



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.

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003967
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2013
Complete List of Authors:	Johansen, Pernille; Copenhagen University Hospital Bispebjerg, Department of Cardiology; Copenhagen University Hospital, Rigshospitalet, The Heart Centre Zwisler, Ann-Dorthe; Copenhagen University Hospital, Rigshospitalet, The Heart Centre Svendsen, Jesper; Copenhagen University Hospital Rigshospitalet, The Heart Centre Frederiksen, Marianne; Copenhagen University Hospital Bispebjerg, Department of Cardiology Lindschou, Jane; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Winkel, Per; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Gluud, Christian; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Giraldi, Annamaria; Copenhagen University Hospital Rigshospitalet, Sexological Clinic, Psychiatric Center Copenhagen Steinke, Elaine; Wichita State University, Jaarsma, Tiny; Linköping University, Department of Social and Welfare Studies Berg, Selina; Copenhagen University Hospital Rigshospitalet, The Heart Centre; Rigshospitalet, Cardiology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sexual health, Nursing, Cardiovascular medicine
Keywords:	CARDIOLOGY, REHABILITATION MEDICINE, SEXUAL MEDICINE

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

Pernille Palm Johansen¹⁺²

Ann-Dorthe Zwisler²⁺³

Jesper Hastrup-Svendsen²⁺⁸

Marianne Fredriksen¹

Jane Lindschou⁴

Per Winkel⁴

Christian Gluud⁴

Annamaria Giraldi⁵

Elaine Steinke⁶

Tiny Jaarsma⁷

Selina Kikkenborg Berg²

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

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

³National Institute of Public Health, University of Southern Denmark

⁴The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

⁵Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁶Wichita State University, Wichita, Kansas, United States

⁷Department of Social and Welfare Studies, Linköping University, Linköping, Sweden

⁸Institute of Clinical Medicine, Faculty of Health Science, University of Copenhagen

Corresponding author:

Pernille Palm Johansen RN. MCN

Copenhagen University Hospital, Bispebjerg Hospital / Rigshospitalet

Copenhagen

Denmark

Mail: pernille.palm.johansen@regionh.dk

For peer review only

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 treated is 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

1
2
3
4 treatment with nitrates, there seems to be no consensus on what treatment should be offered for
5 sexual dysfunction.
6
7

8 9 **Non-pharmacological treatment potentials**

10 Non-pharmacological interventions possess potential in reducing sexual dysfunction. Lifestyle
11 factors such as; cigarette smoking, hyperlipidaemia, and a sedentary lifestyle all predict erectile
12 dysfunction^{4, 5} and these are the same risk factors that predict coronary artery disease. A recent
13 meta-analysis of six randomised trials with 740 patients with no known heart disease, showed that
14 life style modifications such as physical exercise and pharmacotherapy for cardiovascular risk
15 factors were associated with a significant improvement in erectile function.³³ Furthermore, a
16 randomised trial investigating the effect of exercise training 3 hours per week or more in non-heart
17 disease patients showed a significant result in improving the person's erectile functioning compared
18 with controls with no exercise training.³⁴ We hypothesize that these lifestyle modifications can also
19 improve sexual dysfunction in patients with already established heart disease. A systematic
20 literature search showed five randomised clinical trials which examine the effect of physical
21 exercise on sexual dysfunction.³⁵⁻³⁹ Overall, 591 patients with heart disease were included and the
22 effect was significant in three of the five trials.³⁷⁻³⁹ However, the trials are characterised as being of
23 small sample sizes, using non-validated tools and mainly focusing on the time before patients return
24 to sexual activity and not on the ability and quality of the sexual performance. Randomised trials
25 that address the psychological aspects of sexual dysfunction are limited in patients with heart
26 disease. However, one randomised trial testing the effect of sexual therapy showed some promising
27 trends when it comes to improving the frequency and quality of sexual activity in male patients post
28 cardiac event beyond the usual cardiac rehabilitation.⁴⁰ However, due to the limited power of the
29 sample in this trial, it did not allow the detection of significant effects. The role of pelvic floor
30 exercises as a treatment of erectile dysfunction is not tested on patients with heart disease, but in the
31 general population 40% to 47% had regained normal erectile function after 3-4 month of training
32 the pelvic floor muscles.^{41, 42} As the condition sexual dysfunction often includes both physical and
33 psychological components, it is plausible to believe that patients with heart disease and sexual
34 dysfunction benefit from a comprehensive rehabilitation intervention^{43, 44} consisting of a psycho-
35 educational component and an exercise training component including pelvic floor exercises.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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) questionnaire⁴⁷, improves by two points in the experimental group compared with the control group after completing the programme. The estimated increase in secondary outcome is based on two studies that examine the prevalence of sexual dysfunction in patients with heart failure.^{48, 49}

Exploratory analyses will test the hypotheses that comprehensive sexual rehabilitation will improve: health-related quality of life, anxiety and depression, frequency of sexual activity, physical capacity measured by peak oxygen uptake (peak 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 to other randomised clinical trials, CopenHeart_{IE}⁵⁰, CopenHeart_{RFA}⁵¹ and CopenHeart_{VR}⁵².

Study population and eligibility criteria

1
2
3
4 Male patients above 18 years with sexual dysfunction associated with implantable cardioverter
5 defibrillator or with ischaemic heart disease verified by coronary angiography, who have a partner,
6 speak and understand Danish, and provide a written informed consent, are considered eligible for
7 participation. Exclusion criteria are patients at intermediate or high risk in relation to their
8 cardiovascular status according to recommendations from the Princeton consensus group^{32, 53}; those
9 with diseases in the urinary tract; those who perform competitive exercise more than 3 hours a
10 week; patients with neurological or orthopaedic deficits which prevent training; patients with
11 cognitive deficits which prevents consultations; and patients who are included in ongoing research
12 prohibiting additional research participation. A diagram showing the flow of participants through
13 each stage of the randomized trial will be made. (*See figure 1*)
14
15
16
17
18
19
20
21

22 **Experimental intervention**

23
24 The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual
25 rehabilitation in this trial is defined as: a time-bounded planned process with clear goals and means.
26 Sexual rehabilitation is a process where several actors, including the patient, are working towards
27 regaining improved sexual functioning and coping ability according to their sexual function. The
28 comprehensive sexual rehabilitation programme contains a physical exercise component, including
29 training of the pelvic floor and a psycho-educational component.
30
31
32
33
34
35

36 **The physical components**

37 *Physical exercise*

38
39 The goal of physical exercise is to achieve an improvement in the patient's physical work capacity,
40 and to eliminate the fear and uncertainty the patient may feel in relation to sexual activity as a form
41 of physical activity. The physical exercise intervention is based on The European Society of
42 Cardiology recommendations for physical activity for cardiovascular patients.⁵⁴ The European
43 Society of Cardiology recommends that all adults promote and maintain their fitness, muscle
44 strength, flexibility and bone health several hours a week. Training must be of high intensity and of
45 30 minutes duration.⁵⁴ Furthermore, the intervention is supported by European recommendations
46 for physical training in cardiac patients⁵⁵ and has been tested in COPE-ICD and DANREHAB
47 trials.^{56, 57} A professional physiotherapist with specific knowledge of cardiac rehabilitation initiates
48 the physical exercise programme. Together with the patient, the physiotherapist plans and prepares
49 a physical exercise protocol, taking into account the patient's clinical condition and physical
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 upright position to decrease left ventricular filling pressure and risk of ischaemia or heart-failure-
5 triggered ventricular arrhythmias.⁶²
6
7

8 9 *Pelvic floor exercise*

10 The bulbocavernosus muscle and the ischiocavernosus muscle, two superficial pelvic floor muscles,
11 are active during erection and enhance rigidity. The bulbocavernosus muscle encircles 33% to 50%
12 of the base of the penis.⁴¹ The pelvic floor training regimen is inspired by Dorey and colleagues,
13 who have developed a training regimen for male patients for use in randomised clinical trials.⁶³ The
14 regiment is developed and tested in a different patient population, and we have therefore modified it
15 to fit cardiovascular patients. Patients are instructed in pelvic floor exercises by a skilled
16 physiotherapist. Patients are instructed to perform their pelvic floor exercises twice daily. Studies
17 showed that a few strong or maximum contractions are more effective when it comes to gaining
18 muscle hypertrophy than several less strong contractions.⁶³ Patients are instructed to tighten their
19 pelvic floor muscles as strongly as possible (as if to prevent flatus from escaping) three times when
20 lying, three times when sitting, and three times when standing. The duration of the contraction is up
21 to 10 seconds each, and patients are informed to have a 10 second break between each contraction.
22 The physiotherapist instructs the patients on how to contract the bulbocavernosus and
23 ischiocavernosus muscles. In order to ensure that the right muscles are involved, attention is placed
24 on the ability to lift the scrotum and retract the penis. To obtain some degree of pelvic floor muscle
25 endurance, the patients are encouraged to tighten the pelvic floor muscles when walking.
26 To monitor compliance pulse watches (Polar watch) with extended memory and exercise training
27 logs are handed out. A training log contains information about physical exercise as well as pelvic
28 floor exercise. At the end of the intervention the training log and the pulse watch are returned and
29 compliance and intensity level are coded independently.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 **The psycho-educational components**

47 The goal of the psycho-educative intervention is that the patient learns to interpret and react to
48 relevant physical and psychological symptoms, learns to cope with anxiety and fear, including
49 strategies to manage depressive symptoms and ability to be sexually active without fear.
50 A specially trained nurse is responsible for the psycho-educative intervention. The intervention
51 takes a theoretical basis of the patient-centred approach where the emphasis is on support and
52 education. The conversations are based on a holistic view of the patient and focus on the handling
53
54
55
56
57
58
59
60

1
2
3
4 of life and managing sexual dysfunction. The intervention is targeted at the modifiable parameters
5 that are reported to affect sexual dysfunction. The psycho-educative intervention is inspired by RR
6 Parse's 'Human Becoming Practice Methodologies' three dimensions⁶⁴, which can be described as:
7 1. discuss and give meaning to the past, present and future, 2. explore and discuss events and
8 opportunities; and 3. pursue imagined possibilities. According to this theory, there are three ways to
9 alter its perceived health: creative ideas, see, hear and feel how a situation could be if it was lived in
10 a different way; recognising personal patterns and value priorities and shed light on the paradoxes
11 by looking at incongruence in a situation and change the view of reality. The nurse is 'truly present'
12 in the process through discussion, quiet contemplation, and reflection. The psycho-educative
13 intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on
14 psychological well-being (mental health) and the general health sub-scale of the SF-36.⁵⁶ The nurse
15 is trained in the psycho-educative conversation through teaching and supervision of nurses who
16 have experience with the 'Human Becoming Practice Methodology' from the COPE-ICD trial. It is
17 based on the theoretical literature that forms the basis for understanding the processes of practice
18 methodology and existing specialty specific knowledge about heart disease, related symptoms, and
19 sexology. The supervisor observes and provides feedback in relation to the methods and goals of the
20 conversation. The emphasis is on openness in the interviews, and on the nurse's ability to: be
21 silently present while the patient talks, ask questions that encourage reflection, let the patient find
22 answers and solutions and contribute with knowledge, provide advice and guidance when requested
23 and relevant. The training of the nurse takes place prior to the intervention. In practice the
24 intervention will be handled by one nurse with several years of experience working with cardiac
25 patients and trained in sexology. The sexology experience is gained in a two-week intensive course
26 on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist is
27 available during the intervention. The nurse will conduct consultations with patients individually,
28 and patients are informed that they are welcome to bring spouses/relatives. The consultation will
29 take place in a quiet room in an outpatient settings and last for 45 minutes. An inspirational guide
30 will form the basis for the consultations. The guide consists of several elements and issues (medical,
31 psychosocial, educational and sexual) that work as inspiration (see table 1):
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 the 'gold standard' measure for efficacy assessment in clinical trials of erectile dysfunction. It has
5 been linguistically validated in 32 languages including Danish and used as a primary outcome in
6 more than 50 clinical trials.^{34, 45, 46} It consists of 15 items including five domains of sexual function:
7 erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
8 The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of
9 sensitivity and specificity.⁴⁶ The IIEF is self-assessed, which in sexological research is widely used
10 and well acclaimed.

11 12 13 14 15 16 17 18 *Secondary outcome*

19
20 Sexual function is measured by the Psychosocial Adjustment to Illness Scale (self-reported version)
21 (PAIS-SR) sexual relationship domain.⁴⁷ The overall PAIS-SR measure psychosocial adjustment to
22 illness in terms of 7 primary domains of adjustment: Health Care Orientation, Vocational
23 Environment, Domestic Environment, Sexual Relationships, Extended Family Relationships, Social
24 Environment and Psychological Distress. Each PAIS/PAIS-SR item is rated on a 4-point (0 through
25 3) scale of adjustment, with higher ratings indicating poorer adjustment status. The sexual
26 relationship domain evaluates shifts in the quality of sexual relations due to the current illness or
27 treatment. It consists of six items and the total score ranges from 0 to 18. Low scores indicates good
28 adjustment, and high scores poor adjustment.

29 30 31 32 33 34 35 36 37 *Exploratory outcomes*

38
39 A more extensive evaluation of physical, psychological, and demographic status over time will be
40 performed. Physical examination will include pelvic floor strength and endurance assessed
41 according to the Modified Oxford grading scheme which is a manual digital examination of the
42 pelvic floor. It is tested and validated and used in several trials.^{65, 66} Furthermore physical capacity
43 will be measured by peak VO₂ using cardiopulmonary exercise testing (Ergo-Spiro CS-200,
44 Schiller, Switzerland) with measurement of oxygen uptake (VO₂), heart rate (HR, beats
45 /min), ventilation rate (VE, l/min), ventilation frequency (VF, number / min), respiratory expiration
46 ratio (RER, CO₂/O₂in%), blood pressure, physical activity level (METS) and gas exchange (VO₂
47 and VCO₂) during progressive loading and in the following recovery period. The test is conducted
48 before the training programme initiates. Intensity performed as a ramp protocol (load gradually
49 increases) with the initial work load of 25W and increased by 12.5W every minute until exhaustion,
50
51
52
53
54
55
56
57
58
59
60

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		
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 questionnaire⁴⁵ by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score⁴⁶, on the initial screening are invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems. The participant information is 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 randomised 1:1 to the experimental group or the control group. Randomisation will be performed centrally by the trial coordination centre, Copenhagen Trial Unit, according to a computer-generated allocation sequence with a variable block size concealed from the investigators. Allocation to the intervention groups is

1
2
3
4 done when the investigator calls Copenhagen Trial Unit. Relevant information (personal
5 identification number, strata, etc.) is typed into a computer system, and then the participant will be
6 allocated to an intervention group and awarded a four-digit randomisation number. The investigator
7 then informs the patient of the result and on how to proceed by letter. Thus, neither investigators
8 nor patients or relatives can influence to which group the patient are allocated. For both groups,
9 follow-up assessment will take place after 12 weeks (only physical evaluation), 16 weeks, and 6
10 months. Questionnaires will be completed electronically in the questionnaire system Enalyzer with
11 'single user', which meets the data legislation for logging. At inclusion, the trial participant will
12 receive an email with a link to a website through which questionnaires can be completed. The e-
13 mail contains a login and password for the trial participant's personal access. The participant has the
14 opportunity to go through the website www.copenheart.org and login with the log-in and password.
15 If patients do not complete the questionnaire electronically, the material can be sent in paper form
16 and independent trial personnel then enters the responses into the database. Thus data management
17 is handled independently from the researchers who interpret the data.
18
19
20
21
22
23
24
25
26
27
28

