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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.

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## 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 psycho-education possess the potential of reducing sexual dysfunction in patients with heart disease. The CopenHeart$_{SF}$ trial will investigate the effect of a comprehensive sexual rehabilitation programme versus usual care.

**Methods and analysis:** CopenHeart$_{SF}$ 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 program and psycho-educative consultation with a special trained nurse. The primary outcome is sexual function measured by the International Index of Erectile Function. The secondary outcome measure is psycho-social adjustment to illness by the Psychosocial Adjustment to Illness Scale, sexual domain. A number of explorative analyses will also be conducted.

**Ethics and dissemination:** CopenHeart$_{SF}$ 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.

**Registration:** Clinicaltrials.gov identifier: NCT01796353

## ARTICLE SUMMARY

### Article focus

- The CopenHeart$_{SF}$ is a randomised clinical trial investigating the effects of a comprehensive sexual rehabilitation programme versus usual care for patients with sexual dysfunction and implantable cardioverter defibrillator or ischaemic heart disease.
- The hypothesis is, that comprehensive sexual rehabilitation consisting of a psycho-educational component and a physical exercise component including pelvic floor exercise improves sexual function.

### Key messages

- Sexual dysfunction is highly prevalent in cardiovascular patients and a systematic approach seems to be lacking.
- This trial is the first to study the effect of a comprehensive sexual rehabilitation programme in a cardiac population.
- This trial is the first to include pelvic floor exercise in a comprehensive rehabilitation programme in cardiac patients.

### Strengths and limitation of this study

- The study have been designed to meet the criteria for high quality in non-pharmacological randomised clinical 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.

## BACKGROUND

Sexuality is an important part of people's physical and mental health.[1, 2] Patients with cardiovascular disease have 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 both organic and 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 bi-directional, with one element forcing the other.[25, 26]

### Standard treatment

Despite the fact that several international guidelines recommend that health professionals address the topic sexuality in patients with heart disease,[27, 28] this is rarely done in practice.[29, 30] The consensus or practice on how or where patients with heart disease and sexual dysfunction should be treatedis lacking, however, some guidelines about prescription of phosphodiesterase5 (PDE5) inhibitors exist.[6] The PDE5 inhibitors have an overall success rate of 50% to 80% of those treated in patients with cardiovascular disease.[6, 31, 32] PDE5 inhibitors are generally safe. Linking PDE5 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 PDE5 inhibitors, or where PDE5 inhibitors are contra-indicated 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 life style 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 hours per week or more in non-heart disease patients showed a significant result in improving the person's erectile functioning compared with controls with no exercise training.[34] We hypothesize that these lifestyle modifications can also improve sexual dysfunction in patients with already established heart diseasel. 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% to 47% had regained normal erectile function after 3-4 month of training the pelvic floor muscles.[41, 42] As the condition 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 psycho-educational component and an exercise training component including pelvic floor exercises.

## TRIAL OBJECTIVES

The objective of the CopenHeart$_{SF}$ 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 psycho-educative 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 dysfunction (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 PDE5-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) questionnaire[47], 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 VO2), pelvic floor muscle strength and endurance and female assessment of male partner's erectile dysfunction.

## METHODS

CopenHeart$_{SF}$ 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 CopenHeart$_{SF}$ trial is a part of the overall CopenHeart project, consisting of several randomised clinical trials (www.CopenHeart.org), designed to develop evidence-based knowledge of rehabilitation among patients with complex cardiac conditions. Major parts of the CopenHeart$_{SF}$ methods section and trial design in this paper are similar toother randomised clinical trials, CopenHeart$_{IE}$[50], CopenHeart$_{RFA}$[51]and CopenHeart$_{VR}$[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 competitive exercise more than 3 hours 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 randomized trial will be made. ***(See figure 1)***

