

BMJ Open The CopenHeartSF trial – comprehensive sexual rehabilitation programme for male patients with implantable cardioverter defibrillator or ischaemic heart disease and impaired sexual function: protocol of a randomised clinical trial

Pernille Palm Johansen,^{1,2} Ann-Dorthe Zwisler,^{2,3} Jesper Hastrup-Svendsen,^{2,4} Marianne Frederiksen,¹ Jane Lindschou,⁵ Per Winkel,⁵ Christian Gluud,⁵ Annamaria Giraldo,⁶ Elaine Steinke,⁷ Tiny Jaarsma,⁸ Selina Kikkenborg Berg²

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For numbered affiliations see end of article.

Correspondence to

Pernille Palm Johansen;
pernille.palm.johansen@regionh.dk

ABSTRACT

Introduction: Sexuality is an important part of people's physical and mental health. Patients with heart disease often suffer from sexual dysfunction. Sexual dysfunction has a negative impact on quality of life and well-being in persons with heart disease, and sexual dysfunction is associated with anxiety and depression. Treatment and care possibilities seem to be lacking. Studies indicate that non-pharmacological interventions such as exercise training and psychoeducation possess the potential of reducing sexual dysfunction in patients with heart disease. The CopenHeartSF trial will investigate the effect of a comprehensive sexual rehabilitation programme versus usual care.

Methods and analysis: CopenHeartSF is an investigator-initiated randomised clinical superiority trial with blinded outcome assessment, with 1:1 central randomisation to sexual rehabilitation plus usual care versus usual care alone. Based on sample size calculations, 154 male patients with impaired sexual function due to implantable cardioverter defibrillator or ischaemic heart disease will be included from two university hospitals in Denmark. All patients receive usual care and patients allocated to the experimental intervention group follow a 12-week sexual rehabilitation programme consisting of an individualised exercise programme and psychoeducative consultation with a specially trained nurse. The primary outcome is sexual function measured by the International Index of Erectile Function. The secondary outcome measure is psychosocial adjustment to illness by the Psychosocial Adjustment to Illness Scale, sexual domain. A number of explorative analyses will also be conducted.

Ethics and dissemination: CopenHeartSF is approved by the regional ethics committee (no H-4-2012-168) and the Danish Data Protection Agency (no 2007-58-0015) and is performed in accordance with good clinical practice and the Declaration of Helsinki in its latest form.

Strengths and limitations of this study

- The study has been designed to meet the criteria for high quality in non-pharmacological randomised clinical trial with central randomisation, multicentre participation and blinded assessment and analysis.
- We are aware of the subjective nature of the self-reported primary outcome (International Index of Erectile Function). Accordingly, we will interpret data conservatively.
- This trial is the first to test the effect of a comprehensive approach on sexual dysfunction in patients with ischaemic heart disease or implantable defibrillators.

Registration: Clinicaltrials.gov identifier: NCT01796353.

BACKGROUND

Sexuality is an important part of people's physical and mental health.^{1 2} Patients with cardiovascular disease have an increased prevalence of sexual dysfunction.^{3–5} The causes of sexual dysfunction can be related to physical changes due to the disease, mental changes or adverse reactions to drugs and other interventions.^{6 7} Male sexual dysfunction is divided into sexual interest/desire disorders, ejaculation and orgasmic dysfunctions and erectile dysfunction.⁸ The most common disorder is erectile dysfunction, defined as the persistent inability to obtain or maintain an erection which enables satisfying sexual activity.⁹ Erectile dysfunction is associated with age, but can also be triggered by organic as well as psychogenic conditions

and is often related to vascular disease such as diabetes, hypertension and heart disease.¹⁰ Studies including 33 451 males estimate that erectile dysfunction in varying degrees exists in 52% of all men, and that age is the most common variable associated with erectile dysfunction.^{3–5} The probability of complete erectile dysfunction in cardiovascular patients is 39% compared to 10% in the total population when adjusting for age.^{3–4} Physical activity is positively associated with a lower incidence of erectile dysfunction.⁵ The prevalence of sexual dysfunction in patients with heart disease ranges from 15% up to 89%.^{1–11–17} Patients with ischaemic heart disease and patients with implantable cardioverter defibrillator, which are two large and growing patient populations, are especially affected.^{11–16–18–20} Sexual dysfunction has a negative impact on quality of life and well-being in men with cardiovascular disease and sexual dysfunction is associated with an increase in anxiety and depression.^{21–24} The relationship is perceived to be bidirectional, with one element forcing the other.^{25–26}

Standard treatment

Despite the fact that several international guidelines recommend that health professionals address the topic of sexuality in patients with heart disease,^{27–28} this is rarely practiced.^{29–30} The consensus or practice on how or where patients with heart disease and sexual dysfunction should be treated is lacking, however, some guidelines about the prescription of phosphodiesterase-5 (PDE-5) inhibitors exist.⁶ The PDE-5 inhibitors have an overall success rate of 50–80% of those treated among patients with cardiovascular disease.^{6–31–32} PDE-5 inhibitors are generally safe. Linking PDE-5 inhibitors to cardiac events, large randomised trials and a meta-analysis suggest that they are not associated with an increase in myocardial infarction or cardiac events.^{6–32} In patients with heart disease and no effect of PDE-5 inhibitors, or where PDE-5 inhibitors are contraindicated because of treatment with nitrates, there seems to be no consensus on what treatment should be offered for sexual dysfunction.