29 **Statistical analysis**

30 *Analysis of primary and secondary outcomes*

31
32 The analysis will be performed according to the intention-to-treat analysis with two sided
33 significance tests at the 0.05 level. Both outcomes (and outcomes subjected to exploratory analyses)
34 will be analysed using the same procedure. First, we will test if there is an immediate effect of the
35 intervention on the outcome and/or a difference in the response to the intervention between the two
36 patient groups (patients with ischaemic heart disease and patients with implantable cardioverter
37 defibrillator) using model 1 below. Then the follow-up data will be included in the analysis and the
38 long-term effect will be studied using model 2.
39
40
41
42
43
44

45 *Models and analytical techniques*

46
47 *Model 1* The equation (equation 1) showing the dependent variable Y (the outcome) as a function of
48 covariates used in the analysis of the immediate effect of the intervention on the primary outcome
49 is $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot I + c \cdot G + d \cdot I:G$ (equation 1).
50

51
52 Y_{baseline} is the baseline value of the outcome, I is the indicator of intervention, G is the indicator of
53 patient group, and a through d are coefficients to be estimated. The term d·I:G stands for interaction
54 between the two covariates I and G. If the term b·I is significant (the coefficient b differs
55
56
57
58
59
60

1
2
3
4 significantly from 0) there is an effect of the intervention common for the two patient groups
5 (ischaemic patients and patients with implantable cardioverter defibrillator). If the term d:I:G is
6 significant there is an additional effect of the intervention in one of the two patient groups; thus a
7 sub-group analysis is warranted. In the analysis of the data the univariate general linear model is
8 used. The analysis of the primary outcome is the primary analysis. The sub-group analysis and the
9 analysis of the secondary and of other outcomes should be considered exploratory.
10
11
12
13

14
15
16 *Model 2* In the analysis of follow up data the time T (Y is measured 16 weeks and 6 month
17 following randomisation) is included and the mixed model for repeated measures is used. The
18 equation (equation 2) for the fixed effect in this model showing Y as a function of the co-variables
19 is $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot G + c \cdot I + d \cdot I:G + e \cdot T + f \cdot I:T + g \cdot I:T:G$ (equation 2) where a through g
20 are coefficients to be estimated. If the term e:T is significant there is a linear trend over time
21 common for both patient groups. If f:I:T is significant, this trend is supplemented by an additional
22 trend caused by the intervention and therefore specific for the intervention group. If in addition
23 g:I:T:G is significant this added trend differs between the two patient groups (patients with
24 ischaemic heart disease and patients with implantable cardioverter defibrillator). In the mixed
25 model analysis an unstructured covariance matrix will be assumed. If convergence is not attained
26 simpler covariance structure models will be assessed guided by Akaike's criterion or maximum
27 likelihood test as appropriate.
28
29
30
31
32
33
34
35
36

37 *Missing values*

38
39 If the number of missing cases for a given outcome (number of patients with one or more model
40 variables missing) is larger than 5% or p of Little's test is < 5% multiple imputations of the model
41 variables (outcome plus co-variables) is done using SPSS version 17. The range of potential bias in
42 case the missing values should not be random is assessed by doing two imputations (1) imputing
43 missing outcome value in one group by minimum value found in the material and missing outcome
44 value in the other group by maximum value found in material and (2) vice versa. Then in each case
45 an unadjusted analysis is done to estimate the parameter of interest.
46
47
48
49
50
51

52 **ETHICS AND DISSEMINATION**

53
54 Trial protocol has been approved by the Regional Ethics Committee (no H-4-2012-168) and the
55 Danish Data Protection Agency (no 2007-58-0015). The trial complies with the latest declaration of
56
57
58
59
60

1
2
3
4 Helsinki and is registered at ClinicalTrials.gov (NCT01796353). Patients are informed about the
5 trial in writing as well as verbally and only included if a written informed consent is obtained.
6
7 Patients are assessed in accordance to whether it is safe for them to perform sexual activity. This is
8 done according to recommendations from the Princeton consensus group.^{32, 53} If patients are suited
9 and want to participate they will be enrolled in the trial. Trial participants are free to withdraw their
10 informed consent at any time and be treated according to the departments' standard treatment
11 procedures. A patient will be withdrawn from the trial if the trial participant withdraws his consent
12 and will, in connection therewith, be informed that termination of the trial will have no implications
13 for his future treatment. Patients who leave the trial will be politely asked for permission to
14 continue to collect data and to use already collected data. If the patient gives permission, he will be
15 included in the final analysis. Only if the patient refuses use of already collected data, will all data
16 relating to him, be destroyed. All patient data will be handled and stored in accordance with Danish
17 Data Protection Agency rules and patients are ensured anonymity. The trial will be conducted
18 according to the Act. No. 593 of June 14 2011 on Act on Research Ethics Review of Health
19 Research Projects. The investigator will immediately notify the regional ethics committee if, within
20 the interventions period, there occur Serious Adverse Events, Serious Adverse Reactions, or
21 Suspected Unexpected Serious Adverse Reactions. The report will be accompanied by comments
22 on possible implications for the trial, and notification will be made within 7 days after the
23 investigator has knowledge of the event. An internal monitor will perform random checks to see if
24 the trial staff work according to the protocol. No risks are anticipated to occur during the sexual
25 rehabilitation programme. As far as we know, there is no previous risk associated with nursing
26 consultations. If the nurse during the consultation identifies a need for further consultations with
27 professionals, she will encourage the participant to seek help from the general practitioner,
28 psychologist, or in their usual outpatient setting. Risks associated with exercise training and testing
29 are sudden cardiac death associated with ventricular arrhythmias, acute myocardial infarction, and
30 in patients with chronic heart failure, pulmonary oedema and deterioration in left ventricular
31 function.⁷³ The last is only found in one study from 1988⁷⁴ and has not subsequently been
32 demonstrated in larger studies.^{75, 76} In a recent French study of more than 25,000 patients with
33 ischaemic heart disease, one third with chronic heart failure found the risk of cardiac complications
34 at 1:8,500 exercise testing and 1:50,000 patient exercise hours.⁷⁷ Increasing exercise intensity and
35 age are risk indicators. Therefore, the training intensity will be conducted as moderate high intensity
36 (less than 80% of VO₂ max). To achieve cardiovascular adjustment both exercise training and
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 testing begins with a warming-up period and ends with a cool-down period, with a gradual
5 downward adjustment of exercise intensity and heart rate, rather than an abrupt end. This
6 cardiovascular adjustment has been shown to reduce the risk of ischaemia and arrhythmia in
7 connection with physical exercise.^{44, 62} Participants must mainly exercise in an upright position to
8 decrease left ventricular filling pressure and risk of ischemia or heart failure triggered ventricular
9 arrhythmias. When these precautions are respected, both exercise training and exercise testing are
10 considered to possess a low risk for the participants. There is, as far as we know, no previously
11 known risk associated with pelvic floor exercise. Testing or examination of the pelvic floor may be
12 associated with discomfort for the participants but is not considered to be associated with any risk.
13 Staff members will be trained according to guidelines to handle any emergencies.
14
15
16
17
18
19
20
21

22 **Dissemination plan**

23
24 Positive, neutral, and negative results of the trial will be submitted to international peer reviewed
25 journals of nursing, cardiology or sexology. Furthermore, results will be presented at national and
26 international conferences relevant to subject fields. Authorship will be allocated using the
27 guidelines for authorship defined by the International Committee of Medical Journal Editors and
28 depends on the personal involvement. All the articles, abstracts as well as the results will be posted
29 on the website www.copenheart.org. The website will be continuously updated and will be
30 highlighted through the scientific articles.
31
32
33
34
35
36

37 **DISCUSSION**

38
39 This randomised clinical trial testing the effect of a comprehensive sexual rehabilitation
40 intervention on a population of patients with implantable cardioverter defibrillator or patients with
41 ischaemic heart disease seems to be the first one in its field. The trial is expected to contribute with
42 results that can improve patients' problems related to heart disease and sexual function.
43
44

45 Additionally, it is believed that the trial can provide a systematic approach that may one day inform
46 national consensus on how to treat sexual dysfunction in heart patients. Furthermore, the results of
47 the trial are expected to contribute to the international debate on sexual rehabilitation of patients
48 with heart disease.
49
50

51
52 The trial is designed with central stratified randomisation^{78, 79}, blinded assessment and analysis of
53 outcomes^{78, 79}, multicentre participation and meets the SPIRIT and CONSORT criteria for high
54 quality in non-pharmacological randomised clinical trials.^{72, 80}
55
56
57
58
59
60

Trajectory

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

Acknowledgements:

The test and rehabilitation team responsible for the trial is: Karina Jensen, Lars Tang, Helena Tjalk Sørensen, Signe Gils and Katrine Tingholm Erhardsen.

Funding statement:

The CopenHeart trial has received funding from: The Danish Heart Foundation (no. 13-04-R95-A4669-22744); The Health Foundation (no. 2013B208); Danish Council for Strategic Research (no. 10-092790); The Danish Nursing Council. Neither of the funders had influence of the study protocol and design, the execution of the trial or the interpretation of data.

Competing interest:

None

REFERENCES

1. Hoekstra T, Jaarsma T, Sanderman R, van Veldhuisen DJ, Lesman-Leege I. Perceived sexual difficulties and associated factors in patients with heart failure. *Am Heart J* 2012; Feb;163(2):246-51.
2. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; Feb 10;281(6):537-44.
3. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; Jan;151(1):54-61.

- 1
2
3
4 4. Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, et al. Erectile
5
6 dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study.
7
8 *Prev Med* 2000; Apr;30(4):328-38.
- 9
10
11 5. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function
12
13 in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern*
14
15 *Med* 2003; Aug 5;139(3):161-8.
- 16
17
18 6. Levine GN, Steinke EE, Bakaen FG, Bozkurt B, Cheitlin MD, Conti JB, et al. Sexual activity
19
20 and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*
21
22 2012; Feb 28;125(8):1058-72.
- 23
24
25 7. Steinke EE. Sexual dysfunction in women with cardiovascular disease: what do we know?. *J*
26
27 *Cardiovasc Nurs* 2010; Mar-Apr;25(2):151-8.
- 28
29
30 8. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED, Jr, et al.
31
32 Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med* 2010; Apr;7(4 Pt 2):1598-
33
34 607.
- 35
36
37 9. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence.
38
39 *JAMA* 1993; Jul 7;270(1):83-90.
- 40
41
42 10. Rastogi S, Rodriguez JJ, Kapur V, Schwarz ER. Why do patients with heart failure suffer from
43
44 erectile dysfunction? A critical review and suggestions on how to approach this problem. *Int J*
45
46 *Impot Res* 2005; Dec;17 Suppl 1:S25-36.
- 47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 11. Berg SK, Elleman-Jensen L, Zwisler AD, Winkel P, Svendsen JH, Pedersen PU, et al. Sexual
5 concerns and practices after ICD implantation: findings of the COPE-ICD rehabilitation trial. *Eur J*
6 *Cardiovasc Nurs* 2013; Jan 8;.
7
8
9
10
11 12. Bortolotti A, Parazzini F, Colli E, Landoni M. The epidemiology of erectile dysfunction and its
12 risk factors. *Int J Androl* 1997; Dec;20(6):323-34.
13
14
15
16
17 13. Herbert K, Lopez B, Castellano J, Palacio A, Tamari L, Arcemen LM. The prevalence of
18 erectile dysfunction in heart failure patients by race and ethnicity. *Int J Impot Res* 2008; Sep-
19 Oct;20(5):507-11.
20
21
22
23
24
25 14. Kloner RA, Mullin SH, Shook T, Matthews R, Mayeda G, Burstein S, et al. Erectile dysfunction
26 in the cardiac patient: how common and should we treat?. *J Urol* 2003; Aug;170(2 Pt 2):S46,50;
27 discussion S50.
28
29
30
31
32
33 15. Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, et al. Erectile
34 dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients
35 with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003;
36 Sep;44(3):360,4; discussion 364-5.
37
38
39
40
41
42
43 16. Steinke EE. Sexual concerns of patients and partners after an implantable cardioverter
44 defibrillator. *Dimens Crit Care Nurs* 2003; Mar-Apr;22(2):89-96.
45
46
47
48
49 17. Dabrowski R, Smolis-Bak E, Kowalik I, Kazimierska B, Wojcicka M, Szwed H. Quality of life
50 and depression in patients with different patterns of atrial fibrillation. *Kardiol Pol* 2010;
51 Oct;68(10):1133-9.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 18. Drory Y, Kravetz S, Weingarten M. Comparison of sexual activity of women and men after a
5 first acute myocardial infarction. *Am J Cardiol* 2000; Jun 1;85(11):1283-7.
6
7
8
9
10 19. Foroutan SK, Rajabi M. Erectile dysfunction in men with angiographically documented
11 coronary artery disease. *Urol J* 2007; Winter;4(1):28-32.
12
13
14
15 20. Justo D, Arbel Y, Mulat B, Mashav N, Saar N, Steinvil A, et al. Sexual activity and erectile
16 dysfunction in elderly men with angiographically documented coronary artery disease. *Int J Impot*
17 *Res* 2010; Jan-Feb;22(1):40-4.
18
19
20
21
22
23 21. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological,
24 and physical problems in men and women: a cross sectional population survey. *J Epidemiol*
25 *Community Health* 1999; Mar;53(3):144-8.
26
27
28
29
30
31 22. Friedman S. Cardiac disease, anxiety, and sexual functioning. *Am J Cardiol* 2000; Jul
32 20;86(2A):46F-50F.
33
34
35
36 23. Kriston L, Gunzler C, Agyemang A, Bengel J, Berner MM, SPARK Study Group. Effect of
37 sexual function on health-related quality of life mediated by depressive symptoms in cardiac
38 rehabilitation. findings of the SPARK project in 493 patients. *J Sex Med* 2010; Jun;7(6):2044-55.
39
40
41
42
43
44 24. Mulat B, Arbel Y, Mashav N, Saar N, Steinvil A, Heruti R, et al. Depressive symptoms and
45 erectile dysfunction in men with coronary artery disease. *Urology* 2010; Jan;75(1):104-7.
46
47
48
49
50 25. Makhlof A, Kparker A, Niederberger CS. Depression and erectile dysfunction. *Urol Clin*
51 *North Am* 2007; Nov;34(4):565,74, vii.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 26. Roose SP. Depression: links with ischemic heart disease and erectile dysfunction. *J Clin*
5
6 *Psychiatry* 2003;64 Suppl 10:26-30.
7
8
- 9
10 27. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al.
11
12 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task
13
14 Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European
15
16 Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC
17
18 (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*
19
20 2008; Oct;29(19):2388-442.
21
22
- 23
24 28. Heart Failure Society Of A. HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J*
25
26 *Card Fail* 2006; Feb;12(1):e1-2.
27
28
- 29
30 29. Bedell SE, Duperval M, Goldberg R. Cardiologists' discussions about sexuality with patients
31
32 with chronic coronary artery disease. *Am Heart J* 2002; Aug;144(2):239-42.
33
34
- 35
36 30. Jaarsma T, Stromberg A, Fridlund B, De Geest S, Martensson J, Moons P, et al. Sexual
37
38 counselling of cardiac patients: nurses' perception of practice, responsibility and confidence. *Eur J*
39
40 *Cardiovasc Nurs* 2010; Mar;9(1):24-9.
41
42
- 43
44 31. Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, et al. Erectile dysfunction and
45
46 coronary artery disease prediction: evidence-based guidance and consensus. *Int J Clin Pract* 2010;
47
48 Jun;64(7):848-57.
49
50
- 51
52 32. Jackson G, Rosen RC, Kloner RA, Kostis JB. The second Princeton consensus on sexual
53
54 dysfunction and cardiac risk: new guidelines for sexual medicine. *J Sex Med* 2006; Jan;3(1):28,36;
55
56 discussion 36.
57
58
59
60