**Experimental intervention**

The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual rehabilitation in this trial is defined as: a time-bounded 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 psycho-educational 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 minutes duration.[54] Furthermore, the intervention is supported by European recommendations for physical training in cardiac patients [55] and has been tested in COPE-ICD and DANREHAB trials.[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, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST segment changes, T-wave alterations, atrial or ventricular arrhythmias, and training intensity level 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 minutes (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 to 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 intensity 13 to 17 on the Borg scale and time limit (2 to 15 min) varying between each section; the second section with longest and highest intensity. A cool down period of 5 min is included after the 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 degrees flexion, hyperextension not accepted; (4) 90 degrees 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 to 20%) and increased throughout the 12 weeks. Load for leg press is estimated from repetition maximum (RM) testing and increases from 60% of 1 RM to 70% of 1 RM during the 12 weeks of training. All exercises are initiated by 2x12 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% to 50% of the base of the penis.[41] The pelvic floor training regimen is inspired by Dorey and colleagues, who have developed a training regimen for male patients for use in randomised clinical trials.[63] The regiment 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 seconds each, and patients are informed to have a 10 second 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 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 psycho-educational components**

The goal of the psycho-educative 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 ability to be sexually active without fear. A specially trained nurse is responsible for the psycho-educative 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 psycho-educative intervention is inspired by RR Parse's 'Human Becoming Practice Methodologies' three dimensions[64], 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 psycho-educative intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on psychological well-being (mental health) and the general health sub-scale of the SF-36.[56] The nurse is trained in the psycho-educative 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 two-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 settings and last for 45 minutes. 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 table 1):

| Table 1. Inspiration guide for psycho-educational 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 |

**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 PDE5 inhibitors. Patients who are candidates for PDE5 inhibitors are encouraged to contact their general practitioner in order to establish the treatment. Use of PDE5 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 comprehensive sexual rehabilitation programme numerous data will be collected.

*Primary outcome*

Sexual function will be measured by the International Index of Erectile Function (IIEF) questionnaire after 16 weeks and 6 months. International Index of Erectile Function (IIEF) was developed in conjunction with the clinical trial program for sildenafil, and has since been adopted as

the 'gold standard' measure for efficacy assessment in clinical trials of 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 Psychosocial Adjustment to Illness Scale (self-reported version) (PAIS-SR) sexual relationship domain.[47] The overall PAIS-SR measure psychosocial adjustment to illness in terms of 7 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 indicates good adjustment, and high scores 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 VO2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland)withmeasurement of oxygen uptake (VO2), heart rate (HR, beats /min),ventilation rate (VE, l /min), ventilation frequency (VF, number / min), respiratory expiration ratio (RER, CO2/O2in%), blood pressure , physical activity level (METS) and gas exchange (VO2 andVCO2) 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 25W and increased by 12.5W every minute until exhaustion,

usually but not always, is where the patient's oxygen uptake reaches 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 2)

**Table 2 CopenHeart$_{SF}$ - 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; SF-36, Short Form-36; HADS, Hospital Anxiety and Depression Scale; Eq-5D-5L, EuroQol; FAME, Female assessment of male erectile function,

**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 standard deviation 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, a standard deviation 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 one year prior to inclusion and patients with ischaemic heart disease one year from event and backward. The one year limit has been set so that patients are past their rehabilitation if any is provided. Patients will receive the International Index of Erectile Function questionnaire[45] by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score[46], 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 send 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 either 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 years or ≥ 60 years and randomised1:1 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

done when the investigator calls 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 patient 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 Enalyzer 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 e-mail contains a login and password for the trial participant's personal access. The participant has the opportunity to go through the website www.copenheart.org and login with the log-in and password. If patients do not complete the questionnaire electronically, the material can be sent in paper form and independent trial personnel then enters the responses into the database. Thus data management is handled independently from the researchers who interpret the data.

**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 $Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot I + c \cdot G + d \cdot I{:}G$ (equation 1).

