chosen differently to address the various co-morbidities of the three diseases and some disease specific questionnaires are chosen to capture the specific disease relevant issues.

To our knowledge no previous randomised clinical trials or observational studies have been conducted focusing on integrated cardiac rehabilitation for AF patients treated with RFA, so therefore it is not known what effect, if any, rehabilitation has on these patients. However, in the light of evidence from other groups of patients with heart disease a positive effect can be expected.[23, 89, 90]

This trial is different from previous trials because we apply a comprehensive rehabilitation intervention which consists of both a physical training component and a psycho-educational component. This combination is hypothesised to strengthen the patient both physically and mentally even if the patient has AF. Also we use mixed methods, which has its strengths in both using qualitative and quantitative research design.[34]

The major strengths of this randomised clinical trial are that it includes consecutive patients with a reasonable number of inclusion and exclusion criteria securing external validity for the results. The trial employs central, stratified randomisation which secures against selection bias.[91-93] The primary outcome is assessed blinded to intervention and so are all statistical analyses, which should reduce

detection and interpretation bias.[91-93] The long-term outcomes are based on data taken from public registry data, which are also likely not to include biased reporting of outcomes.

The secondary outcomes of self-rated mental health are by nature subjective and are likely to be biased.[91-93] The patients answer questionnaires independently of the researchers. Data management is handled independently from the researchers that interpret data. All questionnaires are distributed electronically. All data entry is stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart Group.

Trial limitations include the fact that it is known from previous rehabilitation trials [33] that patients in the control group have a tendency to do physical training due to the focus on the subject in the recruitment process. We will be aware of that when we recruit and not focus on giving extensive information about the exercise programme, or encourage patients to do physical training before knowing what group they are randomised to. Any difference between patients completing the intervention and those not completing (drop-outs) will be carefully discussed when evaluating the intervention, results and the suitability for implementation. The trial is designed with multiple statistical comparisons so results will be interpreted with caution. Further limitations of the trial and methods used are similar to those of other trials including physical exercise and physical testing, namely time-of-day, and day-to-day variation using exercise testing.[94] To ensure standard testing of all physical exercise tests in the trial, standardised instructions for patients have been developed as described in the methods section. Conversely, the trial population will be representative for the true RFA population, meaning that some patients will have AF and some sinus rhythm while exercising and testing, and this will facilitate implementation of The CopenHeart$_{RFA}$ trial rehabilitation programme in daily clinical practice. We are aware that patients treated with RFA are a highly

selected group of patients with paroxysmal or persistent AF, and they are properly more likely to participate and complete a rehabilitation programme, compared to patients with e.g. permanent AF since patients with permanent AF often are older and suffer from co-morbidity [4]. Therefore we do not expect to generalize the results to all AF patients.

The challenge with the set-up is that patients come from considerable distances and therefore some will decline participation. Also, due to the nature of rehabilitation trials, the patients have to meet at the hospital frequently, especially when randomised to the experimental intervention group.

The trial will, to our knowledge, be the largest trial conducted dealing with rehabilitation AF ablation recipients. If a positive effect of integrated rehabilitation is found, it may have an impact on the rehabilitation offered to patients treated for AF with RFA at international level. The trial is expected to identify an intervention which can improve health and quality of life for the patients, and subsequently reduce healthcare utilization and costs, as well as mortality.

Publication policy

The results of the trial will be published in appropriate peer-reviewed journals regardless of the outcome. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors.

The outcome data will be analysed and published in the short term of 4 and 6 months and the long term of 24 months. Due to the comprehensiveness of the outcome measures further post hoc analysis will be published in separate papers. Economic and long term follow up will be reported as data becomes accessible.

Timetable

Recruitment started in December 2011 in one heart centre and in July 2012 in the other participating heart centre and is planned to finish in December 2013. To achieve adequate participant enrolment, patients in doubt are contacted after hospital discharge by phone. The inclusion rate is closely monitored every week.

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Authors' contributions

SKB and ADZ in collaboration with SSR, JLH, MP, LCT, PW and CG designed the trial. SSR in collaboration with SKB, ADZ, TBR, KLS, JHS, CG, LCT, SD, JLH and SD drafted the manuscript. All revised the manuscript critically. All authors have given their final approval of the version to be published.