1
2
3
4 33. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle
5 modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review
6 and meta-analysis. *Arch Intern Med* 2011; Nov 14;171(20):1797-803.
7
8

9
10
11 34. Maio G, Saraeb S, Marchiori A. Physical activity and PDE5 inhibitors in the treatment of
12 erectile dysfunction: results of a randomized controlled study. *J Sex Med* 2010; Jun;7(6):2201-8.
13
14

15
16
17 35. Roviario R, Holmes D, Holmsten R. Influence of a Cardiac Rehabilitation Program on the
18 Cardiovascular, Psychological, and Social Functioning of Cardiac Patients. *J Beh Med*
19
20 1984;7(1):61.
21
22

23
24
25 36. Froelicher ES, Kee LL, Newton KM, Lindskog B, Livingston M. Return to work, sexual
26 activity, and other activities after acute myocardial infarction. *Heart Lung* 1994; Sep-
27
28 Oct;23(5):423-35.
29
30

31
32
33 37. Belardinelli R, Lacalaprince F, Faccenda E, Purcaro A, Perna G. Effects of short-term moderate
34 exercise training on sexual function in male patients with chronic stable heart failure. *Int J Cardiol*
35
36 2005; May 11;101(1):83-90.
37
38

39
40
41 38. Bertie J, King A, Reed N, Marshall AJ, Ricketts C. Benefits and weaknesses of a cardiac
42 rehabilitation programme. *J R Coll Physicians Lond* 1992; Apr;26(2):147-51.
43
44

45
46 39. Lidell E, Fridlund B. Long-term effects of a comprehensive rehabilitation programme after
47 myocardial infarction. *Scand J Caring Sci* 1996;10(2):67-74.
48
49

50
51
52 40. Klein R, Bar-on E, Klein J, Benbenishty R. The impact of sexual therapy on patients after
53 cardiac events participating in a cardiac rehabilitation program. *Eur J Cardiovasc Prev Rehabil*
54
55 2007; Oct;14(5):672-8.
56
57
58
59
60

- 1
2
3
4 41. Dorey G, Speakman MJ, Feneley RC, Swinkels A, Dunn CD. Pelvic floor exercises for erectile
5 dysfunction. *BJU Int* 2005; Sep;96(4):595-7.
6
7
8
9
10 42. Van Kampen M, De Weerd W, Claes H, Feys H, De Maeyer M, Van Poppel H. Treatment of
11 erectile dysfunction by perineal exercise, electromyographic biofeedback, and electrical stimulation.
12
13 *Phys Ther* 2003; Jun;83(6):536-43.
14
15
16
17 43. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JA, et al. Core components of
18 cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the
19 American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the
20 Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and
21 Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of
22 Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev* 2007; May-
23 Jun;27(3):121-9.
24
25
26
27
28
29
30
31
32
33
34 44. Fitchet A, Doherty PJ, Bundy C, Bell W, Fitzpatrick AP, Garratt CJ. Comprehensive cardiac
35 rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised
36 controlled trial. *Heart* 2003; Feb;89(2):155-60.
37
38
39
40
41
42 45. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of
43 erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*
44 1997; Jun;49(6):822-30.
45
46
47
48
49
50 46. Rosen RC, Cappelleri JC, Gendrano N,3rd. The International Index of Erectile Function (IIEF):
51 a state-of-the-science review. *Int J Impot Res* 2002; Aug;14(4):226-44.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 47. Derogatis LR. The psychosocial adjustment to illness scale (PAIS). *J Psychosom Res*
5
6 1986;30(1):77-91.
7
8
9
10 48. Westlake C, Dracup K, Walden JA, Fonarow G. Sexuality of patients with advanced heart
11 failure and their spouses or partners. *J Heart Lung Transplant* 1999; Nov;18(11):1133-8.
12
13
14
15 49. Jaarsma T. Sexual problems in heart failure patients. *Eur J Cardiovasc Nurs* 2002; Feb;1(1):61-
16
17 7.
18
19
20
21 50. Rasmussen TB, Zwisler AD, Sibilitz KL, Risom SS, Bundgaard H, Glud C, et al. A
22 randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients
23 treated for infective endocarditis--the CopenHeartIE trial protocol. *BMJ Open* 2012; Nov
24
25 21;2(6):10.1136/bmjopen,2012-001929. Print 2012.
26
27
28
29
30
31 51. Risom SS, Zwisler AD, Rasmussen TB, Sibilitz KL, Svendsen JH, Glud C, et al. The effect of
32 integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with
33 ablation: the randomised CopenHeartRFA trial protocol. *BMJ Open* 2013; Feb
34
35 20;3(2):10.1136/bmjopen,2012-002377. Print 2013.
36
37
38
39
40
41 52. Sibilitz KL, Berg SK, Hansen TB, Risom SS, Rasmussen TB, Hassager C, et al. Effect of
42 comprehensive cardiac rehabilitation after heart valve surgery (CopenHeartVR): study protocol for
43 a randomised clinical trial. *Trials* 2013; Apr 22;14(1):104.
44
45
46
47
48
49 53. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III
50 Consensus recommendations for the management of erectile dysfunction and cardiovascular
51 disease. *Mayo Clin Proc* 2012; Aug;87(8):766-78.
52
53
54
55
56
57
58
59
60

1
2
3
4 54. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European
5
6 guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint
7
8 task force of the European society of cardiology and other societies on cardiovascular disease
9
10 prevention in clinical practice (constituted by representatives of nine societies and by invited
11
12 experts). *Int J Behav Med* 2012; Dec;19(4):403-88.

13
14
15
16 55. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary
17
18 prevention through cardiac rehabilitation: from knowledge to implementation. A position paper
19
20 from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention
21
22 and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; Feb;17(1):1-17.

23
24
25
26 56. Berg SK. *Comprehensive rehabilitation for patients with ICD: PhD dissertation*. [Aarhus]:
27
28 Faculty of Health Sciences, Aarhus University; 2011.

29
30
31
32 57. Zwisler AD, Soja AM, Rasmussen S, Frederiksen M, Abedini S, Appel J, et al. Hospital-based
33
34 comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure,
35
36 ischemic heart disease, or high risk of ischemic heart disease: 12-month results of a randomized
37
38 clinical trial. *Am Heart J* 2008; Jun;155(6):1106-13.

39
40
41
42 58. Ashworth NL, Chad KE, Harrison EL, Reeder BA, Marshall SC. Home versus center based
43
44 physical activity programs in older adults. *Cochrane Database Syst Rev* 2005; Jan
45
46 25;(1)(1):CD004017.

47
48
49
50 59. Oerkild B, Frederiksen M, Hansen JF, Simonsen L, Skovgaard LT, Prescott E. Home-based
51
52 cardiac rehabilitation is as effective as centre-based cardiac rehabilitation among elderly with
53
54 coronary heart disease: results from a randomised clinical trial. *Age Ageing* 2011; Jan;40(1):78-85.

- 1
2
3
4 60. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-
5
6 81.
7
8
9
10 61. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, et al. Resistance
11
12 exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement
13
14 from the American Heart Association Council on Clinical Cardiology and Council on Nutrition,
15
16 Physical Activity, and Metabolism. *Circulation* 2007; Jul 31;116(5):572-84.
17
18
19 62. Lampman RM, Knight BP. Prescribing exercise training for patients with defibrillators. *Am J*
20
21 *Phys Med Rehabil* 2000; May-Jun;79(3):292-7.
22
23
24 63. Dorey G, Glazener C, Buckley B, Cochran C, Moore K. Developing a pelvic floor muscle
25
26 training regimen for use in a trial intervention. *Physiotherapy* 2009; Sep;95(3):199-209.
27
28
29
30 64. Parse RR. *The human becoming school of thought: a perspective for nurses and other health*
31
32 *professionals*. Thousand Oaks, Calif.: Sage; 1998.
33
34
35
36 65. Tibaek S, Klarskov P, Lund Hansen B, Thomsen H, Andresen H, Schmidt Jensen C, et al.
37
38 Pelvic floor muscle training before transurethral resection of the prostate: a randomized, controlled,
39
40 blinded study. *Scand J Urol Nephrol* 2007;41(4):329-34.
41
42
43
44 66. Schüssler B. *Pelvic floor re-education: principles and practice*. London: Springer; 1994.
45
46
47
48 67. Mezzani A, Agostoni P, Cohen-Solal A, Corra U, Jegier A, Kouidi E, et al. Standards for the
49
50 use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report
51
52 from the Exercise Physiology Section of the European Association for Cardiovascular Prevention
53
54 and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2009; Jun;16(3):249-67.
55
56
57
58
59
60

- 1
2
3
4 68. Ware JE, Kosinski M, Gandek B. SF-36 Health Survey.: Manual and Interpretation guide
5
6 2005;The Health Institute, New England Medical Center, Boston, Massachussetts.
7
8
9
10 69. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;
11
12 Jun;67(6):361-70.
13
14
15 70. Drummond MF. *Methods for the economic evaluation of health care programmes*. 3rd edition
16
17 ed. Oxford: Oxford University Press; 2005.
18
19
20
21 71. Rubio-Aurioles E, Sand M, Terrein-Roccatti N, Dean J, Longworth J, Eardley I, et al. Female
22
23 Assessment of Male Erectile dysfunction detection scale (FAME): development and validation. *J*
24
25 *Sex Med* 2009; Aug;6(8):2255-70.
26
27
28
29 72. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Extending the
30
31 CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and
32
33 elaboration. *Ann Intern Med* 2008; Feb 19;148(4):295-309.
34
35
36
37 73. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards
38
39 for testing and training: a statement for healthcare professionals from the American Heart
40
41 Association. *Circulation* 2001; Oct 2;104(14):1694-740.
42
43
44 74. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave
45
46 myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll*
47
48 *Cardiol* 1988; Aug;12(2):362-72.
49
50
51
52 75. Giannuzzi P, Tavazzi L, Temporelli PL, Corra U, Imparato A, Gattone M, et al. Long-term
53
54 physical training and left ventricular remodeling after anterior myocardial infarction: results of the
55
56
57
58
59
60

1
2
3
4 Exercise in Anterior Myocardial Infarction (EAMI) trial. EAMI Study Group. *J Am Coll Cardiol*
5
6 1993; Dec;22(7):1821-9.
7
8

9
10 76. Otsuka Y, Takaki H, Okano Y, Satoh T, Aihara N, Matsumoto T, et al. Exercise training
11 without ventricular remodeling in patients with moderate to severe left ventricular dysfunction early
12 after acute myocardial infarction. *Int J Cardiol* 2003; Feb;87(2-3):237-44.
13
14

15
16
17 77. Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S, Functional Evaluation and Cardiac
18 Rehabilitation Working Group of the French Society of Cardiology. Safety of exercise training for
19 cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch*
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Intern Med 2006; Nov 27;166(21):2329-34.

78. Savovic J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study
design characteristics on intervention effect estimates from randomized, controlled trials. *Ann*
Intern Med 2012; Sep 18;157(6):429-38.

79. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias
in treatment effect estimates in controlled trials with different interventions and outcomes: meta-
epidemiological study. *BMJ* 2008; Mar 15;336(7644):601-5.

80. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT
2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* 2013; Feb
5;158(3):200-7.



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

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	NA
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	15
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	16
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	NA
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	NA
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	NA
13		14b Why the trial ended or was stopped	NA
14	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	NA
15	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	NA
16		by original assigned groups	
17	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	NA
18	estimation	precision (such as 95% confidence interval)	
19		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
20	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	NA
21		pre-specified from exploratory	
22	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
23			
24	Discussion		
25	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
26		21 Generalisability (external validity, applicability) of the trial findings	NA
27	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
28			
29	Other information		
30	Registration	23 Registration number and name of trial registry	16
31	Protocol	24 Where the full trial protocol can be accessed, if available	18
32	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	In the article
33			registration,
34			which will be
35			published
36			
37			
38			
39			
40			
41			
42			
43			
44	CONSORT 2010 checklist		
45			
46			
47			
48			
49			

1
2 *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
3 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
4 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only



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.

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003967.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Oct-2013
Complete List of Authors:	Johansen, Pernille; Copenhagen University Hospital Bispebjerg, Department of Cardiology; Copenhagen University Hospital, Rigshospitalet, The Heart Centre Zwisler, Ann-Dorthe; Copenhagen University Hospital, Rigshospitalet, The Heart Centre Svendsen, Jesper; Copenhagen University Hospital Rigshospitalet, The Heart Centre Frederiksen, Marianne; Copenhagen University Hospital Bispebjerg, Department of Cardiology Lindschou, Jane; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Winkel, Per; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Gluud, Christian; Copenhagen University Hospital Rigshospitalet, The Copenhagen Trial Unit, Centre for Clinical Intervention Research Giraldi, Annamaria; Copenhagen University Hospital Rigshospitalet, Sexological Clinic, Psychiatric Center Copenhagen Steinke, Elaine; Wichita State University, Jaarsma, Tiny; Linköping University, Department of Social and Welfare Studies Berg, Selina; Copenhagen University Hospital Rigshospitalet, The Heart Centre
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sexual health, Nursing, Cardiovascular medicine
Keywords:	CARDIOLOGY, REHABILITATION MEDICINE, SEXUAL MEDICINE

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

Pernille Palm Johansen¹⁺²

Ann-Dorthe Zwisler²⁺³

Jesper Hastrup-Svendsen²⁺⁸

Marianne Fredriksen¹

Jane Lindschou⁴

Per Winkel⁴

Christian Gluud⁴

Annamaria Giraldi⁵

Elaine Steinke⁶

Tiny Jaarsma⁷

Selina Kikkenborg Berg²

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

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

³National Institute of Public Health, University of Southern Denmark

⁴The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

⁵Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁶Wichita State University, Wichita, Kansas, United States

⁷Department of Social and Welfare Studies, Linköping University, Linköping, Sweden

⁸Institute of Clinical Medicine, Faculty of Health Science, University of Copenhagen

Date: October 7. 2013. Version 1.2

Corresponding author:

Pernille Palm Johansen RN. MCN

Copenhagen University Hospital, Bispebjerg Hospital / Rigshospitalet

Copenhagen

Denmark

Mail: pernille.palm.johansen@regionh.dk

For peer review only

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 treated is 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

1
2
3
4 treatment with nitrates, there seems to be no consensus on what treatment should be offered for
5 sexual dysfunction.
6
7