Non-pharmacological treatment potentials

Non-pharmacological interventions possess potential in reducing sexual dysfunction. Lifestyle factors such as cigarette smoking, hyperlipidaemia and a sedentary lifestyle all predict erectile dysfunction^{4–5} and these are the same risk factors that predict coronary artery disease. A recent meta-analysis of six randomised trials with 740 patients with no known heart disease, showed that lifestyle modifications such as physical exercise and pharmacotherapy for cardiovascular risk factors were associated with a significant improvement in erectile function.³³ Furthermore, a randomised trial investigating the effect of exercise training 3 h/week or more in patients with no heart disease showed a significant result in improving the person's erectile function compared with controls with no exercise training.³⁴ We hypothesise that these lifestyle modifications can also improve sexual dysfunction in patients with already established heart disease. A systematic literature search showed

five randomised clinical trials which examine the effect of physical exercise on sexual dysfunction.^{35–39} Overall, 591 patients with heart disease were included and the effect was significant in three of the five trials.^{37–39} However, the trials are characterised as being of small sample sizes, using non-validated tools and mainly focusing on the time before patients return to sexual activity and not on the ability and quality of the sexual performance. Randomised trials that address the psychological aspects of sexual dysfunction are limited in patients with heart disease. However, one randomised trial testing the effect of sexual therapy showed some promising trends when it comes to improving the frequency and quality of sexual activity in male patients post-cardiac event beyond the usual cardiac rehabilitation.⁴⁰ However, due to the limited power of the sample in this trial, it did not allow the detection of significant effects. The role of pelvic floor exercises as a treatment of erectile dysfunction is not tested on patients with heart disease, but in the general population 40–47% had regained normal erectile function after 3–4 months of training the pelvic floor muscles.^{41–42} As the condition of sexual dysfunction often includes both physical and psychological components, it is plausible to believe that patients with heart disease and sexual dysfunction benefit from a comprehensive rehabilitation intervention^{43–44} consisting of a psychoeducational component and an exercise training component including pelvic floor exercises.

TRIAL OBJECTIVES

The objective of the CopenHeartSF is to investigate benefit and harm on the sexual function of male patients with ischaemic heart disease or patients with implantable cardioverter defibrillator of a comprehensive sexual rehabilitation programme, consisting of a psychoeducative component and a physical exercise component, including pelvic floor exercises. The primary hypothesis is that, a comprehensive sexual rehabilitation programme improves sexual function, as assessed by the International Index of Erectile Function (IIEF) questionnaire^{45–46} in males with sexual dysfunction and ischaemic heart disease or patients with implantable cardioverter by 3.5 points in the experimental group compared with the control group after completion of the programme. The estimated increase in primary outcome is based on a study that examines the effect of a physical intervention in patients with cardiovascular disease taking PDE-5 inhibitors.³⁴ The secondary hypothesis is that sexual function, measured by the sexual domain in the Psychosocial Adjustment to Illness Scale (self-reported version; PAIS-SR) questionnaire⁴⁷ improves by two points in the experimental group compared with the control group after completing the programme. The estimated increase in secondary outcome is based on two studies that examine the prevalence of sexual dysfunction in patients with heart failure.^{48–49}

Exploratory analyses will test the hypotheses that comprehensive sexual rehabilitation will improve: health-related quality of life, anxiety and depression, frequency of sexual

activity, physical capacity measured by peak oxygen uptake (peak VO_2), pelvic floor muscle strength and endurance and female assessment of male partner's erectile dysfunction.