$Y_{baseline}$ is the baseline value of the outcome, I is the indicator of intervention, G is the indicator of patient group, and a through d are coefficients to be estimated. The term d·I:G stands for interaction between the two covariates I and G. If the term b·I 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 d·I:G is significant there is an additional effect of the intervention in one of the two patient groups; thus a sub-group 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 sub-group 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 month 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 co-variates is$Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot G + c \cdot I + d \cdot I:G + e \cdot T + f \cdot I:T + g \cdot I:T:G$ (equation 2)where a through g are coefficients to be estimated. If the term e·T is significant there is a linear trend over time common for both patient groups. If f·I: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 g·I: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 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 co-variates) is done using SPSS version 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 done to estimate the parameter of interest.

## ETHICS AND DISSEMINATION

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). 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 done 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 June 14 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. 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 1988 [74] 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 1:8,500 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 VO2 max). To achieve cardiovascular adjustment both exercise training and

testing begins with a warming-up period and ends with a cool-down period, with a gradual downward adjustment of exercise intensity and heart rate, 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 ischemia or heart failure triggered ventricular arrhythmias. When these precautions are respected, both exercise training and 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 www.copenheart.org. The website will be continuously updated and will be highlighted through the scientific articles.

## 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 one 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[78, 79], blinded assessment and analysis of outcomes[78, 79], multicentre participation and meets the SPIRIT and CONSORT criteria for high quality in non-pharmacological randomised clinical trials.[72, 80]

**Trajectory**

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

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**Competing interest:**

None

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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 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-5 |
| | 2b | Specific objectives or hypotheses | 6 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | NA |
| Participants | 4a | Eligibility criteria for participants | 7 |
| | 4b | Settings and locations where the data were collected | 8,10 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 7-11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 11-13 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | NA |
| Sample size | 7a | How sample size was determined | 11-12 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | 17 |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 14 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 14 |
| 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 | 14 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 14 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 6 |

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

*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.

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.



| | |
|---|---|
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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.

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## 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 psycho-education possess the potential of reducing sexual dysfunction in patients with heart disease. The CopenHeart$_{SF}$ trial will investigate the effect of a comprehensive sexual rehabilitation programme versus usual care.

**Methods and analysis:** CopenHeart$_{SF}$ 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 program and psycho-educative consultation with a special trained nurse. The primary outcome is sexual function measured by the International Index of Erectile Function. The secondary outcome measure is psycho-social adjustment to illness by the Psychosocial Adjustment to Illness Scale, sexual domain. A number of explorative analyses will also be conducted.

**Ethics and dissemination:** CopenHeart$_{SF}$ 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.

**Registration:** Clinicaltrials.gov identifier: NCT01796353

## ARTICLE SUMMARY

### Article focus

- The CopenHeart$_{SF}$ is a randomised clinical trial investigating the effects of a comprehensive sexual rehabilitation programme versus usual care for patients with sexual dysfunction and implantable cardioverter defibrillator or ischaemic heart disease.
- The hypothesis is, that comprehensive sexual rehabilitation consisting of a psycho-educational component and a physical exercise component including pelvic floor exercise improves sexual function.

### Key messages

- Sexual dysfunction is highly prevalent in cardiovascular patients and a systematic approach seems to be lacking.
- This trial is the first to study the effect of a comprehensive sexual rehabilitation programme in a cardiac population.
- This trial is the first to include pelvic floor exercise in a comprehensive rehabilitation programme in cardiac patients.

### Strengths and limitation of this study

- The study have been designed to meet the criteria for high quality in non-pharmacological randomised clinical 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.