8 9 **Non-pharmacological treatment potentials**

10 Non-pharmacological interventions possess potential in reducing sexual dysfunction. Lifestyle
11 factors such as; cigarette smoking, hyperlipidaemia, and a sedentary lifestyle all predict erectile
12 dysfunction^{4, 5} and these are the same risk factors that predict coronary artery disease. A recent
13 meta-analysis of six randomised trials with 740 patients with no known heart disease, showed that
14 life style modifications such as physical exercise and pharmacotherapy for cardiovascular risk
15 factors were associated with a significant improvement in erectile function.³³ Furthermore, a
16 randomised trial investigating the effect of exercise training 3 hours per week or more in non-heart
17 disease patients showed a significant result in improving the person's erectile functioning compared
18 with controls with no exercise training.³⁴ We hypothesize that these lifestyle modifications can also
19 improve sexual dysfunction in patients with already established heart disease. A systematic
20 literature search showed five randomised clinical trials which examine the effect of physical
21 exercise on sexual dysfunction.³⁵⁻³⁹ Overall, 591 patients with heart disease were included and the
22 effect was significant in three of the five trials.³⁷⁻³⁹ However, the trials are characterised as being of
23 small sample sizes, using non-validated tools and mainly focusing on the time before patients return
24 to sexual activity and not on the ability and quality of the sexual performance. Randomised trials
25 that address the psychological aspects of sexual dysfunction are limited in patients with heart
26 disease. However, one randomised trial testing the effect of sexual therapy showed some promising
27 trends when it comes to improving the frequency and quality of sexual activity in male patients post
28 cardiac event beyond the usual cardiac rehabilitation.⁴⁰ However, due to the limited power of the
29 sample in this trial, it did not allow the detection of significant effects. The role of pelvic floor
30 exercises as a treatment of erectile dysfunction is not tested on patients with heart disease, but in the
31 general population 40% to 47% had regained normal erectile function after 3-4 month of training
32 the pelvic floor muscles.^{41, 42} As the condition sexual dysfunction often includes both physical and
33 psychological components, it is plausible to believe that patients with heart disease and sexual
34 dysfunction benefit from a comprehensive rehabilitation intervention^{43, 44} consisting of a psycho-
35 educational component and an exercise training component including pelvic floor exercises.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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) questionnaire⁴⁷, improves by two points in the experimental group compared with the control group after completing the programme. The estimated increase in secondary outcome is based on two studies that examine the prevalence of sexual dysfunction in patients with heart failure.^{48, 49}

Exploratory analyses will test the hypotheses that comprehensive sexual rehabilitation will improve: health-related quality of life, anxiety and depression, frequency of sexual activity, physical capacity measured by peak oxygen uptake (peak 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 to other 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 patients⁵⁵ 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

1
2
3
4 a physical exercise protocol, taking into account the patient's clinical condition and physical
5 abilities. Sixty minutes is allocated for the initial consultation and preparation of individual training
6 protocol, including pelvic floor exercise instructions.
7
8

9
10 Physical exercise is initiated at a physiotherapist-supervised setting at the Heart Centre,
11 Rigshospitalet. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and
12 Corus Exercise Assistant, version 2.0.16, Finland) potential cardiac arrhythmias,
13 electrocardiographic abnormalities such as ST segment changes, T-wave alterations, atrial or
14 ventricular arrhythmias, and training intensity level are monitored. The training is initiated with two
15 to three mandatory exercise sessions at Rigshospitalet. Subsequently, the patients can choose to
16 continue the intensive physical exercise regimen either at Rigshospitalet, or at a local CopenHeart-
17 certified facility, supervised by physiotherapists, or as supervised home-based training. Supervised
18 home-based physical training has previously shown similar results to hospital-based training.⁵⁸ This
19 finding has been confirmed in a Danish setting.⁵⁹
20
21

22
23 One session is structured with 10 minutes (min) warm-up bicycling, 20 min bicycling with
24 increased intensity (cardiovascular training), 20 min strength exercises, and 10 min stretching and
25 cool-down period. The warm-up session is performed at the intensity of 11 to 12 on the Borg
26 scale.⁶⁰ The 20 min cardiovascular training is performed as interval training. Each session is divided
27 into three sections. Each section contains intensity 13 to 17 on the Borg scale and time limit (2 to 15
28 min) varying between each section; the second section with longest and highest intensity. A cool
29 down period of 5 min is included after the 20 min of cardiovascular training. The strength and
30 strength-related exercises primarily target lower body muscles, and comprise the following four
31 exercises: (1) heel rise performed by repetitions of maximal flexion from standing position; (2)
32 step-up by using a step bench of 27 cm; (3) leg press standardised, starting with 90 degrees flexion,
33 hyperextension not accepted; (4) 90 degrees pull-down performed in a cable machine to target
34 abdominal muscles. For step-ups and heel-rises, weight load is calculated as a percentage of body
35 weight (5 to 20%) and increased throughout the 12 weeks. Load for leg press is estimated from
36 repetition maximum (RM) testing and increases from 60% of 1 RM to 70% of 1 RM during the 12
37 weeks of training. All exercises are initiated by 2x12 repetitions and increased through the
38 programme according to standard guidelines for strength training.⁶¹
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 To achieve cardiovascular adjustment the training begins with a warming-up period and ends with a
54 cool-down period. This cardiovascular adjustment has been shown to reduce the risk of ischaemia
55 and arrhythmia in connection to physical exercise.^{44, 62} Participants must mainly exercise in an
56
57
58
59
60

1
2
3
4 upright position to decrease left ventricular filling pressure and risk of ischaemia or heart-failure-
5 triggered ventricular arrhythmias.⁶²
6
7

8 9 *Pelvic floor exercise*

10 The bulbocavernosus muscle and the ischiocavernosus muscle, two superficial pelvic floor muscles,
11 are active during erection and enhance rigidity. The bulbocavernosus muscle encircles 33% to 50%
12 of the base of the penis.⁴¹ The pelvic floor training regimen is inspired by Dorey and colleagues,
13 who have developed a training regimen for male patients for use in randomised clinical trials.⁶³ The
14 regiment is developed and tested in a different patient population, and we have therefore modified it
15 to fit cardiovascular patients. Patients are instructed in pelvic floor exercises by a skilled
16 physiotherapist. Patients are instructed to perform their pelvic floor exercises twice daily. Studies
17 showed that a few strong or maximum contractions are more effective when it comes to gaining
18 muscle hypertrophy than several less strong contractions.⁶³ Patients are instructed to tighten their
19 pelvic floor muscles as strongly as possible (as if to prevent flatus from escaping) three times when
20 lying, three times when sitting, and three times when standing. The duration of the contraction is up
21 to 10 seconds each, and patients are informed to have a 10 second break between each contraction.
22 The physiotherapist instructs the patients on how to contract the bulbocavernosus and
23 ischiocavernosus muscles. In order to ensure that the right muscles are involved, attention is placed
24 on the ability to lift the scrotum and retract the penis. To obtain some degree of pelvic floor muscle
25 endurance, the patients are encouraged to tighten the pelvic floor muscles when walking.
26 To encourage adherence and monitor compliance pulse watches (Polar watch) with extended
27 memory and exercise training logs are handed out. A training log contains information about
28 physical exercise as well as pelvic floor exercise. At the end of the intervention the training log and
29 the pulse watch are returned and compliance and intensity level are coded independently.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 46 **The psycho-educational components**

47 The goal of the psycho-educative intervention is that the patient learns to interpret and react to
48 relevant physical and psychological symptoms, learns to cope with anxiety and fear, including
49 strategies to manage depressive symptoms and ability to be sexually active without fear.
50 A specially trained nurse is responsible for the psycho-educative intervention. The intervention
51 takes a theoretical basis of the patient-centred approach where the emphasis is on support and
52 education. The conversations are based on a holistic view of the patient and focus on the handling
53
54
55
56
57
58
59
60

1
2
3
4 of life and managing sexual dysfunction. The intervention is targeted at the modifiable parameters
5 that are reported to affect sexual dysfunction. The psycho-educative intervention is inspired by RR
6 Parse's 'Human Becoming Practice Methodologies' three dimensions⁶⁴, which can be described as:
7 1. discuss and give meaning to the past, present and future, 2. explore and discuss events and
8 opportunities; and 3. pursue imagined possibilities. According to this theory, there are three ways to
9 alter its perceived health: creative ideas, see, hear and feel how a situation could be if it was lived in
10 a different way; recognising personal patterns and value priorities and shed light on the paradoxes
11 by looking at incongruence in a situation and change the view of reality. The nurse is 'truly present'
12 in the process through discussion, quiet contemplation, and reflection. The psycho-educative
13 intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on
14 psychological well-being (mental health) and the general health sub-scale of the SF-36.⁵⁶ The nurse
15 is trained in the psycho-educative conversation through teaching and supervision of nurses who
16 have experience with the 'Human Becoming Practice Methodology' from the COPE-ICD trial. It is
17 based on the theoretical literature that forms the basis for understanding the processes of practice
18 methodology and existing specialty specific knowledge about heart disease, related symptoms, and
19 sexology. The supervisor observes and provides feedback in relation to the methods and goals of the
20 conversation. The emphasis is on openness in the interviews, and on the nurse's ability to: be
21 silently present while the patient talks, ask questions that encourage reflection, let the patient find
22 answers and solutions and contribute with knowledge, provide advice and guidance when requested
23 and relevant. The training of the nurse takes place prior to the intervention. In practice the
24 intervention will be handled by one nurse with several years of experience working with cardiac
25 patients and trained in sexology. The sexology experience is gained in a two-week intensive course
26 on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist is
27 available during the intervention. The nurse will conduct consultations with patients individually,
28 and patients are informed that they are welcome to bring spouses/relatives. The consultation will
29 take place in a quiet room in an outpatient settings and last for 45 minutes. An inspirational guide
30 will form the basis for the consultations. The guide consists of several elements and issues (medical,
31 psychosocial, educational and sexual) that work as inspiration (see table 1):
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 the 'gold standard' measure for efficacy assessment in clinical trials of erectile dysfunction. It has
5 been linguistically validated in 32 languages including Danish and used as a primary outcome in
6 more than 50 clinical trials.^{34, 45, 46} It consists of 15 items including five domains of sexual function:
7 erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
8 The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of
9 sensitivity and specificity.⁴⁶ The IIEF is self-assessed, which in sexological research is widely used
10 and well acclaimed.

11 12 13 14 15 16 17 18 *Secondary outcome*

19
20 Sexual function is measured by the Psychosocial Adjustment to Illness Scale (self-reported version)
21 (PAIS-SR) sexual relationship domain.⁴⁷ The overall PAIS-SR measure psychosocial adjustment to
22 illness in terms of 7 primary domains of adjustment: Health Care Orientation, Vocational
23 Environment, Domestic Environment, Sexual Relationships, Extended Family Relationships, Social
24 Environment and Psychological Distress. Each PAIS/PAIS-SR item is rated on a 4-point (0 through
25 3) scale of adjustment, with higher ratings indicating poorer adjustment status. The sexual
26 relationship domain evaluates shifts in the quality of sexual relations due to the current illness or
27 treatment. It consists of six items and the total score ranges from 0 to 18. Low scores indicates good
28 adjustment, and high scores poor adjustment.

29 30 31 32 33 34 35 36 37 *Exploratory outcomes*

38
39 A more extensive evaluation of physical, psychological, and demographic status over time will be
40 performed. Physical examination will include pelvic floor strength and endurance assessed
41 according to the Modified Oxford grading scheme which is a manual digital examination of the
42 pelvic floor. It is tested and validated and used in several trials.^{65, 66} Furthermore physical capacity
43 will be measured by peak VO₂ using cardiopulmonary exercise testing (Ergo-Spiro CS-200,
44 Schiller, Switzerland) with measurement of oxygen uptake (VO₂), heart rate (HR, beats
45 /min), ventilation rate (VE, l/min), ventilation frequency (VF, number / min), respiratory expiration
46 ratio (RER, CO₂/O₂in%), blood pressure, physical activity level (METS) and gas exchange (VO₂
47 and VCO₂) during progressive loading and in the following recovery period. The test is conducted
48 before the training programme initiates. Intensity performed as a ramp protocol (load gradually
49 increases) with the initial work load of 25W and increased by 12.5W every minute until exhaustion,
50
51
52
53
54
55
56
57
58
59
60

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		
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 questionnaire⁴⁵ by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score⁴⁶, on the initial screening are invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems. The participant information is 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 randomised 1:1 to the experimental group or the control group. Randomisation will be performed centrally by the trial coordination centre, Copenhagen Trial Unit, according to a computer-generated allocation sequence with a variable block size concealed from the investigators. Allocation to the intervention groups is

1
2
3
4 done when the investigator calls Copenhagen Trial Unit. Relevant information (personal
5 identification number, strata, etc.) is typed into a computer system, and then the participant will be
6 allocated to an intervention group and awarded a four-digit randomisation number. The investigator
7 then informs the patient of the result and on how to proceed by letter. Thus, neither investigators
8 nor patients or relatives can influence to which group the patient are allocated. For both groups,
9 follow-up assessment will take place after 12 weeks (only physical evaluation), 16 weeks, and 6
10 months. Questionnaires will be completed electronically in the questionnaire system Enalyzer with
11 'single user', which meets the data legislation for logging. At inclusion, the trial participant will
12 receive an email with a link to a website through which questionnaires can be completed. The e-
13 mail contains a login and password for the trial participant's personal access. The participant has the
14 opportunity to go through the website www.copenheart.org and login with the log-in and password.
15 If patients do not complete the questionnaire electronically, the material can be sent in paper form
16 and independent trial personnel then enters the responses into the database. Thus data management
17 is handled independently from the researchers who interpret the data. All data are stored
18 electronically in a coded database, and in an independent spread sheet, only accessible for the
19 CopenHeart group. The recruitment process will continue until the number of 154 has been reached.
20
21
22
23
24
25
26
27
28
29
30
31

32 **Statistical analysis**

33 *Analysis of primary and secondary outcomes*

34
35 The analysis will be performed according to the intention-to-treat analysis with two sided
36 significance tests at the 0.05 level. Both outcomes (and outcomes subjected to exploratory analyses)
37 will be analysed using the same procedure. First, we will test if there is an immediate effect of the
38 intervention on the outcome and/or a difference in the response to the intervention between the two
39 patient groups (patients with ischaemic heart disease and patients with implantable cardioverter
40 defibrillator) using model 1 below. Then the follow-up data will be included in the analysis and the
41 long-term effect will be studied using model 2.
42
43
44
45
46
47
48

49 *Models and analytical techniques*

50 *Model 1* The equation (equation 1) showing the dependent variable Y (the outcome) as a function of
51 covariates used in the analysis of the immediate effect of the intervention on the primary outcome
52 is $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot I + c \cdot G + d \cdot I : G$ (equation 1).
53
54
55
56
57
58
59
60

1
2
3
4 Y_{baseline} is the baseline value of the outcome, I is the indicator of intervention, G is the indicator of
5 patient group, and a through d are coefficients to be estimated. The term d·I:G stands for interaction
6 between the two covariates I and G. If the term b·I is significant (the coefficient b differs
7 significantly from 0) there is an effect of the intervention common for the two patient groups
8 (ischaemic patients and patients with implantable cardioverter defibrillator). If the term d·I:G is
9 significant there is an additional effect of the intervention in one of the two patient groups; thus a
10 sub-group analysis is warranted. In the analysis of the data the univariate general linear model is
11 used. The analysis of the primary outcome is the primary analysis. The sub-group analysis and the
12 analysis of the secondary and of other outcomes should be considered exploratory.
13
14
15
16
17
18
19