METHODS

CopenHeartSF is an investigator-initiated randomised clinical superiority trial with blinded outcome assessment, with 1:1 central randomisation to a comprehensive sexual rehabilitation programme plus usual care or usual care alone. Based on sample-size calculations, 154 patients will be recruited from two university hospitals in Denmark. The CopenHeartSF trial is a part of the overall CopenHeart project, consisting of several randomised clinical trials (<http://www.CopenHeart.org>), designed to develop evidence-based knowledge of rehabilitation among patients with complex cardiac conditions. Major parts of the CopenHeartSF methods section and trial design in this article are similar to other randomised clinical trials, CopenHeartIE,⁵⁰ CopenHeartREA⁵¹ and CopenHeartVR.⁵²

Study population and eligibility criteria

Male patients above 18 years with sexual dysfunction associated with implantable cardioverter defibrillator or with ischaemic heart disease verified by coronary angiography, who have a partner, speak and understand Danish, and provide a written informed consent, are considered eligible for participation. Exclusion criteria are patients at intermediate or high risk in relation to their cardiovascular status according to recommendations from the Princeton consensus group^{32 53}; those with diseases in the urinary tract; those who perform intense exercise more than 3 h a week; patients with neurological or orthopaedic deficits which prevent training; patients with cognitive deficits which prevents consultations and patients who are included in ongoing research prohibiting additional research participation. A diagram showing the flow of participants through each stage of the randomised trial will be made (figure 1).

Experimental intervention

The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual rehabilitation in this trial is defined as: a time-bound planned process with clear goals and means. Sexual rehabilitation is a process where several actors, including the patient, are working towards regaining improved sexual functioning and coping ability according to their sexual function. The comprehensive sexual rehabilitation programme contains a physical exercise component, including training of the pelvic floor and a psychoeducational component.

The physical components

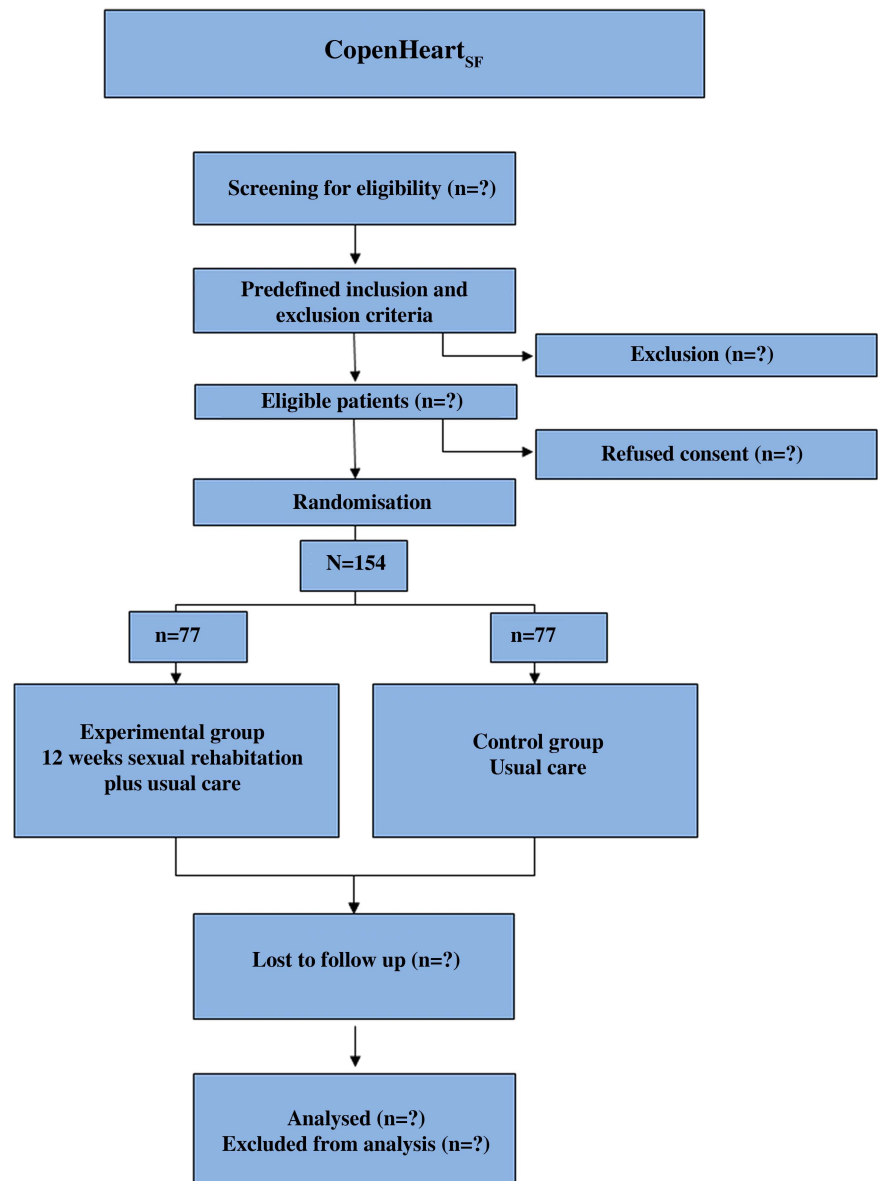
Physical exercise

The goal of physical exercise is to achieve an improvement in the patient's physical work capacity, and to eliminate the fear and uncertainty the patient may feel in relation to