## BACKGROUND

Sexuality is an important part of people's physical and mental health.[1, 2] Patients with cardiovascular disease have 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 both organic and 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 bi-directional, with one element forcing the other.[25, 26]

### Standard treatment

Despite the fact that several international guidelines recommend that health professionals address the topic sexuality in patients with heart disease,[27, 28] this is rarely done in practice.[29, 30] The consensus or practice on how or where patients with heart disease and sexual dysfunction should be treatedis lacking, however, some guidelines about prescription of phosphodiesterase5 (PDE5) inhibitors exist.[6] The PDE5 inhibitors have an overall success rate of 50% to 80% of those treated in patients with cardiovascular disease.[6, 31, 32] PDE5 inhibitors are generally safe. Linking PDE5 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 PDE5 inhibitors, or where PDE5 inhibitors are contra-indicated 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 life style 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 hours per week or more in non-heart disease patients showed a significant result in improving the person's erectile functioning compared with controls with no exercise training.[34] We hypothesize that these lifestyle modifications can also improve sexual dysfunction in patients with already established heart diseasel. 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% to 47% had regained normal erectile function after 3-4 month of training the pelvic floor muscles.[41, 42] As the condition 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 psycho-educational component and an exercise training component including pelvic floor exercises.

## TRIAL OBJECTIVES

The objective of the CopenHeart$_{SF}$ 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 psycho-educative 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 dysfunction (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 PDE5-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) questionnaire[47], 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 VO2), pelvic floor muscle strength and endurance and female assessment of male partner's erectile dysfunction.

## METHODS

CopenHeart$_{SF}$ 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 CopenHeart$_{SF}$ trial is a part of the overall CopenHeart project, consisting of several randomised clinical trials (www.CopenHeart.org), designed to develop evidence-based knowledge of rehabilitation among patients with complex cardiac conditions. Major parts of the CopenHeart$_{SF}$ methods section and trial design in this paper are similar toother randomised clinical trials, CopenHeart$_{IE}$[50], CopenHeart$_{RFA}$[51]and CopenHeart$_{VR}$[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 hours 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 randomized trial will be made. ***(See figure 1)***

**Experimental intervention**

The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual rehabilitation in this trial is defined as: a time-bounded 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 psycho-educational 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 minutes duration.[54] Furthermore, the intervention is supported by European recommendations for physical training in cardiac patients [55] and has been tested in COPE-ICD and DANREHAB trials.[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, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST segment changes, T-wave alterations, atrial or ventricular arrhythmias, and training intensity level 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 minutes (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 to 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 intensity 13 to 17 on the Borg scale and time limit (2 to 15 min) varying between each section; the second section with longest and highest intensity. A cool down period of 5 min is included after the 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 degrees flexion, hyperextension not accepted; (4) 90 degrees 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 to 20%) and increased throughout the 12 weeks. Load for leg press is estimated from repetition maximum (RM) testing and increases from 60% of 1 RM to 70% of 1 RM during the 12 weeks of training. All exercises are initiated by 2x12 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% to 50% of the base of the penis.[41] The pelvic floor training regimen is inspired by Dorey and colleagues, who have developed a training regimen for male patients for use in randomised clinical trials.[63] The regiment 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 seconds each, and patients are informed to have a 10 second 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 psycho-educational components**

The goal of the psycho-educative 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 ability to be sexually active without fear. A specially trained nurse is responsible for the psycho-educative 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 psycho-educative intervention is inspired by RR Parse's 'Human Becoming Practice Methodologies' three dimensions[64], 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 psycho-educative intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on psychological well-being (mental health) and the general health sub-scale of the SF-36.[56] The nurse is trained in the psycho-educative 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 two-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 settings and last for 45 minutes. 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 table 1):

| Table 1. Inspiration guide for psycho-educational 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 |

**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 PDE5 inhibitors. Patients who are candidates for PDE5 inhibitors are encouraged to contact their general practitioner in order to establish the treatment. Use of PDE5 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 comprehensive sexual rehabilitation programme numerous data will be collected.