20
21 *Model 2* In the analysis of follow up data the time T (Y is measured 16 weeks and 6 month
22 following randomisation) is included and the mixed model for repeated measures is used. The
23 equation (equation 2) for the fixed effect in this model showing Y as a function of the co-variates
24 is $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot G + c \cdot I + d \cdot I:G + e \cdot T + f \cdot I:T + g \cdot I:T:G$ (equation 2) where a through g
25 are coefficients to be estimated. If the term e·T is significant there is a linear trend over time
26 common for both patient groups. If f·I:T is significant, this trend is supplemented by an additional
27 trend caused by the intervention and therefore specific for the intervention group. If in addition
28 g·I:T:G is significant this added trend differs between the two patient groups (patients with
29 ischaemic heart disease and patients with implantable cardioverter defibrillator). In the mixed
30 model analysis an unstructured covariance matrix will be assumed. If convergence is not attained
31 simpler covariance structure models will be assessed guided by Akaike's criterion or maximum
32 likelihood test as appropriate.
33
34
35
36
37
38
39
40
41

42 *Missing values*

43
44 If the number of missing cases for a given outcome (number of patients with one or more model
45 variables missing) is larger than 5% or p of Little's test is < 5% multiple imputations of the model
46 variables (outcome plus co-variates) is done using SPSS version 17. The range of potential bias in
47 case the missing values should not be random is assessed by doing two imputations (1) imputing
48 missing outcome value in one group by minimum value found in the material and missing outcome
49 value in the other group by maximum value found in material and (2) vice versa. Then in each case
50 an unadjusted analysis is done to estimate the parameter of interest.
51
52
53
54
55
56
57
58
59
60

ETHICS AND DISSEMINATION

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 1988⁷⁴ and has not subsequently been demonstrated in larger studies.^{75, 76} In a recent French study of more than 25,000 patients with ischaemic heart disease, one third with chronic heart failure

1
2
3
4 found the risk of cardiac complications at 1:8,500 exercise testing and 1:50,000 patient exercise
5 hours.⁷⁷ Increasing exercise intensity and age are risk indicators. Therefore, the training intensity
6 will be conducted as moderate high intensity (less than 80% of VO₂ max). To achieve
7 cardiovascular adjustment both exercise training and testing begins with a warming-up period and
8 ends with a cool-down period, with a gradual downward adjustment of exercise intensity and heart
9 rate, rather than an abrupt end. This cardiovascular adjustment has been shown to reduce the risk of
10 ischaemia and arrhythmia in connection with physical exercise.^{44, 62} Participants must mainly
11 exercise in an upright position to decrease left ventricular filling pressure and risk of ischemia or
12 heart failure triggered ventricular arrhythmias. When these precautions are respected, both exercise
13 training and exercise testing are considered to possess a low risk for the participants. There is, as far
14 as we know, no previously known risk associated with pelvic floor exercise. Testing or examination
15 of the pelvic floor may be associated with discomfort for the participants but is not considered to be
16 associated with any risk. Staff members will be trained according to guidelines to handle any
17 emergencies.
18
19
20
21
22
23
24
25
26
27
28

29 **Dissemination plan**

30 Positive, neutral, and negative results of the trial will be submitted to international peer reviewed
31 journals of nursing, cardiology or sexology. Furthermore, results will be presented at national and
32 international conferences relevant to subject fields. Authorship will be allocated using the
33 guidelines for authorship defined by the International Committee of Medical Journal Editors and
34 depends on the personal involvement. All the articles, abstracts as well as the results will be posted
35 on the website www.copenheart.org. The website will be continuously updated and will be
36 highlighted through the scientific articles. CopenHeart staff will have access to data. Ethic committees
37 and competent authorities will be able to obtain direct access to data and documentation.
38
39
40
41
42
43
44
45

46 **DISCUSSION**

47 This randomised clinical trial testing the effect of a comprehensive sexual rehabilitation
48 intervention on a population of patients with implantable cardioverter defibrillator or patients with
49 ischaemic heart disease seems to be the first one in its field. The trial is expected to contribute with
50 results that can improve patients' problems related to heart disease and sexual function.
51 Additionally, it is believed that the trial can provide a systematic approach that may one day inform
52 national consensus on how to treat sexual dysfunction in heart patients. Furthermore, the results of
53
54
55
56
57
58
59
60

1
2
3
4 the trial are expected to contribute to the international debate on sexual rehabilitation of patients
5 with heart disease.

6
7 The trial is designed with central stratified randomisation which secures against selection bias.^{78, 79}

8
9 The primary outcome is assessed blinded to intervention and so are all statistical analysis, which
10 should reduce detection and interpretation bias.^{78, 79}

11 12 13 **Trajectory**

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

15 16 17 **Acknowledgements:**

18
19 The test and rehabilitation team responsible for the trial is: Karina Jensen, Lars Tang, Helena Tjalk
20 Sørensen, Signe Gils and Katrine Tingholm Erhardsen.

21 22 23 24 25 26 **Contributorship Statement**

27
28 PPJ, SKB, ADZ, JHs, MF, JL, PW, CG, AG, ES, TJ all designed the study and developed the protocol. PW
29 specifically designed the statistical analysis plan. PPJ, SKB, ADZ drafted the manuscript. PPJ, SKB, ADZ, JHS,
30 MF, JL, PW, CG, AG, ES, TJ all revised the manuscript critically. All authors have given their final approval of
31 the version to be published

32 33 34 35 36 **Funding statement:**

37
38 The CopenHeart trial has received funding from: The Danish Heart Foundation (no. 13-04-R95-
39 A4669-22744); The Health Foundation (no. 2013B208); Danish Council for Strategic Research
40 (no. 10-092790); The Danish Nursing Council. Neither of the funders had influence of the study
41 protocol and design, the execution of the trial or the interpretation of data.

42 43 44 45 46 **Competing interest:**

47
48 None

REFERENCES

1. Hoekstra T, Jaarsma T, Sanderman R, et al. Perceived sexual difficulties and associated factors in patients with heart failure. *Am Heart J* 2012; Feb;163(2):246-51.
2. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; Feb 10;281(6):537-44.
3. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; Jan;151(1):54-61.
4. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med* 2000; Apr;30(4):328-38.
5. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med* 2003; Aug 5;139(3):161-8.
6. Levine GN, Steinke EE, Bakaeen FG, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2012; Feb 28;125(8):1058-72.
7. Steinke EE. Sexual dysfunction in women with cardiovascular disease: what do we know?. *J Cardiovasc Nurs* 2010; Mar-Apr;25(2):151-8.
8. Lewis RW, Fugl-Meyer KS, Corona G, et al. Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med* 2010; Apr;7(4 Pt 2):1598-607.
9. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993; Jul 7;270(1):83-90.

1
2
3
4 10. Rastogi S, Rodriguez JJ, Kapur V, et al. Why do patients with heart failure suffer from erectile
5
6 dysfunction? A critical review and suggestions on how to approach this problem. *Int J Impot Res*
7
8 2005; Dec;17 Suppl 1:S25-36.

9
10
11 11. Berg SK, Elleman-Jensen L, Zwisler AD, et al. Sexual concerns and practices after ICD
12
13 implantation: findings of the COPE-ICD rehabilitation trial. *Eur J Cardiovasc Nurs* 2013; Jan 8;.

14
15
16
17 12. Bortolotti A, Parazzini F, Colli E, et al. The epidemiology of erectile dysfunction and its risk
18
19 factors. *Int J Androl* 1997; Dec;20(6):323-34.

20
21
22
23 13. Herbert K, Lopez B, Castellano J, et al. The prevalence of erectile dysfunction in heart failure
24
25 patients by race and ethnicity. *Int J Impot Res* 2008; Sep-Oct;20(5):507-11.

26
27
28
29 14. Kloner RA, Mullin SH, Shook T, et al. Erectile dysfunction in the cardiac patient: how common
30
31 and should we treat?. *J Urol* 2003; Aug;170(2 Pt 2):S46,50; discussion S50.

32
33
34 15. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and
35
36 association with risk factors in 300 consecutive patients with acute chest pain and angiographically
37
38 documented coronary artery disease. *Eur Urol* 2003; Sep;44(3):360,4; discussion 364-5.

39
40
41
42 16. Steinke EE. Sexual concerns of patients and partners after an implantable cardioverter
43
44 defibrillator. *Dimens Crit Care Nurs* 2003; Mar-Apr;22(2):89-96.

45
46
47 17. Dabrowski R, Smolis-Bak E, Kowalik I, et al. Quality of life and depression in patients with
48
49 different patterns of atrial fibrillation. *Kardiol Pol* 2010; Oct;68(10):1133-9.

50
51
52
53 18. Drory Y, Kravetz S, Weingarten M. Comparison of sexual activity of women and men after a
54
55 first acute myocardial infarction. *Am J Cardiol* 2000; Jun 1;85(11):1283-7.

- 1
2
3
4 19. Foroutan SK, Rajabi M. Erectile dysfunction in men with angiographically documented
5 coronary artery disease. *Urol J* 2007; Winter;4(1):28-32.
6
7
8
9
10 20. Justo D, Arbel Y, Mulat B, et al. Sexual activity and erectile dysfunction in elderly men with
11 angiographically documented coronary artery disease. *Int J Impot Res* 2010; Jan-Feb;22(1):40-4.
12
13
14
15 21. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological,
16 and physical problems in men and women: a cross sectional population survey. *J Epidemiol*
17
18
19
20
21
22
23 22. Friedman S. Cardiac disease, anxiety, and sexual functioning. *Am J Cardiol* 2000; Jul
24
25
26
27
28
29 23. Kriston L, Gunzler C, Agyemang A, et al. Effect of sexual function on health-related quality of
30 life mediated by depressive symptoms in cardiac rehabilitation. findings of the SPARK project in
31
32
33
34
35
36
37 24. Mulat B, Arbel Y, Mashav N, et al. Depressive symptoms and erectile dysfunction in men with
38 coronary artery disease. *Urology* 2010; Jan;75(1):104-7.
39
40
41
42 25. Makhlof A, Kparker A, Niederberger CS. Depression and erectile dysfunction. *Urol Clin*
43
44
45
46
47
48 26. Roose SP. Depression: links with ischemic heart disease and erectile dysfunction. *J Clin*
49
50
51
52
53 27. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment
54 of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute
55
56
57
58
59
60

1
2
3
4 and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration
5
6 with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of
7
8 Intensive Care Medicine (ESICM). *Eur Heart J* 2008; Oct;29(19):2388-442.
9

10
11 28. Heart Failure Society Of A. HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J*
12
13 *Card Fail* 2006; Feb;12(1):e1-2.
14

15
16
17 29. Bedell SE, Duperval M, Goldberg R. Cardiologists' discussions about sexuality with patients
18
19 with chronic coronary artery disease. *Am Heart J* 2002; Aug;144(2):239-42.
20

21
22
23 30. Jaarsma T, Stromberg A, Fridlund B, et al. Sexual counselling of cardiac patients: nurses'
24
25 perception of practice, responsibility and confidence. *Eur J Cardiovasc Nurs* 2010; Mar;9(1):24-9.
26

27
28
29 31. Jackson G, Boon N, Eardley I, et al. Erectile dysfunction and coronary artery disease prediction:
30
31 evidence-based guidance and consensus. *Int J Clin Pract* 2010; Jun;64(7):848-57.
32

33
34 32. Jackson G, Rosen RC, Kloner RA, et al. The second Princeton consensus on sexual dysfunction
35
36 and cardiac risk: new guidelines for sexual medicine. *J Sex Med* 2006; Jan;3(1):28,36; discussion
37
38 36.
39

40
41
42 33. Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and
43
44 cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis.
45
46 *Arch Intern Med* 2011; Nov 14;171(20):1797-803.
47

48
49
50 34. Maio G, Saraeb S, Marchiori A. Physical activity and PDE5 inhibitors in the treatment of
51
52 erectile dysfunction: results of a randomized controlled study. *J Sex Med* 2010; Jun;7(6):2201-8.
53
54
55
56
57
58
59
60

- 1
2
3
4 35. Roviario R, Holmes D, Holmsten R. Influence of a Cardiac Rehabilitation Program on the
5
6 Cardiovascular, Psychological, and Social Functioning of Cardiac Patients. *J Beh Med*
7
8 1984;7(1):61.
9
10
11 36. Froelicher ES, Kee LL, Newton KM, et al. Return to work, sexual activity, and other activities
12
13 after acute myocardial infarction. *Heart Lung* 1994; Sep-Oct;23(5):423-35.
14
15
16
17 37. Belardinelli R, Lacalaprice F, Faccenda E, et al. Effects of short-term moderate exercise training
18
19 on sexual function in male patients with chronic stable heart failure. *Int J Cardiol* 2005; May
20
21 11;101(1):83-90.
22
23
24
25 38. Bertie J, King A, Reed N, et al. Benefits and weaknesses of a cardiac rehabilitation programme.
26
27 *J R Coll Physicians Lond* 1992; Apr;26(2):147-51.
28
29
30
31 39. Lidell E, Fridlund B. Long-term effects of a comprehensive rehabilitation programme after
32
33 myocardial infarction. *Scand J Caring Sci* 1996;10(2):67-74.
34
35
36
37 40. Klein R, Bar-on E, Klein J, et al. The impact of sexual therapy on patients after cardiac events
38
39 participating in a cardiac rehabilitation program. *Eur J Cardiovasc Prev Rehabil* 2007;
40
41 Oct;14(5):672-8.
42
43
44 41. Dorey G, Speakman MJ, Feneley RC, et al. Pelvic floor exercises for erectile dysfunction. *BJU*
45
46 *Int* 2005; Sep;96(4):595-7.
47
48
49
50 42. Van Kampen M, De Weerd W, Claes H, et al. Treatment of erectile dysfunction by perineal
51
52 exercise, electromyographic biofeedback, and electrical stimulation. *Phys Ther* 2003;
53
54 Jun;83(6):536-43.
55
56
57
58
59
60

1
2
3
4 43. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary
5 prevention programs: 2007 update: a scientific statement from the American Heart Association
6 Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology;
7 the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical
8 Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary
9 Rehabilitation. *J Cardiopulm Rehabil Prev* 2007; May-Jun;27(3):121-9.

10
11
12
13
14
15
16
17
18 44. Fitchet A, Doherty PJ, Bundy C, et al. Comprehensive cardiac rehabilitation programme for
19 implantable cardioverter-defibrillator patients: a randomised controlled trial. *Heart* 2003;
20 Feb;89(2):155-60.

21
22
23
24
25
26 45. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a
27 multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; Jun;49(6):822-30.

28
29
30
31
32 46. Rosen RC, Cappelleri JC, Gendrano N,3rd. The International Index of Erectile Function (IIEF):
33 a state-of-the-science review. *Int J Impot Res* 2002; Aug;14(4):226-44.

34
35
36
37 47. Derogatis LR. The psychosocial adjustment to illness scale (PAIS). *J Psychosom Res*
38 1986;30(1):77-91.

39
40
41
42 48. Westlake C, Dracup K, Walden JA, et al. Sexuality of patients with advanced heart failure and
43 their spouses or partners. *J Heart Lung Transplant* 1999; Nov;18(11):1133-8.

44
45
46
47
48 49. Jaarsma T. Sexual problems in heart failure patients. *Eur J Cardiovasc Nurs* 2002; Feb;1(1):61-
49 7.