sexual activity as a form of physical activity. The physical exercise intervention is based on The European Society of Cardiology recommendations for physical activity for cardiovascular patients.⁵⁴ The European Society of Cardiology recommends that all adults promote and maintain their fitness, muscle strength, flexibility and bone health several hours a week. Training must be of high intensity and of 30 min duration.⁵⁴ Furthermore, the intervention is supported by European recommendations for physical training in cardiac patients⁵⁵ and has been tested in two large rehabilitation trials, COPE-ICD and DANREHAB.^{56 57} A professional physiotherapist with specific knowledge of cardiac rehabilitation initiates the physical exercise programme. Together with the patient, the physiotherapist plans and prepares a physical exercise protocol, taking into account the patient's clinical condition and physical abilities. Sixty minutes is allocated for the initial consultation and preparation of individual training protocol, including pelvic floor exercise instructions.

Physical exercise is initiated at a physiotherapist-supervised setting at the Heart Centre, Rigshospitalet. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and Corus Exercise Assistant, V.2.0.16, Finland) potential cardiac arrhythmias, ECG abnormalities such as ST segment changes, T wave alterations, atrial or ventricular arrhythmias and training intensity levels are monitored. The training is initiated with two to three mandatory exercise sessions at Rigshospitalet. Subsequently, the patients can choose to continue the intensive physical exercise regimen either at Rigshospitalet, or at a local CopenHeart-certified facility, supervised by physiotherapists, or as supervised home-based training. Supervised home-based physical training has previously shown similar results to hospital-based training.⁵⁸ This finding has been confirmed in a Danish setting.⁵⁹

One session is structured with 10 min warm-up bicycling, 20 min bicycling with increased intensity (cardiovascular training), 20 min strength exercises and 10 min stretching and cool-down period. The warm-up session is performed at the intensity of 11–12 on the Borg scale.⁶⁰ The 20 min cardiovascular training is performed as interval training. Each session is divided into three sections. Each section contains an intensity of 13–17 on the Borg scale and time limit (2–15 min) varying between each section; the second section with longest and highest intensity. A cool-down period of 5 min is included after 20 min of cardiovascular training. The strength and strength-related exercises primarily target lower body muscles, and comprise the following four exercises: (1) heel rise performed by repetitions of maximal flexion from standing position; (2) step-up by using a step bench of 27 cm; (3) leg press standardised, starting with 90° flexion, hyperextension not accepted; (4) 90° pull-down performed in a cable machine to target abdominal muscles. For step-ups and heel-rises, weight load is calculated as a percentage of body weight (5–20%) and increased throughout the 12 weeks. Load for leg press is estimated from repetition maximum (RM) testing and increases from 60% to 70% of 1 RM during 12 weeks of

Figure 1 Flow chart.

training. All exercises are initiated by 2×12 repetitions and increased through the programme according to standard guidelines for strength training.⁶¹

To achieve cardiovascular adjustment the training begins with a warming-up period and ends with a cool-down period. This cardiovascular adjustment has been shown to reduce the risk of ischaemia and arrhythmia in connection to physical exercise.^{44 62} Participants must mainly exercise in an upright position to decrease left ventricular filling pressure and risk of ischaemia or heart-failure-triggered ventricular arrhythmias.⁶²

Pelvic floor exercise

The bulbocavernosus muscle and the ischiocavernosus muscle, two superficial pelvic floor muscles, are active during erection and enhance rigidity. The bulbocavernosus muscle encircles 33–50% of the base of the penis.⁴¹ The pelvic floor training regimen is inspired by Dorey *et al*,⁶³ who have developed a training regimen for male

patients for use in randomised clinical trials. The regimen is developed and tested in a different patient population, and we have therefore modified it to fit cardiovascular patients. Patients are instructed in pelvic floor exercises by a skilled physiotherapist. Patients are instructed to perform their pelvic floor exercises twice daily. Studies showed that a few strong or maximum contractions are more effective when it comes to gaining muscle hypertrophy than several less strong contractions.⁶³ Patients are instructed to tighten their pelvic floor muscles as strongly as possible (as if to prevent flatus from escaping) three times when lying, three times when sitting and three times when standing. The duration of the contraction is up to 10 s each, and patients are informed to have a 10 s break between each contraction. The physiotherapist instructs the patients on how to contract the bulbocavernosus and ischiocavernosus muscles. In order to ensure that the right muscles are involved, attention is placed on the

ability to lift the scrotum and retract the penis. To obtain some degree of pelvic floor muscle endurance, the patients are encouraged to tighten the pelvic floor muscles when walking.

To encourage adherence and monitor compliance pulse watches (Polar watch) with extended memory and exercise training logs are handed out. A training log contains information about physical exercise as well as pelvic floor exercise. At the end of the intervention the training log and the pulse watch are returned and compliance and intensity level are coded independently.