*Primary outcome*

Sexual function will be measured by the International Index of Erectile Function (IIEF) questionnaire after 16 weeks and 6 months. International Index of Erectile Function (IIEF) was developed in conjunction with the clinical trial program for sildenafil, and has since been adopted as

the 'gold standard' measure for efficacy assessment in clinical trials of 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 Psychosocial Adjustment to Illness Scale (self-reported version) (PAIS-SR) sexual relationship domain.[47] The overall PAIS-SR measure psychosocial adjustment to illness in terms of 7 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 indicates good adjustment, and high scores 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 VO2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland)withmeasurement of oxygen uptake (VO2), heart rate (HR, beats /min),ventilation rate (VE, l /min), ventilation frequency (VF, number / min), respiratory expiration ratio (RER, CO2/O2in%), blood pressure , physical activity level (METS) and gas exchange (VO2 andVCO2) 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 25W and increased by 12.5W every minute until exhaustion,

usually but not always, is where the patient's oxygen uptake reaches 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 2)

**Table 2 CopenHeart$_{SF}$ - 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; SF-36, Short Form-36; HADS, Hospital Anxiety and Depression Scale; Eq-5D-5L, EuroQol; FAME, Female assessment of male erectile function,

**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 standard deviation 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, a standard deviation 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 one year prior to inclusion and patients with ischaemic heart disease one year from event and backward. The one year limit has been set so that patients are past their rehabilitation if any is provided. Patients will receive the International Index of Erectile Function questionnaire[45] by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score[46], 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 send 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 either 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 years or ≥ 60 years and randomised1:1 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

done when the investigator calls 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 patient 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 Enalyzer 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 e-mail contains a login and password for the trial participant's personal access. The participant has the opportunity to go through the website www.copenheart.org and login with the log-in and password. If patients do not complete the questionnaire electronically, the material can be sent in paper form and 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 $Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot I + c \cdot G + d \cdot I{:}G$ (equation 1).

$Y_{baseline}$ is the baseline value of the outcome, I is the indicator of intervention, G is the indicator of patient group, and a through d are coefficients to be estimated. The term d·I:G stands for interaction between the two covariates I and G. If the term b·I 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 d·I:G is significant there is an additional effect of the intervention in one of the two patient groups; thus a sub-group 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 sub-group 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 month 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 co-variates is$Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot G + c \cdot I + d \cdot I:G + e \cdot T + f \cdot I:T + g \cdot I:T:G$ (equation 2)where a through g are coefficients to be estimated. If the term e·T is significant there is a linear trend over time common for both patient groups. If f·I: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 g·I: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 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 co-variates) is done using SPSS version 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 done to estimate the parameter of interest.

## ETHICS AND DISSEMINATION

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). 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 done 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 June 14 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 1988 [74] 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 1:8,500 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 VO2 max). To achieve cardiovascular adjustment both exercise training and testing begins with a warming-up period and ends with a cool-down period, with a gradual downward adjustment of exercise intensity and heart rate, 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 ischemia or heart failure triggered ventricular arrhythmias. When these precautions are respected, both exercise training and 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 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 one 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 February 2013 and is expected to continue until June 2014.

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**Contributorship Statement**

PPJ, SKB, ADZ, JHs, MF, JL, PW, CG, AG, ES, TJ all designed the study and developed the protocl. PW specifically designed the statistical analysis plan. PPJ, SKB, ADZ drafted the manuscript. PPJ, SKB, ADZ, JHS, MF, JL, PW, CG, AG, ES, TJ all revised the manuscript critically. All authors have given their final approval of the version to be published

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**Competing interest:**

None

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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.

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## 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 psycho-education possess the potential of reducing sexual dysfunction in patients with heart disease. The CopenHeart$_{SF}$ trial will investigate the effect of a comprehensive sexual rehabilitation programme versus usual care.

**Methods and analysis:** CopenHeart$_{SF}$ 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 program and psycho-educative consultation with a special trained nurse. The primary outcome is sexual function measured by the International Index of Erectile Function. The secondary outcome measure is psycho-social adjustment to illness by the Psychosocial Adjustment to Illness Scale, sexual domain. A number of explorative analyses will also be conducted.