50
51
52
53
54 50. Rasmussen TB, Zwisler AD, Sibilitz KL, et al. A randomised clinical trial of comprehensive
55 cardiac rehabilitation versus usual care for patients treated for infective endocarditis--the
56

1
2
3
4 CopenHeartIE trial protocol. *BMJ Open* 2012; Nov 21;2(6):10.1136/bmjopen,2012-001929. Print
5
6 2012.

7
8
9
10 51. Risom SS, Zwisler AD, Rasmussen TB, et al. The effect of integrated cardiac rehabilitation
11 versus treatment as usual for atrial fibrillation patients treated with ablation: the randomised
12 CopenHeartRFA trial protocol. *BMJ Open* 2013; Feb 20;3(2):10.1136/bmjopen,2012-002377. Print
13
14 2013.

15
16
17
18 52. Sibilitz KL, Berg SK, Hansen TB, et al. Effect of comprehensive cardiac rehabilitation after
19 heart valve surgery (CopenHeartVR): study protocol for a randomised clinical trial. *Trials* 2013;
20
21 Apr 22;14(1):104.

22
23
24
25 53. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the
26 management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012;
27
28 Aug;87(8):766-78.

29
30
31
32 54. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention
33 in clinical practice (version 2012) : the fifth joint task force of the European society of cardiology
34 and other societies on cardiovascular disease prevention in clinical practice (constituted by
35 representatives of nine societies and by invited experts). *Int J Behav Med* 2012; Dec;19(4):403-88.

36
37
38
39 55. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation:
40 from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the
41 European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev
42 Rehabil* 2010; Feb;17(1):1-17.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 56. Berg SK. *Comprehensive rehabilitation for patients with ICD: PhD dissertation*. [Aarhus]:
5
6
7

8
9
10 Faculty of Health Sciences, Aarhus University; 2011.

11
12 57. Zwisler AD, Soja AM, Rasmussen S, et al. Hospital-based comprehensive cardiac rehabilitation
13
14 versus usual care among patients with congestive heart failure, ischemic heart disease, or high risk
15
16 of ischemic heart disease: 12-month results of a randomized clinical trial. *Am Heart J* 2008;
17
18 Jun;155(6):1106-13.

19
20 58. Ashworth NL, Chad KE, Harrison EL, et al. Home versus center based physical activity
21
22 programs in older adults. *Cochrane Database Syst Rev* 2005; Jan 25;(1)(1):CD004017.

23
24 59. Oerkild B, Frederiksen M, Hansen JF, et al. Home-based cardiac rehabilitation is as effective as
25
26 centre-based cardiac rehabilitation among elderly with coronary heart disease: results from a
27
28 randomised clinical trial. *Age Ageing* 2011; Jan;40(1):78-85.

29
30 60. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-
31
32 81.

33
34 61. Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without
35
36 cardiovascular disease: 2007 update: a scientific statement from the American Heart Association
37
38 Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Circulation 2007; Jul 31;116(5):572-84.

62. Lampman RM, Knight BP. Prescribing exercise training for patients with defibrillators. *Am J
Phys Med Rehabil* 2000; May-Jun;79(3):292-7.

63. Dorey G, Glazener C, Buckley B, et al. Developing a pelvic floor muscle training regimen for
use in a trial intervention. *Physiotherapy* 2009; Sep;95(3):199-209.

- 1
2
3
4 64. Parse RR. *The human becoming school of thought: a perspective for nurses and other health*
5
6 *professionals*. Thousand Oaks, Calif.: Sage; 1998.
7
8
9
10 65. Tibaek S, Klarskov P, Lund Hansen B, et al. Pelvic floor muscle training before transurethral
11
12 resection of the prostate: a randomized, controlled, blinded study. *Scand J Urol Nephrol*
13
14 2007;41(4):329-34.
15
16
17 66. Schüssler B. *Pelvic floor re-education: principles and practice*. London: Springer; 1994.
18
19
20
21 67. Mezzani A, Agostoni P, Cohen-Solal A, et al. Standards for the use of cardiopulmonary exercise
22
23 testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology
24
25 Section of the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J*
26
27 *Cardiovasc Prev Rehabil* 2009; Jun;16(3):249-67.
28
29
30
31 68. Ware JE, Kosinski M, Gandek B. SF-36 Health Survey.: Manual and Interpretation guide
32
33 2005;The Health Institute, New England Medical Center, Boston, Massachusetts.
34
35
36 69. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;
37
38 Jun;67(6):361-70.
39
40
41
42 70. Drummond MF. *Methods for the economic evaluation of health care programmes*. 3rd edition
43
44 ed. Oxford: Oxford University Press; 2005.
45
46
47 71. Rubio-Aurioles E, Sand M, Terrein-Roccatti N, et al. Female Assessment of Male Erectile
48
49 dysfunction detection scale (FAME): development and validation. *J Sex Med* 2009; Aug;6(8):2255-
50
51 70.
52
53
54
55
56
57
58
59
60

1
2
3
4 72. Boutron I, Moher D, Altman DG, et al. Extending the CONSORT statement to randomized
5
6 trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; Feb
7
8 19;148(4):295-309.
9

10
11 73. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a
12
13 statement for healthcare professionals from the American Heart Association. *Circulation* 2001; Oct
14
15 2;104(14):1694-740.
16
17

18
19 74. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave
20
21 myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll*
22
23 *Cardiol* 1988; Aug;12(2):362-72.
24
25

26
27 75. Giannuzzi P, Tavazzi L, Temporelli PL, et al. Long-term physical training and left ventricular
28
29 remodeling after anterior myocardial infarction: results of the Exercise in Anterior Myocardial
30
31 Infarction (EAMI) trial. EAMI Study Group. *J Am Coll Cardiol* 1993; Dec;22(7):1821-9.
32
33

34
35 76. Otsuka Y, Takaki H, Okano Y, et al. Exercise training without ventricular remodeling in
36
37 patients with moderate to severe left ventricular dysfunction early after acute myocardial infarction.
38
39 *Int J Cardiol* 2003; Feb;87(2-3):237-44.
40
41

42
43 77. Pavy B, Iliou MC, Meurin P, et al. Safety of exercise training for cardiac patients: results of the
44
45 French registry of complications during cardiac rehabilitation. *Arch Intern Med* 2006; Nov
46
47 27;166(21):2329-34.
48
49

50
51 78. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on
52
53 intervention effect estimates from randomized, controlled trials. *Ann Intern Med* 2012; Sep
54
55 18;157(6):429-38.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

79. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; Mar 15;336(7644):601-5.

For peer review only

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

Pernille Palm Johansen¹⁺²

Ann-Dorthe Zwisler²⁺³

Jesper Hastrup-Svendsen²⁺⁸

Marianne Fredriksen¹

Jane Lindschou⁴

Per Winkel⁴

Christian Gluud⁴

Annamaria Giraldi⁵

Elaine Steinke⁶

Tiny Jaarsma⁷

Selina Kikkenborg Berg²

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

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

³National Institute of Public Health, University of Southern Denmark

⁴The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

⁵Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁶Wichita State University, Wichita, Kansas, United States

⁷Department of Social and Welfare Studies, Linköping University, Linköping, Sweden

⁸Institute of Clinical Medicine, Faculty of Health Science, University of Copenhagen

[Date: October 7, 2013. Version 1.2](#)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Corresponding author:

Pernille Palm Johansen RN. MCN

Copenhagen University Hospital, Bispebjerg Hospital / Rigshospitalet

Copenhagen

Denmark

Mail: pernille.palm.johansen@regionh.dk

For peer review only

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 treated is 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

1
2
3
4 inhibitors to cardiac events, large randomised trials and a meta-analysis suggest that they are not
5 associated with an increase in myocardial infarction or cardiac events.^{6, 32} In patients with heart
6 disease and no effect of PDE5 inhibitors, or where PDE5 inhibitors are contra-indicated because of
7 treatment with nitrates, there seems to be no consensus on what treatment should be offered for
8 sexual dysfunction.
9
10
11
12

13 14 **Non-pharmacological treatment potentials**

15 Non-pharmacological interventions possess potential in reducing sexual dysfunction. Lifestyle
16 factors such as; cigarette smoking, hyperlipidaemia, and a sedentary lifestyle all predict erectile
17 dysfunction^{4, 5} and these are the same risk factors that predict coronary artery disease. A recent
18 meta-analysis of six randomised trials with 740 patients with no known heart disease, showed that
19 life style modifications such as physical exercise and pharmacotherapy for cardiovascular risk
20 factors were associated with a significant improvement in erectile function.³³ Furthermore, a
21 randomised trial investigating the effect of exercise training 3 hours per week or more in non-heart
22 disease patients showed a significant result in improving the person's erectile functioning compared
23 with controls with no exercise training.³⁴ We hypothesize that these lifestyle modifications can also
24 improve sexual dysfunction in patients with already established heart disease. A systematic
25 literature search showed five randomised clinical trials which examine the effect of physical
26 exercise on sexual dysfunction.³⁵⁻³⁹ Overall, 591 patients with heart disease were included and the
27 effect was significant in three of the five trials.³⁷⁻³⁹ However, the trials are characterised as being of
28 small sample sizes, using non-validated tools and mainly focusing on the time before patients return
29 to sexual activity and not on the ability and quality of the sexual performance. Randomised trials
30 that address the psychological aspects of sexual dysfunction are limited in patients with heart
31 disease. However, one randomised trial testing the effect of sexual therapy showed some promising
32 trends when it comes to improving the frequency and quality of sexual activity in male patients post
33 cardiac event beyond the usual cardiac rehabilitation.⁴⁰ However, due to the limited power of the
34 sample in this trial, it did not allow the detection of significant effects. The role of pelvic floor
35 exercises as a treatment of erectile dysfunction is not tested on patients with heart disease, but in the
36 general population 40% to 47% had regained normal erectile function after 3-4 month of training
37 the pelvic floor muscles.^{41, 42} As the condition sexual dysfunction often includes both physical and
38 psychological components, it is plausible to believe that patients with heart disease and sexual
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 dysfunction benefit from a comprehensive rehabilitation intervention^{43, 44} consisting of a psycho-
5 educational component and an exercise training component including pelvic floor exercises.
6
7
8
9

10 TRIAL OBJECTIVES

11
12 The objective of the CopenHeart_{SF} is to investigate benefit and harm on the sexual function of male
13 patients with ischaemic heart disease or patients with implantable cardioverter defibrillator of a
14 comprehensive sexual rehabilitation programme, consisting of a psycho-educative component and a
15 physical exercise component, including pelvic floor exercises. The primary hypothesis is that, a
16 comprehensive sexual rehabilitation programme improves sexual function, as assessed by the
17 International Index of Erectile dysfunction (IIEF) questionnaire^{45, 46}, in males with sexual
18 dysfunction and ischaemic heart disease or patients with implantable cardioverter by 3.5 points in
19 the experimental group compared with the control group after completion of the programme. The
20 estimated increase in primary outcome is based on a study that examines the effect of a physical
21 intervention in patients with cardiovascular disease taking PDE5-inhibitors.³⁴ The secondary
22 hypothesis is that sexual function, measured by the sexual domain in the Psychosocial Adjustment
23 to Illness Scale (self-reported version) (PAIS-SR) questionnaire⁴⁷, improves by two points in the
24 experimental group compared with the control group after completing the programme. The
25 estimated increase in secondary outcome is based on two studies that examine the prevalence of
26 sexual dysfunction in patients with heart failure.^{48, 49}
27
28
29

30 Exploratory analyses will test the hypotheses that comprehensive sexual rehabilitation will improve:
31 health-related quality of life, anxiety and depression, frequency of sexual activity, physical capacity
32 measured by peak oxygen uptake (peak VO₂), pelvic floor muscle strength and endurance and
33 female assessment of male partner's erectile dysfunction.
34
35
36
37
38
39

40 METHODS

41 CopenHeart_{SF} is an investigator-initiated randomised clinical superiority trial with blinded outcome
42 assessment, with 1:1 central randomisation to a comprehensive sexual rehabilitation programme
43 plus usual care or usual care alone. Based on sample-size calculations 154 patients will be recruited
44 from two university hospitals in Denmark. The CopenHeart_{SF} trial is a part of the overall
45 CopenHeart project, consisting of several randomised clinical trials (www.CopenHeart.org),
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 designed to develop evidence-based knowledge of rehabilitation among patients with complex
5 cardiac conditions. Major parts of the CopenHeart_{SF} methods section and trial design in this paper
6 are similar to other randomised clinical trials, CopenHeart_{IE}⁵⁰, CopenHeart_{RFA}⁵¹ and CopenHeart_{VR}⁵².

7 8 9 10 **Study population and eligibility criteria**

11 Male patients above 18 years with sexual dysfunction associated with implantable cardioverter
12 defibrillator or with ischaemic heart disease verified by coronary angiography, who have a partner,
13 speak and understand Danish, and provide a written informed consent, are considered eligible for
14 participation. Exclusion criteria are patients at intermediate or high risk in relation to their
15 cardiovascular status according to recommendations from the Princeton consensus group^{32, 53}; those
16 with diseases in the urinary tract; those who perform intense competitive exercise more than 3 hours
17 a week; patients with neurological or orthopaedic deficits which prevent training; patients with
18 cognitive deficits which prevents consultations; and patients who are included in ongoing research
19 prohibiting additional research participation. A diagram showing the flow of participants through
20 each stage of the randomized trial will be made. (*See figure 1*)
21
22
23
24
25
26
27
28
29

30 **Experimental intervention**

31 The experimental intervention is a comprehensive sexual rehabilitation programme. Sexual
32 rehabilitation in this trial is defined as: a time-bounded planned process with clear goals and means.
33 Sexual rehabilitation is a process where several actors, including the patient, are working towards
34 regaining improved sexual functioning and coping ability according to their sexual function. The
35 comprehensive sexual rehabilitation programme contains a physical exercise component, including
36 training of the pelvic floor and a psycho-educational component.
37
38
39
40
41
42
43

44 **The physical components**

45 *Physical exercise*

46 The goal of physical exercise is to achieve an improvement in the patient's physical work capacity,
47 and to eliminate the fear and uncertainty the patient may feel in relation to sexual activity as a form
48 of physical activity. The physical exercise intervention is based on The European Society of
49 Cardiology recommendations for physical activity for cardiovascular patients.⁵⁴ The European
50 Society of Cardiology recommends that all adults promote and maintain their fitness, muscle
51 strength, flexibility and bone health several hours a week. Training must be of high intensity and of
52
53
54
55
56
57
58
59
60

1
2
3
4 30 minutes duration.⁵⁴ Furthermore, the intervention is supported by European recommendations
5 for physical training in cardiac patients⁵⁵ and has been tested in COPE-ICD and DANREHAB
6 trials.^{56, 57} A professional physiotherapist with specific knowledge of cardiac rehabilitation initiates
7 the physical exercise programme. Together with the patient, the physiotherapist plans and prepares
8 a physical exercise protocol, taking into account the patient's clinical condition and physical
9 abilities. Sixty minutes is allocated for the initial consultation and preparation of individual training
10 protocol, including pelvic floor exercise instructions.