The psychoeducational components

The goal of the psychoeducative intervention is that the patient learns to interpret and react to relevant physical and psychological symptoms, learns to cope with anxiety and fear, including strategies to manage depressive symptoms and the ability to be sexually active without fear.

A specially trained nurse is responsible for the psychoeducative intervention. The intervention takes a theoretical basis of the patient-centred approach where the emphasis is on support and education. The conversations are based on a holistic view of the patient and focus on the handling of life and managing sexual dysfunction. The intervention is targeted at the modifiable parameters that are reported to affect sexual dysfunction. The psychoeducative intervention is inspired by RR Parse's⁶⁴ 'Human Becoming Practice Methodologies' three dimensions which can be described as (1) discuss and give meaning to the past, present and future; (2) explore and discuss events and opportunities and (3) pursue imagined possibilities. According to this theory, there are three ways to alter its perceived health: creative ideas, see, hear and feel how a situation could be if it was lived in a different way; recognising personal patterns and value priorities and shed light on the paradoxes by looking at incongruence in a situation and change the view of reality. The nurse is 'truly present' in the process through discussion, quiet contemplation and reflection. The psychoeducative intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on psychological well-being (mental health) and the general health subscale of the Short Form-36.⁵⁶ The nurse is trained in the psychoeducative conversation through teaching and supervision of nurses who have experience with the 'Human Becoming Practice Methodology' from the COPE-ICD trial. It is based on the theoretical literature that forms the basis for understanding the processes of practice methodology and existing specialty specific knowledge about heart disease, related symptoms and sexology. The supervisor observes and provides feedback in relation to the methods and goals of the conversation. The emphasis is on openness in the interviews and on the nurse's ability to: be silently present while the patient talks, ask questions that encourage reflection, let the patient find answers and solutions and contribute with knowledge, provide advice

and guidance when requested and relevant. The training of the nurse takes place prior to the intervention. In practice the intervention will be handled by one nurse with several years of experience working with cardiac patients and trained in sexology. The sexology experience is gained in a 2-week intensive course on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist is available during the intervention. The nurse will conduct consultations with patients individually, and patients are informed that they are welcome to bring spouses/relatives. The consultation will take place in a quiet room in an outpatient setting and last for 45 min. An inspirational guide will form the basis for the consultations. The guide consists of several elements and issues (medical, psychosocial, educational and sexual) that work as inspiration (see box 1).

Usual care

Participants in the experimental group and in the control group will receive the usual care according to current guidelines. Usual care is, for patients for whom it is not contraindicated, treatment with PDE-5 inhibitors. Patients who are candidates for PDE-5 inhibitors are encouraged to contact their general practitioner in order to establish the treatment. Use of PDE-5 inhibitors will be monitored in both intervention groups. To assess outcome measures, patients in the control group will be asked to complete questionnaires on equal terms with participants in the experimental group. In addition, they will be tested in the form of cardiopulmonary testing (peak VO₂) and pelvic floor muscle strength and endurance at baseline and at the end of the trial.

Outcomes and data collection

In order to evaluate the effect of the comprehensive sexual rehabilitation programme numerous data will be collected.

Primary outcome

Sexual function will be measured by the IIEF questionnaire after 16 weeks and 6 months. IIEF was developed in conjunction with the clinical trial programme for sildenafil, and has since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of

Box 1 Inspiration guide for psychoeducational consultations

- A brief medical history
- Actual thoughts and questions regarding their heart disease and sexual function
- Sexual dysfunction
- Safety issues
- Angina or ICD shock
- How the sexual problems affect daily live
- Provide the patient with recommendations
- Relationship

erectile dysfunction. It has been linguistically validated in 32 languages including Danish and used as a primary outcome in more than 50 clinical trials.^{34 45 46} It consists of 15 items including five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of sensitivity and specificity.⁴⁶ The IIEF is self-assessed, which in sexological research is widely used and well acclaimed.

Secondary outcome

Sexual function is measured by the PAIS-SR sexual relationship domain.⁴⁷ The overall PAIS-SR measure psychosocial adjustment to illness in terms of seven primary domains of adjustment: Health Care Orientation, Vocational Environment, Domestic Environment, Sexual Relationships, Extended Family Relationships, Social Environment and Psychological Distress. Each PAIS/PAIS-SR item is rated on a 4-point (0 through 3) scale of adjustment, with higher ratings indicating poorer adjustment status. The sexual relationship domain evaluates shifts in the quality of sexual relations due to the current illness or treatment. It consists of six items and the total score ranges from 0 to 18. Low scores indicate good adjustment, and high scores indicate poor adjustment.