**Ethics and dissemination:** CopenHeart$_{SF}$ 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.

**Registration:** Clinicaltrials.gov identifier: NCT01796353

## ARTICLE SUMMARY

### Article focus

- The CopenHeart$_{SF}$ is a randomised clinical trial investigating the effects of a comprehensive sexual rehabilitation programme versus usual care for patients with sexual dysfunction and implantable cardioverter defibrillator or ischaemic heart disease.
- The hypothesis is, that comprehensive sexual rehabilitation consisting of a psycho-educational component and a physical exercise component including pelvic floor exercise improves sexual function.

### Key messages

- Sexual dysfunction is highly prevalent in cardiovascular patients and a systematic approach seems to be lacking.
- This trial is the first to study the effect of a comprehensive sexual rehabilitation programme in a cardiac population.
- This trial is the first to include pelvic floor exercise in a comprehensive rehabilitation programme in cardiac patients.

### Strengths and limitation of this study

- The study have been designed to meet the criteria for high quality in non-pharmacological randomised clinical 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.

## BACKGROUND

Sexuality is an important part of people's physical and mental health.[1, 2] Patients with cardiovascular disease have 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 both organic and 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 bi-directional, with one element forcing the other.[25, 26]

### Standard treatment

Despite the fact that several international guidelines recommend that health professionals address the topic sexuality in patients with heart disease,[27, 28] this is rarely done in practice.[29, 30] The consensus or practice on how or where patients with heart disease and sexual dysfunction should be treatedis lacking, however, some guidelines about prescription of phosphodiesterase5 (PDE5) inhibitors exist.[6] The PDE5 inhibitors have an overall success rate of 50% to 80% of those treated in patients with cardiovascular disease.[6, 31, 32] PDE5 inhibitors are generally safe. Linking PDE5

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 PDE5 inhibitors, or where PDE5 inhibitors are contra-indicated 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 life style 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 hours per week or more in non-heart disease patients showed a significant result in improving the person's erectile functioning compared with controls with no exercise training.[34] We hypothesize that these lifestyle modifications can also improve sexual dysfunction in patients with already established heart diseasel. 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% to 47% had regained normal erectile function after 3-4 month of training the pelvic floor muscles.[41, 42] As the condition 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 psycho-educational component and an exercise training component including pelvic floor exercises.

## TRIAL OBJECTIVES

The objective of the CopenHeart$_{SF}$ 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 psycho-educative 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 dysfunction (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 PDE5-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) questionnaire[47], 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 VO2), pelvic floor muscle strength and endurance and female assessment of male partner's erectile dysfunction.

## METHODS

CopenHeart$_{SF}$ 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 CopenHeart$_{SF}$ trial is a part of the overall CopenHeart project, consisting of several randomised clinical trials (www.CopenHeart.org),

designed to develop evidence-based knowledge of rehabilitation among patients with complex cardiac conditions. Major parts of the CopenHeart$_{SF}$ methods section and trial design in this paper are similar toother randomised clinical trials, CopenHeart$_{IE}$[50], CopenHeart$_{RFA}$[51]and CopenHeart$_{VR}$[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~~competitive~~ exercise more than 3 hours 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 randomized trial will be made. ***(See figure 1)***

**Experimental intervention**

The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual rehabilitation in this trial is defined as: a time-bounded 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 psycho-educational 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 minutes duration.[54] Furthermore, the intervention is supported by European recommendations for physical training in cardiac patients [55] and has been tested in COPE-ICD and DANREHAB trials.[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, version 2.0.16, Finland) potential cardiac arrhythmias, electrocardiographic abnormalities such as ST segment changes, T-wave alterations, atrial or ventricular arrhythmias, and training intensity level 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 minutes (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 to 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 intensity 13 to 17 on the Borg scale and time limit (2 to 15 min) varying between each section; the second section with longest and highest intensity. A cool down period of 5 min is included after the 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 degrees flexion, hyperextension not accepted; (4) 90 degrees 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 to 20%) and increased throughout the 12 weeks. Load for leg press is estimated from repetition maximum (RM) testing and increases from 60% of 1 RM to 70% of 1 RM during the 12

weeks of training. All exercises are initiated by 2x12 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% to 50% of the base of the penis.[41] The pelvic floor training regimen is inspired by Dorey and colleagues, who have developed a training regimen for male patients for use in randomised clinical trials.[63] The regiment 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 seconds each, and patients are informed to have a 10 second 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 psycho-educational components**