11
12
13
14
15
16
17 Physical exercise is initiated at a physiotherapist-supervised setting at the Heart Centre,
18 Rigshospitalet. Using wireless electrodes integrated into t-shirts (Corus-Fit, CardioCardio and
19 Corus Exercise Assistant, version 2.0.16, Finland) potential cardiac arrhythmias,
20 electrocardiographic abnormalities such as ST segment changes, T-wave alterations, atrial or
21 ventricular arrhythmias, and training intensity level are monitored. The training is initiated with two
22 to three mandatory exercise sessions at Rigshospitalet. Subsequently, the patients can choose to
23 continue the intensive physical exercise regimen either at Rigshospitalet, or at a local CopenHeart-
24 certified facility, supervised by physiotherapists, or as supervised home-based training. Supervised
25 home-based physical training has previously shown similar results to hospital-based training.⁵⁸ This
26 finding has been confirmed in a Danish setting.⁵⁹

27
28
29
30
31
32
33 One session is structured with 10 minutes (min) warm-up bicycling, 20 min bicycling with
34 increased intensity (cardiovascular training), 20 min strength exercises, and 10 min stretching and
35 cool-down period. The warm-up session is performed at the intensity of 11 to 12 on the Borg
36 scale.⁶⁰ The 20 min cardiovascular training is performed as interval training. Each session is divided
37 into three sections. Each section contains intensity 13 to 17 on the Borg scale and time limit (2 to 15
38 min) varying between each section; the second section with longest and highest intensity. A cool
39 down period of 5 min is included after the 20 min of cardiovascular training. The strength and
40 strength-related exercises primarily target lower body muscles, and comprise the following four
41 exercises: (1) heel rise performed by repetitions of maximal flexion from standing position; (2)
42 step-up by using a step bench of 27 cm; (3) leg press standardised, starting with 90 degrees flexion,
43 hyperextension not accepted; (4) 90 degrees pull-down performed in a cable machine to target
44 abdominal muscles. For step-ups and heel-rises, weight load is calculated as a percentage of body
45 weight (5 to 20%) and increased throughout the 12 weeks. Load for leg press is estimated from
46 repetition maximum (RM) testing and increases from 60% of 1 RM to 70% of 1 RM during the 12
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 weeks of training. All exercises are initiated by 2x12 repetitions and increased through the
5 programme according to standard guidelines for strength training.⁶¹

6
7 To achieve cardiovascular adjustment the training begins with a warming-up period and ends with a
8 cool-down period. This cardiovascular adjustment has been shown to reduce the risk of ischaemia
9 and arrhythmia in connection to physical exercise.^{44, 62} Participants must mainly exercise in an
10 upright position to decrease left ventricular filling pressure and risk of ischaemia or heart-failure-
11 triggered ventricular arrhythmias.⁶²
12
13
14
15

16 17 *Pelvic floor exercise*

18 The bulbocavernosus muscle and the ischiocavernosus muscle, two superficial pelvic floor muscles,
19 are active during erection and enhance rigidity. The bulbocavernosus muscle encircles 33% to 50%
20 of the base of the penis.⁴¹ The pelvic floor training regimen is inspired by Dorey and colleagues,
21 who have developed a training regimen for male patients for use in randomised clinical trials.⁶³ The
22 regiment is developed and tested in a different patient population, and we have therefore modified it
23 to fit cardiovascular patients. Patients are instructed in pelvic floor exercises by a skilled
24 physiotherapist. Patients are instructed to perform their pelvic floor exercises twice daily. Studies
25 showed that a few strong or maximum contractions are more effective when it comes to gaining
26 muscle hypertrophy than several less strong contractions.⁶³ Patients are instructed to tighten their
27 pelvic floor muscles as strongly as possible (as if to prevent flatus from escaping) three times when
28 lying, three times when sitting, and three times when standing. The duration of the contraction is up
29 to 10 seconds each, and patients are informed to have a 10 second break between each contraction.
30 The physiotherapist instructs the patients on how to contract the bulbocavernosus and
31 ischiocavernosus muscles. In order to ensure that the right muscles are involved, attention is placed
32 on the ability to lift the scrotum and retract the penis. To obtain some degree of pelvic floor muscle
33 endurance, the patients are encouraged to tighten the pelvic floor muscles when walking.
34
35
36
37
38
39
40
41
42
43
44
45

46 To [encourage adherence and](#) monitor compliance pulse watches (Polar watch) with extended
47 memory and exercise training logs are handed out. A training log contains information about
48 physical exercise as well as pelvic floor exercise. At the end of the intervention the training log and
49 the pulse watch are returned and compliance and intensity level are coded independently.
50
51
52
53

54 **The psycho-educational components**

55
56
57
58
59
60

1
2
3
4 The goal of the psycho-educative intervention is that the patient learns to interpret and react to
5 relevant physical and psychological symptoms, learns to cope with anxiety and fear, including
6 strategies to manage depressive symptoms and ability to be sexually active without fear.
7
8 A specially trained nurse is responsible for the psycho-educative intervention. The intervention
9 takes a theoretical basis of the patient-centred approach where the emphasis is on support and
10 education. The conversations are based on a holistic view of the patient and focus on the handling
11 of life and managing sexual dysfunction. The intervention is targeted at the modifiable parameters
12 that are reported to affect sexual dysfunction. The psycho-educative intervention is inspired by RR
13 Parse's 'Human Becoming Practice Methodologies' three dimensions⁶⁴, which can be described as:
14 1. discuss and give meaning to the past, present and future, 2. explore and discuss events and
15 opportunities; and 3. pursue imagined possibilities. According to this theory, there are three ways to
16 alter its perceived health: creative ideas, see, hear and feel how a situation could be if it was lived in
17 a different way; recognising personal patterns and value priorities and shed light on the paradoxes
18 by looking at incongruence in a situation and change the view of reality. The nurse is 'truly present'
19 in the process through discussion, quiet contemplation, and reflection. The psycho-educative
20 intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on
21 psychological well-being (mental health) and the general health sub-scale of the SF-36.⁵⁶ The nurse
22 is trained in the psycho-educative conversation through teaching and supervision of nurses who
23 have experience with the 'Human Becoming Practice Methodology' from the COPE-ICD trial. It is
24 based on the theoretical literature that forms the basis for understanding the processes of practice
25 methodology and existing specialty specific knowledge about heart disease, related symptoms, and
26 sexology. The supervisor observes and provides feedback in relation to the methods and goals of the
27 conversation. The emphasis is on openness in the interviews, and on the nurse's ability to: be
28 silently present while the patient talks, ask questions that encourage reflection, let the patient find
29 answers and solutions and contribute with knowledge, provide advice and guidance when requested
30 and relevant. The training of the nurse takes place prior to the intervention. In practice the
31 intervention will be handled by one nurse with several years of experience working with cardiac
32 patients and trained in sexology. The sexology experience is gained in a two-week intensive course
33 on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist is
34 available during the intervention. The nurse will conduct consultations with patients individually,
35 and patients are informed that they are welcome to bring spouses/relatives. The consultation will
36 take place in a quiet room in an outpatient settings and last for 45 minutes. An inspirational guide
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 will form the basis for the consultations. The guide consists of several elements and issues (medical,
5 psychosocial, educational and sexual) that work as inspiration (see table 1):
6
7
8
9
10
11
12
13
14
15
16
17
18

19 **Table 1. Inspiration guide for psycho-educational consultations**

20 A brief medical history
21 Actual thoughts and questions regarding their heart disease and sexual function
22 Sexual dysfunction
23 Safety issues
24 Angina or ICD shock
25 How the sexual problems affect daily live
26 Provide the patient with recommendations
27 Relationship
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4 In order to evaluate the effect of comprehensive sexual rehabilitation programme numerous data
5 will be collected.
6

7
8 *Primary outcome*
9

10 Sexual function will be measured by the International Index of Erectile Function (IIEF)
11 questionnaire after 16 weeks and 6 months. International Index of Erectile Function (IIEF) was
12 developed in conjunction with the clinical trial program for sildenafil, and has since been adopted as
13 the 'gold standard' measure for efficacy assessment in clinical trials of erectile dysfunction. It has
14 been linguistically validated in 32 languages including Danish and used as a primary outcome in
15 more than 50 clinical trials.^{34, 45, 46} It consists of 15 items including five domains of sexual function:
16 erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.
17 The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of
18 sensitivity and specificity.⁴⁶ The IIEF is self-assessed, which in sexological research is widely used
19 and well acclaimed.
20
21
22
23
24
25
26
27

28
29 *Secondary outcome*
30

31 Sexual function is measured by the Psychosocial Adjustment to Illness Scale (self-reported version)
32 (PAIS-SR) sexual relationship domain.⁴⁷ The overall PAIS-SR measure psychosocial adjustment to
33 illness in terms of 7 primary domains of adjustment: Health Care Orientation, Vocational
34 Environment, Domestic Environment, Sexual Relationships, Extended Family Relationships, Social
35 Environment and Psychological Distress. Each PAIS/PAIS-SR item is rated on a 4-point (0 through
36 3) scale of adjustment, with higher ratings indicating poorer adjustment status. The sexual
37 relationship domain evaluates shifts in the quality of sexual relations due to the current illness or
38 treatment. It consists of six items and the total score ranges from 0 to 18. Low scores indicates good
39 adjustment, and high scores poor adjustment.
40
41
42
43
44
45
46
47

48 *Exploratory outcomes*
49

50 A more extensive evaluation of physical, psychological, and demographic status over time will be
51 performed. Physical examination will include pelvic floor strength and endurance assessed
52 according to the Modified Oxford grading scheme which is a manual digital examination of the
53 pelvic floor. It is tested and validated and used in several trials.^{65, 66} Furthermore physical capacity
54
55
56
57
58
59
60

will be measured by peak VO₂ using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) with measurement of oxygen uptake (VO₂), heart rate (HR, beats /min), ventilation rate (VE, l/min), ventilation frequency (VF, number / min), respiratory expiration ratio (RER, CO₂/O₂ in%), blood pressure, physical activity level (METS) and gas exchange (VO₂ and VCO₂) 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 questionnaire⁴⁵ by mail including a stamped return envelope. Patients with a score less than or equal to 25, the accepted cut-off score⁴⁶, on the initial screening are invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems. The participant information is sent to the patient along with the invitation. This gives the patient an opportunity to read the material in advance and to prepare

possible questions. At the initial interview/meeting it is determined whether the patient meets the criteria for participating in the trial. If patients are suited and want to participate they will be randomised to 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 randomised 1:1 to the experimental group or the control group. Randomisation will be performed centrally by the trial coordination centre, Copenhagen Trial Unit, according to a computer-generated allocation sequence with a variable block size concealed from the investigators. Allocation to the intervention groups is 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 email 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 $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot I + c \cdot G + d \cdot I \cdot G$ (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 $d \cdot I \cdot G$ stands for interaction between the two covariates I and G. If the term $b \cdot I$ 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 $d \cdot I \cdot G$ 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 $Y = \text{intercept} + a \cdot Y_{\text{baseline}} + b \cdot G + c \cdot I + d \cdot I \cdot G + e \cdot T + f \cdot I \cdot T + g \cdot I \cdot T \cdot G$ (equation 2) where a through g are coefficients to be estimated. If the term $e \cdot T$ is significant there is a linear trend over time common for both patient groups. If $f \cdot I \cdot T$ is significant, this trend is supplemented by an additional trend caused by the intervention and therefore specific for the intervention group. If in addition $g \cdot I \cdot T \cdot G$ 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

1
2
3
4 If the number of missing cases for a given outcome (number of patients with one or more model
5 variables missing) is larger than 5% or p of Little's test is < 5% multiple imputations of the model
6 variables (outcome plus co-variables) is done using SPSS version 17. The range of potential bias in
7 case the missing values should not be random is assessed by doing two imputations (1) imputing
8 missing outcome value in one group by minimum value found in the material and missing outcome
9 value in the other group by maximum value found in material and (2) vice versa. Then in each case
10 an unadjusted analysis is done to estimate the parameter of interest.
11
12
13
14
15
16

17 **ETHICS AND DISSEMINATION**

18
19 Trial protocol has been approved by the Regional Ethics Committee (no H-4-2012-168) and the
20 Danish Data Protection Agency (no 2007-58-0015). The trial complies with the latest declaration of
21 Helsinki and is registered at ClinicalTrials.gov (NCT01796353). Patients are informed about the
22 trial in writing as well as verbally and only included if a written informed consent is obtained.
23
24 Patients are assessed in accordance to whether it is safe for them to perform sexual activity. This is
25 done according to recommendations from the Princeton consensus group.^{32, 53} If patients are suited
26 and want to participate they will be enrolled in the trial. Trial participants are free to withdraw their
27 informed consent at any time and be treated according to the departments' standard treatment
28 procedures. A patient will be withdrawn from the trial if the trial participant withdraws his consent
29 and will, in connection therewith, be informed that termination of the trial will have no implications
30 for his future treatment. Patients who leave the trial will be politely asked for permission to
31 continue to collect data and to use already collected data. If the patient gives permission, he will be
32 included in the final analysis. Only if the patient refuses use of already collected data, will all data
33 relating to him, be destroyed. All patient data will be handled and stored in accordance with Danish
34 Data Protection Agency rules and patients are ensured anonymity. The trial will be conducted
35 according to the Act. No. 593 of June 14 2011 on Act on Research Ethics Review of Health
36 Research Projects. The investigator will immediately notify the regional ethics committee if, within
37 the interventions period, there occur Serious Adverse Events, Serious Adverse Reactions, or
38 Suspected Unexpected Serious Adverse Reactions. The report will be accompanied by comments
39 on possible implications for the trial, and notification will be made within 7 days after the
40 investigator has knowledge of the event. [The trial has no data monitoring committee however an An](#)
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

1
2
3
4 there is no previous risk associated with nursing consultations. If the nurse during the consultation
5 identifies a need for further consultations with professionals, she will encourage the participant to
6 seek help from the general practitioner, psychologist, or in their usual outpatient setting. Risks
7 associated with exercise training and testing are sudden cardiac death associated with ventricular
8 arrhythmias, acute myocardial infarction, and in patients with chronic heart failure, pulmonary
9 oedema and deterioration in left ventricular function.⁷³ The last is only found in one study from
10 1988⁷⁴ and has not subsequently been demonstrated in larger studies.^{75, 76} In a recent French study
11 of more than 25,000 patients with ischaemic heart disease, one third with chronic heart failure
12 found the risk of cardiac complications at 1:8,500 exercise testing and 1:50,000 patient exercise
13 hours.⁷⁷ Increasing exercise intensity and age are risk indicators. Therefore, the training intensity
14 will be conducted as moderate high intensity (less than 80% of VO₂ max). To achieve
15 cardiovascular adjustment both exercise training and testing begins with a warming-up period and
16 ends with a cool-down period, with a gradual downward adjustment of exercise intensity and heart
17 rate, rather than an abrupt end. This cardiovascular adjustment has been shown to reduce the risk of
18 ischaemia and arrhythmia in connection with physical exercise.^{44, 62} Participants must mainly
19 exercise in an upright position to decrease left ventricular filling pressure and risk of ischemia or
20 heart failure triggered ventricular arrhythmias. When these precautions are respected, both exercise
21 training and exercise testing are considered to possess a low risk for the participants. There is, as far
22 as we know, no previously known risk associated with pelvic floor exercise. Testing or examination
23 of the pelvic floor may be associated with discomfort for the participants but is not considered to be
24 associated with any risk. Staff members will be trained according to guidelines to handle any
25 emergencies.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 **Dissemination plan**

43
44 Positive, neutral, and negative results of the trial will be submitted to international peer reviewed
45 journals of nursing, cardiology or sexology. Furthermore, results will be presented at national and
46 international conferences relevant to subject fields. Authorship will be allocated using the
47 guidelines for authorship defined by the International Committee of Medical Journal Editors and
48 depends on the personal involvement. All the articles, abstracts as well as the results will be posted
49 on the website www.copenheart.org. The website will be continuously updated and will be
50 highlighted through the scientific articles. [CopenHeart staff will have access to data. Ethic committees
51 and competent authorities will be able to obtain direct access to data and documentation.](#)
52
53
54
55
56
57
58
59
60

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}; [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.