Exploratory outcomes

A more extensive evaluation of physical, psychological and demographic status over time will be performed. Physical examination will include pelvic floor strength and endurance assessed according to the Modified Oxford grading scheme which is a manual digital examination of the pelvic floor. It is tested and validated and used in several trials.^{65 66} Furthermore, physical capacity will be measured by peak VO_2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) with measurement of oxygen uptake (VO_2), heart rate (HR, bpm), ventilation rate (l/min), ventilation frequency (number/min), respiratory expiration ratio (CO_2/O_2 in %), blood pressure, physical activity level (METs) and gas exchange (VO_2 and VCO_2) during progressive loading and in the following recovery period. The test is conducted before the training programme initiates. Intensity performed as a ramp protocol (load gradually increases) with the initial work load of 25 W and increased by 12.5 W every minute until exhaustion, usually but not always, is where the patient's oxygen uptake reaches a steady state despite additional load. The test follows current standards for cardiopulmonary exercise testing.⁶⁷ The full test procedure is described by Rasmussen *et al.*⁵⁰ Additionally a series of questionnaires, regarding health-related quality of life, anxiety and depression and sexual dysfunction are administered (see table 1).

Table 1 CopenHeartSF—exploratory quantities subjected to post-hoc analysis

Quantity	Time of measure	Type of quantity
Demographic		
Age, height, weight	Baseline	Continuous
Marital, educational, occupational status	Baseline	Categorical
Smoking	Baseline	Binary (Y/N)
Clinical		
Nutritional status (BMI)	Baseline	Continuous
NYHA classification	Baseline	Continuous
Type of heart disease	Baseline	Categorical
Type of sexual dysfunction	Baseline	Categorical
Diabetes mellitus	Baseline	Binary (Y/N)
Level of physical activity	Baseline	Categorical
Level of rehabilitation offered	Baseline	Categorical
PDE-5 inhibitor intake, Level of activity within the last 4 weeks, level of sexual activity	Baseline, W12, W16, M6	Categorical
Para clinical		
Cholesterol level	Baseline	Continuous
Functional capacity		
Peak VO_2	Baseline, W12	Continuous
Pelvic floor strength and endurance	Baseline, W12	Continuous
Serious adverse events	W12, W16, M6	Continuous
Questionnaires		
SF-36 ⁶⁸ HADS ⁶⁹ EQ-5D-5L ⁷⁰ FAME ⁷¹ Sex after ICD questionnaire ¹⁶	Baseline, W16, M6	Continuous

BMI, body mass index; Eq-5D-5L, EuroQol; FAME, Female Assessment of Male Erectile Function; HADS, Hospital Anxiety and Depression Scale; NYHA, New York Heart Association; PDE-5, phosphodiesterase-5; SF-36, Short Form-36; Y/N, yes/no.

Blinding

It is not possible to blind the allocated intervention group for the staff and the participants.⁷² All physical testing, data collection and administration will be conducted by blinded staff, however. Statistical analyses and drawing of conclusions from these will also be conducted blinded to the intervention group.

Sample size and power calculations

We are planning a trial of the continuous response variable IIEF^{45 46} from independent control and experimental participants with one control per experimental participant. In a previous trial the IIEF within each participant group was normally distributed with a SD of 6 points.³⁴ If the true difference in the experimental and control means is 3.5 points, we will need to include 77 experimental participants and 77 control participants (total 154 participants) to obtain a power of 95%

($\beta=5\%$) and a type 1 error probability of 5%. Using this sample size, an SD of 4 points and an alternative hypothesis of a mean difference of 2 points for the secondary outcome and a type 1 error probability of 5% the corresponding power for the secondary outcome is found to be 87%.

Study procedure and randomisation

To achieve our estimated sample size of 154 participants, patients will be identified from the hospital databases. Patients will be selected consecutively. Patients with an implantable cardioverter defibrillator are required to have the device implanted more than 1 year prior to inclusion and patients with ischaemic heart disease 1 year from event and backward. The 1 year limit has been set so that patients are past their rehabilitation if any is provided. Patients will receive the IIEF questionnaire⁴⁵ by mail including a stamped return envelope. Patients with a score ≤ 25 , the accepted cut-off score⁴⁶ on the initial screening, are invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems. The participant information is sent to the patient along with the invitation. This gives the patient an opportunity to read the material in advance and to prepare possible questions. At the initial interview/meeting it is determined whether the patient meets the criteria for participating in the trial. If patients are suited and want to participate they will be randomised to a comprehensive sexual rehabilitation programme plus usual care versus usual care alone. Stratification will be according to patient group (patients with ischaemic heart disease or implantable cardioverter defibrillator) and age (≤ 59 or ≥ 60 years) and randomised 1:1 to the experimental group or the control group. Randomisation will be performed centrally by the trial coordination centre, Copenhagen Trial Unit, according to a computer-generated allocation sequence with a variable block size concealed from the investigators. Allocation to the intervention groups is carried out when the investigator calls the Copenhagen Trial Unit. Relevant information (personal identification number, strata, etc) is typed into a computer system, and then the participant will be allocated to an intervention group and awarded a four-digit randomisation number. The investigator then informs the patient of the result and on how to proceed by letter. Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. For both groups, follow-up assessment will take place after 12 weeks (only physical evaluation), 16 weeks and 6 months. Questionnaires will be completed electronically in the questionnaire system Analyzer with 'single user', which meets the data legislation for logging. At inclusion, the trial participant will receive an email with a link to a website through which questionnaires can be completed. The email contains a login and password for the trial participant's personal access. The participant has the opportunity to go through the website <http://www.copenheart.org> and enter with the login and password. If patients do not complete the