The goal of the psycho-educative 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 ability to be sexually active without fear. A specially trained nurse is responsible for the psycho-educative 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 psycho-educative intervention is inspired by RR Parse's 'Human Becoming Practice Methodologies' three dimensions[64], 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 psycho-educative intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on psychological well-being (mental health) and the general health sub-scale of the SF-36.[56] The nurse is trained in the psycho-educative 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 two-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 settings and last for 45 minutes. 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 table 1):

| Table 1. Inspiration guide for psycho-educational 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 |

**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 PDE5 inhibitors. Patients who are candidates for PDE5 inhibitors are encouraged to contact their general practitioner in order to establish the treatment. Use of PDE5 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 comprehensive sexual rehabilitation programme numerous data will be collected.

*Primary outcome*

Sexual function will be measured by the International Index of Erectile Function (IIEF) questionnaire after 16 weeks and 6 months. International Index of Erectile Function (IIEF) was developed in conjunction with the clinical trial program for sildenafil, and has since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of 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 Psychosocial Adjustment to Illness Scale (self-reported version) (PAIS-SR) sexual relationship domain.[47] The overall PAIS-SR measure psychosocial adjustment to illness in terms of 7 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 indicates good adjustment, and high scores 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 VO2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland)withmeasurement of oxygen uptake (VO2), heart rate (HR, beats /min),ventilation rate (VE, l /min), ventilation frequency (VF, number / min), respiratory expiration ratio (RER, CO2/O2in%), blood pressure , physical activity level (METS) and gas exchange (VO2 andVCO2) 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 25W and increased by 12.5W every minute until exhaustion, usually but not always, is where the patient's oxygen uptake reaches 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 2)

**Table 2 CopenHeart$_{SF}$ - 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; SF-36, Short Form-36; HADS, Hospital Anxiety and Depression Scale; Eq-5D-5L, EuroQol; FAME, Female assessment of male erectile function,

**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 standard deviation 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, a standard deviation 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 one year prior to inclusion and patients with ischaemic heart disease one year from event and backward. The one year limit has been set so that patients are past their rehabilitation if any is provided. Patients will receive the International Index of Erectile Function questionnaire[45] by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score[46], 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 send 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 either 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 years or ≥ 60 years and randomised1:1 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 done when the investigator calls 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 patient 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 Enalyzer 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 e-mail contains a login and password for the trial participant's personal access. The participant has the opportunity to go through the website www.copenheart.org and login with the log-in and password. If patients do not complete the questionnaire electronically, the material can be sent in paper form and 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$Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot I + c \cdot G + d \cdot I{:}G$ (equation 1).

$Y_{baseline}$ is the baseline value of the outcome, I is the indicator of intervention, G is the indicator of patient group, and a through d are coefficients to be estimated. The term d·I:G stands for interaction between the two covariates I and G. If the term b·I 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 d·I:G is significant there is an additional effect of the intervention in one of the two patient groups; thus a sub-group 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 sub-group 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 month 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 co-variates is$Y = \text{intercept} + a \cdot Y_{baseline} + b \cdot G + c \cdot I + d \cdot I{:}G + e \cdot T + f \cdot I{:}T + g \cdot I{:}T{:}G$ (equation 2)where a through g are coefficients to be estimated. If the term e·T is significant there is a linear trend over time common for both patient groups. If f·I: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 g·I: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 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 co-variates) is done using SPSS version 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 done to estimate the parameter of interest.