Competing interests

None.

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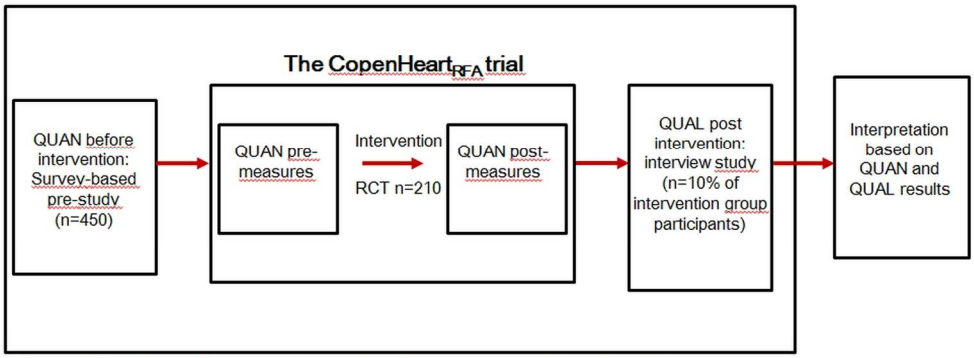

Figure 1. The CopenHeart$_{RFA}$ trial. Mixed methods research design. Embedded Experimental Model. QUAN= quantitative data, QUAL= qualitative data

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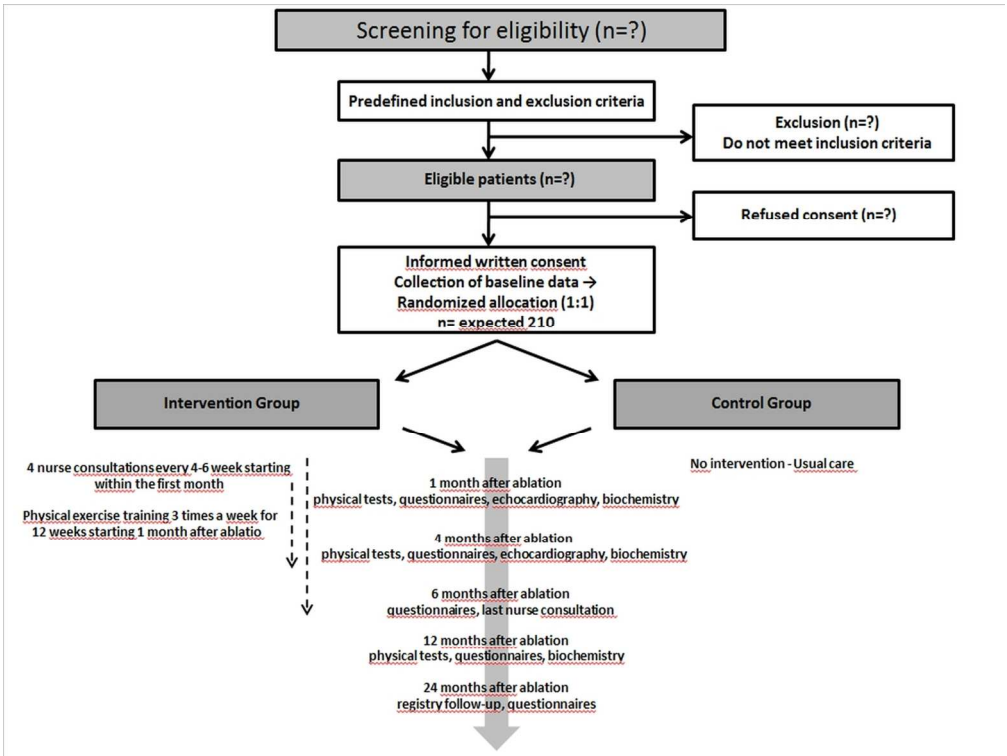

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-8
	2b	Specific objectives or hypotheses	10
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	10-11
	4b	Settings and locations where the data were collected	10-11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	12-17
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	18-21
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	21-22
	7b	When applicable, explanation of any interim analyses and stopping guidelines	24-25
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	11-12
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	11-12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	11
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	11 + 22

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	22-24
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	25-26
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	29-30
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	30
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			27
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	31

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.