questionnaire electronically, the material can be sent in paper form and an independent trial personnel then enters the responses into the database. Thus data management is handled independently from the researchers who interpret the data. All data are stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group. The recruitment process will continue until the number of 154 has been reached.

Statistical analysis

Analysis of primary and secondary outcomes

The analysis will be performed according to the intention-to-treat analysis with two-sided significance tests at the 0.05 level. Both outcomes (and outcomes subjected to exploratory analyses) will be analysed using the same procedure. First, we will test if there is an immediate effect of the intervention on the outcome and/or a difference in the response to the intervention between the two patient groups (patients with ischaemic heart disease and patients with implantable cardioverter defibrillator) using model 1 below. Then the follow-up data will be included in the analysis and the long-term effect will be studied using model 2.

Models and analytical techniques

Model 1 The equation (equation 1) showing the dependent variable Y (the outcome) as a function of covariates used in the analysis of the immediate effect of the intervention on the primary outcome is

$$Y = \text{intercept} + aY_{\text{baseline}} + bI + cG + dI:G \quad (1)$$

Y_{baseline} is the baseline value of the outcome, I the indicator of intervention, G the indicator of patient group, and a through d are coefficients to be estimated. The term dI:G stands for interaction between the two covariates I and G. If the term bI is significant (the coefficient b differs significantly from 0) there is an effect of the intervention common for the two patient groups (ischaemic patients and patients with implantable cardioverter defibrillator). If the term dI:G is significant there is an additional effect of the intervention in one of the two patient groups; thus a subgroup analysis is warranted. In the analysis of the data the univariate general linear model is used. The analysis of the primary outcome is the primary analysis. The subgroup analysis and the analysis of the secondary and of other outcomes should be considered exploratory.

Model 2 In the analysis of follow-up data the time T (Y is measured 16 weeks and 6 months following randomisation) is included and the mixed model for repeated measures is used. The equation (equation 2) for the fixed effect in this model showing Y as a function of the covariates is

$$Y = \text{intercept} + aY_{\text{baseline}} + bG + cI + dI:G + eT + fI:T + gI:T:G \quad (2)$$

where a through g are coefficients to be estimated. If the term eT is significant there is a linear trend over time common for both patient groups. If $fI:T$ is significant, this trend is supplemented by an additional trend caused by the intervention and therefore specific for the intervention group. If in addition $gI:T:G$ is significant this added trend differs between the two patient groups (patients with ischaemic heart disease and patients with implantable cardioverter defibrillator). In the mixed model analysis an unstructured covariance matrix will be assumed. If convergence is not attained simpler covariance structure models will be assessed guided by Akaike's criterion or the maximum likelihood test as appropriate.

Missing values

If the number of missing cases for a given outcome (number of patients with one or more model variables missing) is larger than 5% or p of Little's test is $<5\%$ multiple imputations of the model variables (outcome plus covariates) is performed using SPSS V.17. The range of potential bias in case the missing values should not be random is assessed by doing two imputations (1) imputing missing outcome value in one group by minimum value found in the material and missing outcome value in the other group by maximum value found in material and (2) vice versa. Then in each case an unadjusted analysis is performed to estimate the parameter of interest.

ETHICS AND DISSEMINATION

The trial complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01796353). Patients are informed about the trial in writing as well as verbally and only included if a written informed consent is obtained. Patients are assessed in accordance to whether it is safe for them to perform sexual activity. This is carried out according to recommendations from the Princeton consensus group.^{32 53} If patients are suited and want to participate they will be enrolled in the trial. Trial participants are free to withdraw their informed consent at any time and be treated according to the departments' standard treatment procedures. A patient will be withdrawn from the trial if the trial participant withdraws his consent and will, in connection therewith, be informed that termination of the trial will have no implications for his future treatment. Patients who leave the trial will be politely asked for permission to continue to collect data and to use already collected data. If the patient gives permission, he will be included in the final analysis. Only if the patient refuses use of already collected data, will all data relating to him be destroyed. All patient data will be handled and stored in accordance with Danish Data Protection Agency rules and patients are ensured anonymity. The trial will be conducted according to the Act No. 593 of 14 June 2011 on Act on Research Ethics Review of Health Research Projects. The investigator will