## ETHICS AND DISSEMINATION

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). 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 done 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 June 14 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 ~~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 1988 [74] 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 1:8,500 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 VO2 max). To achieve cardiovascular adjustment both exercise training and testing begins with a warming-up period and ends with a cool-down period, with a gradual downward adjustment of exercise intensity and heart rate, 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 ischemia or heart failure triggered ventricular arrhythmias. When these precautions are respected, both exercise training and 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 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 one 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~~blinded assessment and analysis of outcomes~~.[78, 79]; ~~multicentre participation and meets the SPIRIT and CONSORT criteria for high quality in non-pharmacological randomised clinical trials.~~

### Trajectory

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

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**Competing interest:**

None

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| 17 | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | na |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 20 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| | 5b | Name and contact information for the trial sponsor | na |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 20 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 18 |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | 5-6 |
| Objectives | 7 | Specific objectives or hypotheses | 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 7 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8-12 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 18 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | Na |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12-14 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 15 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 15-16 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 15-16 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 15-16 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 15-16 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | Na |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12-14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 18 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 16 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 16 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 16-17 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 18 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | Na |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 18 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 18 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 18 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 16 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | Na |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 15 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 20 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 19 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Na |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 19 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 19 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Na |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Na |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | Na |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

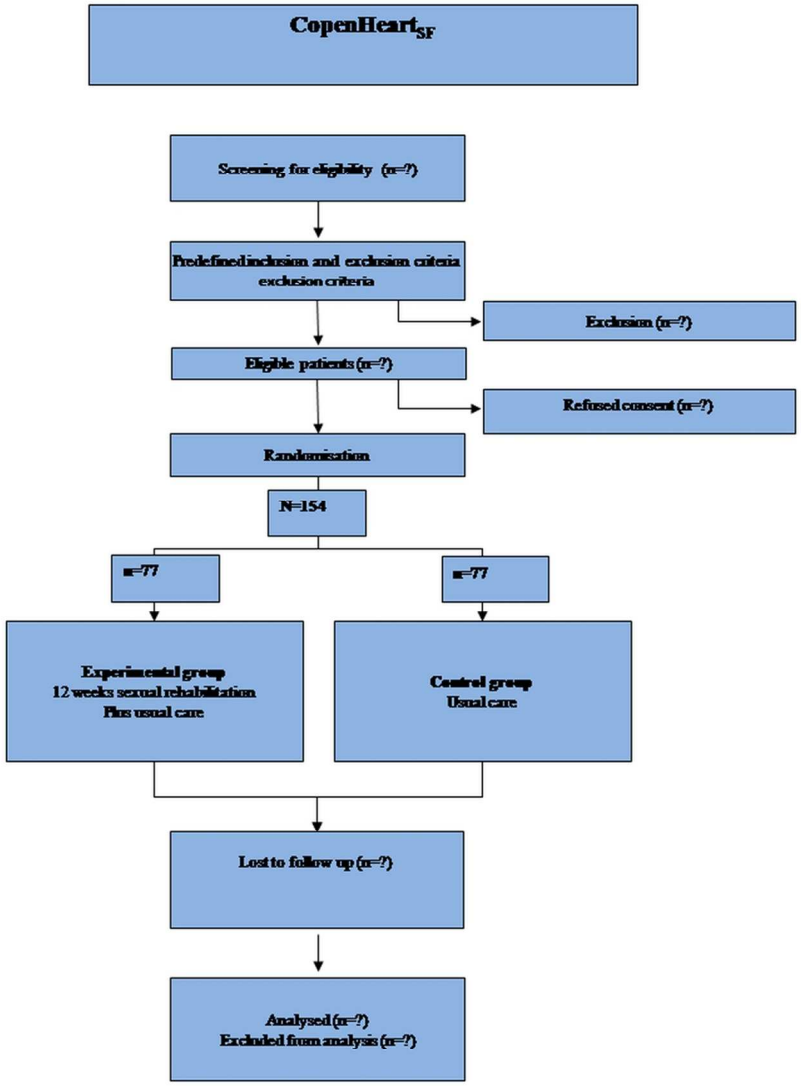


**Figure 1. Flowchart**

Flowchart
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