immediately notify the regional ethics committee if, within the interventions period, there occur serious adverse events, serious adverse reactions or suspected unexpected serious adverse reactions. The report will be accompanied by comments on possible implications for the trial, and notification will be made within 7 days after the investigator has knowledge of the event. The trial has no data monitoring committee however an internal monitor will perform random checks to see if the trial staff work according to the protocol. No risks are anticipated to occur during the sexual rehabilitation programme. As far as we know, there is no previous risk associated with nursing consultations. If the nurse, during the consultation, identifies a need for further consultations with professionals, she will encourage the participant to seek help from the general practitioner, psychologist or in their usual outpatient setting. Risks associated with exercise training and testing are sudden cardiac death associated with ventricular arrhythmias, acute myocardial infarction, and in patients with chronic heart failure, pulmonary oedema and deterioration in left ventricular function.⁷³ The last is only found in one study from 1988⁷⁴ and has not subsequently been demonstrated in larger studies.^{75 76} In a recent French study of more than 25 000 patients with ischaemic heart disease, one-third with chronic heart failure found the risk of cardiac complications at 1:8500 exercise testing and 1:50 000 patient exercise hours.⁷⁷ Increasing exercise intensity and age are risk indicators. Therefore, the training intensity will be conducted as moderate high intensity (less than 80% of VO_2 max). To achieve cardiovascular adjustment exercise training as well as testing begins with a warming-up period and ends with a cool-down period, with a gradual downward adjustment of exercise intensity and HR, rather than an abrupt end. This cardiovascular adjustment has been shown to reduce the risk of ischaemia and arrhythmia in connection with physical exercise.^{44 62} Participants must mainly exercise in an upright position to decrease left ventricular filling pressure and risk of ischaemia or heart failure triggered ventricular arrhythmias. When these precautions are respected, exercise training as well as exercise testing are considered to possess a low risk for the participants. There is, as far as we know, no previously known risk associated with pelvic floor exercise. Testing or examination of the pelvic floor may be associated with discomfort for the participants but is not considered to be associated with any risk. Staff members will be trained according to guidelines to handle any emergencies.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer reviewed journals of nursing, cardiology or sexology. Furthermore, results will be presented at national and international conferences relevant to subject fields. Authorship will be allocated using the guidelines for authorship defined by the International Committee of Medical Journal Editors and depends on the personal involvement. All the articles,

abstracts as well as the results will be posted on the website <http://www.copenheart.org>. The website will be continuously updated and will be highlighted through the scientific articles. CopenHeart staff will have access to data. Ethic committees and competent authorities will be able to obtain direct access to data and documentation.

DISCUSSION

This randomised clinical trial testing the effect of a comprehensive sexual rehabilitation intervention on a population of patients with implantable cardioverter defibrillator or patients with ischaemic heart disease seems to be the first one in its field. The trial is expected to contribute with results that can improve patients' problems related to heart disease and sexual function. Additionally, it is believed that the trial can provide a systematic approach that may 1 day inform national consensus on how to treat sexual dysfunction in heart patients. Furthermore, the results of the trial are expected to contribute to the international debate on sexual rehabilitation of patients with heart disease.

The trial is designed with central stratified randomisation which secures against selection bias.^{78 79} The primary outcome is assessed blinded to intervention and so are all statistical analysis, which should reduce detection and interpretation bias.^{78 79}

Trajectory

Inclusion was initiated on February 2013 and is expected to continue until June 2014.

Author affiliations

¹Department of Cardiology, Copenhagen University Hospital, Bispebjerg Hospital, Copenhagen, Denmark

²The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

³National Institute of Public Health, University of Southern Denmark, Denmark

⁴Faculty of Health Science, Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

⁵The CopenHeart Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

⁶Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁷Wichita State University, Wichita, Kansas, USA

⁸Department of Social and Welfare Studies, Linköping University, Linköping, Sweden

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Contributors PW specifically designed the statistical analysis plan. PPJ, SKB and A-DZ drafted the manuscript. All authors designed the study and developed the protocol, revised the manuscript critically and have given their final approval of the version to be published.

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Competing interests None.

Ethics approval Trial protocol has been approved by the Regional Ethics Committee (no H-4-2012-168) and the Danish Data Protection Agency (no 2007-58-0015).

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The CopenHeartSF trial—comprehensive sexual rehabilitation programme for male patients with implantable cardioverter defibrillator or ischaemic heart disease and impaired sexual function: protocol of a randomised clinical trial

Pernille Palm Johansen, Ann-Dorthe Zwisler, Jesper Hastrup-Svendsen, Marianne Frederiksen, Jane Lindschou, Per Winkel, Christian Gluud, Annamaria Giral di, Elaine Steinke, Tiny Jaarsma and Selina Kikkenborg Berg

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