Acknowledgements:

The test and rehabilitation team responsible for the trial is: Karina Jensen, Lars Tang, Helena Tjalk Sørensen, Signe Gils and Katrine Tingholm Erhardsen.

Funding statement:

The CopenHeart trial has received funding from: The Danish Heart Foundation (no. 13-04-R95-A4669-22744); The Health Foundation (no. 2013B208); Danish Council for Strategic Research (no. 10-092790); The Danish Nursing Council. Neither of the funders had influence of the study protocol and design, the execution of the trial or the interpretation of data.

Competing interest:

None

REFERENCES

1. Hoekstra T, Jaarsma T, Sanderman R, van Veldhuisen DJ, Lesman-Leegte I. Perceived sexual difficulties and associated factors in patients with heart failure. *Am Heart J* 2012; Feb;163(2):246-51.
2. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; Feb 10;281(6):537-44.
3. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; Jan;151(1):54-61.
4. Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, Araujo AB, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. *Prev Med* 2000; Apr;30(4):328-38.
5. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med* 2003; Aug 5;139(3):161-8.
6. Levine GN, Steinke EE, Bakaeen FG, Bozkurt B, Cheitlin MD, Conti JB, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2012; Feb 28;125(8):1058-72.
7. Steinke EE. Sexual dysfunction in women with cardiovascular disease: what do we know?. *J Cardiovasc Nurs* 2010; Mar-Apr;25(2):151-8.

- 1
2
3
4 8. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED, Jr, et al.
5
6 Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med* 2010; Apr;7(4 Pt 2):1598-
7
8 607.
9
- 10
11 9. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence.
12
13 *JAMA* 1993; Jul 7;270(1):83-90.
14
15
- 16
17 10. Rastogi S, Rodriguez JJ, Kapur V, Schwarz ER. Why do patients with heart failure suffer from
18
19 erectile dysfunction? A critical review and suggestions on how to approach this problem. *Int J*
20
21 *Impot Res* 2005; Dec;17 Suppl 1:S25-36.
22
23
- 24
25 11. Berg SK, Elleman-Jensen L, Zwisler AD, Winkel P, Svendsen JH, Pedersen PU, et al. Sexual
26
27 concerns and practices after ICD implantation: findings of the COPE-ICD rehabilitation trial. *Eur J*
28
29 *Cardiovasc Nurs* 2013; Jan 8;.
30
31
- 32
33 12. Bortolotti A, Parazzini F, Colli E, Landoni M. The epidemiology of erectile dysfunction and its
34
35 risk factors. *Int J Androl* 1997; Dec;20(6):323-34.
36
37
- 38
39 13. Herbert K, Lopez B, Castellano J, Palacio A, Tamari L, Arcemen LM. The prevalence of
40
41 erectile dysfunction in heart failure patients by race and ethnicity. *Int J Impot Res* 2008; Sep-
42
43 Oct;20(5):507-11.
44
45
- 46
47 14. Kloner RA, Mullin SH, Shook T, Matthews R, Mayeda G, Burstein S, et al. Erectile dysfunction
48
49 in the cardiac patient: how common and should we treat?. *J Urol* 2003; Aug;170(2 Pt 2):S46,50;
50
51 discussion S50.
52
53
- 54
55 15. Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, et al. Erectile
56
57 dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients
58
59
60

1
2
3
4 with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003;
5
6 Sep;44(3):360,4; discussion 364-5.
7

8
9
10 16. Steinke EE. Sexual concerns of patients and partners after an implantable cardioverter
11
12 defibrillator. *Dimens Crit Care Nurs* 2003; Mar-Apr;22(2):89-96.
13

14
15 17. Dabrowski R, Smolis-Bak E, Kowalik I, Kazimierska B, Wojcicka M, Szwed H. Quality of life
16
17 and depression in patients with different patterns of atrial fibrillation. *Kardiol Pol* 2010;
18
19 Oct;68(10):1133-9.
20
21

22
23 18. Drory Y, Kravetz S, Weingarten M. Comparison of sexual activity of women and men after a
24
25 first acute myocardial infarction. *Am J Cardiol* 2000; Jun 1;85(11):1283-7.
26
27

28
29 19. Foroutan SK, Rajabi M. Erectile dysfunction in men with angiographically documented
30
31 coronary artery disease. *Urol J* 2007; Winter;4(1):28-32.
32
33

34
35 20. Justo D, Arbel Y, Mulat B, Mashav N, Saar N, Steinvil A, et al. Sexual activity and erectile
36
37 dysfunction in elderly men with angiographically documented coronary artery disease. *Int J Impot*
38
39 *Res* 2010; Jan-Feb;22(1):40-4.
40
41

42
43 21. Dunn KM, Croft PR, Hackett GI. Association of sexual problems with social, psychological,
44
45 and physical problems in men and women: a cross sectional population survey. *J Epidemiol*
46
47 *Community Health* 1999; Mar;53(3):144-8.
48
49

50
51 22. Friedman S. Cardiac disease, anxiety, and sexual functioning. *Am J Cardiol* 2000; Jul
52
53 20;86(2A):46F-50F.
54
55
56
57
58
59
60

- 1
2
3
4 23. Kriston L, Gunzler C, Agyemang A, Bengel J, Berner MM, SPARK Study Group. Effect of
5
6 sexual function on health-related quality of life mediated by depressive symptoms in cardiac
7
8 rehabilitation. findings of the SPARK project in 493 patients. *J Sex Med* 2010; Jun;7(6):2044-55.
9
- 10
11 24. Mulat B, Arbel Y, Mashav N, Saar N, Steinvil A, Heruti R, et al. Depressive symptoms and
12
13 erectile dysfunction in men with coronary artery disease. *Urology* 2010; Jan;75(1):104-7.
14
15
- 16
17 25. Makhoulouf A, Kparker A, Niederberger CS. Depression and erectile dysfunction. *Urol Clin*
18
19 *North Am* 2007; Nov;34(4):565,74, vii.
20
21
- 22
23 26. Roose SP. Depression: links with ischemic heart disease and erectile dysfunction. *J Clin*
24
25 *Psychiatry* 2003;64 Suppl 10:26-30.
26
27
- 28
29 27. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al.
30
31 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task
32
33 Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European
34
35 Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC
36
37 (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*
38
39 2008; Oct;29(19):2388-442.
40
41
- 42
43 28. Heart Failure Society Of A. HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J*
44
45 *Card Fail* 2006; Feb;12(1):e1-2.
46
47
- 48
49 29. Bedell SE, Duperval M, Goldberg R. Cardiologists' discussions about sexuality with patients
50
51 with chronic coronary artery disease. *Am Heart J* 2002; Aug;144(2):239-42.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 30. Jaarsma T, Stromberg A, Fridlund B, De Geest S, Martensson J, Moons P, et al. Sexual
5
6 counselling of cardiac patients: nurses' perception of practice, responsibility and confidence. *Eur J*
7
8 *Cardiovasc Nurs* 2010; Mar;9(1):24-9.
9
10
11 31. Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, et al. Erectile dysfunction and
12
13 coronary artery disease prediction: evidence-based guidance and consensus. *Int J Clin Pract* 2010;
14
15 Jun;64(7):848-57.
16
17
18 32. Jackson G, Rosen RC, Kloner RA, Kostis JB. The second Princeton consensus on sexual
19
20 dysfunction and cardiac risk: new guidelines for sexual medicine. *J Sex Med* 2006; Jan;3(1):28,36;
21
22 discussion 36.
23
24
25 33. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle
26
27 modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review
28
29 and meta-analysis. *Arch Intern Med* 2011; Nov 14;171(20):1797-803.
30
31
32
33 34. Maio G, Saraeb S, Marchiori A. Physical activity and PDE5 inhibitors in the treatment of
34
35 erectile dysfunction: results of a randomized controlled study. *J Sex Med* 2010; Jun;7(6):2201-8.
36
37
38
39 35. Roviario R, Holmes D, Holmsten R. Influence of a Cardiac Rehabilitation Program on the
40
41 Cardiovascular, Psychological, and Social Functioning of Cardiac Patients. *J Beh Med*
42
43 1984;7(1):61.
44
45
46 36. Froelicher ES, Kee LL, Newton KM, Lindskog B, Livingston M. Return to work, sexual
47
48 activity, and other activities after acute myocardial infarction. *Heart Lung* 1994; Sep-
49
50 Oct;23(5):423-35.
51
52
53
54
55
56
57
58
59
60

1
2
3
4 37. Belardinelli R, Lacalaprice F, Faccenda E, Purcaro A, Perna G. Effects of short-term moderate
5
6 exercise training on sexual function in male patients with chronic stable heart failure. *Int J Cardiol*
7
8 2005; May 11;101(1):83-90.
9

10
11 38. Bertie J, King A, Reed N, Marshall AJ, Ricketts C. Benefits and weaknesses of a cardiac
12
13 rehabilitation programme. *J R Coll Physicians Lond* 1992; Apr;26(2):147-51.
14
15

16
17 39. Lidell E, Fridlund B. Long-term effects of a comprehensive rehabilitation programme after
18
19 myocardial infarction. *Scand J Caring Sci* 1996;10(2):67-74.
20
21

22
23 40. Klein R, Bar-on E, Klein J, Benbenishty R. The impact of sexual therapy on patients after
24
25 cardiac events participating in a cardiac rehabilitation program. *Eur J Cardiovasc Prev Rehabil*
26
27 2007; Oct;14(5):672-8.
28
29

30
31 41. Dorey G, Speakman MJ, Feneley RC, Swinkels A, Dunn CD. Pelvic floor exercises for erectile
32
33 dysfunction. *BJU Int* 2005; Sep;96(4):595-7.
34
35

36
37 42. Van Kampen M, De Weerd W, Claes H, Feys H, De Maeyer M, Van Poppel H. Treatment of
38
39 erectile dysfunction by perineal exercise, electromyographic biofeedback, and electrical stimulation.
40
41 *Phys Ther* 2003; Jun;83(6):536-43.
42
43

44
45 43. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JA, et al. Core components of
46
47 cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the
48
49 American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the
50
51 Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and
52
53 Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of
54
55
56
57
58
59
60

1
2
3
4 Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev* 2007; May-
5 Jun;27(3):121-9.
6
7

8
9
10 44. Fitchet A, Doherty PJ, Bundy C, Bell W, Fitzpatrick AP, Garratt CJ. Comprehensive cardiac
11 rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised
12 controlled trial. *Heart* 2003; Feb;89(2):155-60.
13
14

15
16
17 45. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of
18 erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*
19
20 1997; Jun;49(6):822-30.
21
22

23
24
25 46. Rosen RC, Cappelleri JC, Gendrano N,3rd. The International Index of Erectile Function (IIEF):
26 a state-of-the-science review. *Int J Impot Res* 2002; Aug;14(4):226-44.
27
28

29
30
31 47. Derogatis LR. The psychosocial adjustment to illness scale (PAIS). *J Psychosom Res*
32 1986;30(1):77-91.
33
34

35
36
37 48. Westlake C, Dracup K, Walden JA, Fonarow G. Sexuality of patients with advanced heart
38 failure and their spouses or partners. *J Heart Lung Transplant* 1999; Nov;18(11):1133-8.
39
40

41
42 49. Jaarsma T. Sexual problems in heart failure patients. *Eur J Cardiovasc Nurs* 2002; Feb;1(1):61-
43 7.
44
45

46
47
48 50. Rasmussen TB, Zwisler AD, Sibilitz KL, Risom SS, Bundgaard H, Glud C, et al. A
49 randomised clinical trial of comprehensive cardiac rehabilitation versus usual care for patients
50 treated for infective endocarditis--the CopenHeartIE trial protocol. *BMJ Open* 2012; Nov
51 21;2(6):10.1136/bmjopen,2012-001929. Print 2012.
52
53
54
55
56
57
58
59
60

1
2
3
4 51. Risom SS, Zwisler AD, Rasmussen TB, Sibilitz KL, Svendsen JH, Gluud C, et al. The effect of
5
6 integrated cardiac rehabilitation versus treatment as usual for atrial fibrillation patients treated with
7
8 ablation: the randomised CopenHeartRFA trial protocol. *BMJ Open* 2013; Feb
9
10 20;3(2):10.1136/bmjopen,2012-002377. Print 2013.

11
12
13
14 52. Sibilitz KL, Berg SK, Hansen TB, Risom SS, Rasmussen TB, Hassager C, et al. Effect of
15
16 comprehensive cardiac rehabilitation after heart valve surgery (CopenHeartVR): study protocol for
17
18 a randomised clinical trial. *Trials* 2013; Apr 22;14(1):104.

19
20
21
22 53. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III
23
24 Consensus recommendations for the management of erectile dysfunction and cardiovascular
25
26 disease. *Mayo Clin Proc* 2012; Aug;87(8):766-78.

27
28
29
30 54. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European
31
32 guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint
33
34 task force of the European society of cardiology and other societies on cardiovascular disease
35
36 prevention in clinical practice (constituted by representatives of nine societies and by invited
37
38 experts). *Int J Behav Med* 2012; Dec;19(4):403-88.

39
40
41
42 55. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary
43
44 prevention through cardiac rehabilitation: from knowledge to implementation. A position paper
45
46 from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention
47
48 and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; Feb;17(1):1-17.

49
50
51
52 56. Berg SK. *Comprehensive rehabilitation for patients with ICD: PhD dissertation*. [Aarhus]:
53
54 Faculty of Health Sciences, Aarhus University; 2011.

1
2
3
4 57. Zwisler AD, Soja AM, Rasmussen S, Frederiksen M, Abedini S, Appel J, et al. Hospital-based
5
6 comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure,
7
8 ischemic heart disease, or high risk of ischemic heart disease: 12-month results of a randomized
9
10 clinical trial. *Am Heart J* 2008; Jun;155(6):1106-13.

11
12
13
14 58. Ashworth NL, Chad KE, Harrison EL, Reeder BA, Marshall SC. Home versus center based
15
16 physical activity programs in older adults. *Cochrane Database Syst Rev* 2005; Jan
17
18 25;(1)(1):CD004017.

19
20
21 59. Oerkild B, Frederiksen M, Hansen JF, Simonsen L, Skovgaard LT, Prescott E. Home-based
22
23 cardiac rehabilitation is as effective as centre-based cardiac rehabilitation among elderly with
24
25 coronary heart disease: results from a randomised clinical trial. *Age Ageing* 2011; Jan;40(1):78-85.

26
27
28
29 60. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-
30
31 81.

32
33
34
35 61. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, et al. Resistance
36
37 exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement
38
39 from the American Heart Association Council on Clinical Cardiology and Council on Nutrition,
40
41 Physical Activity, and Metabolism. *Circulation* 2007; Jul 31;116(5):572-84.

42
43
44
45 62. Lampman RM, Knight BP. Prescribing exercise training for patients with defibrillators. *Am J*
46
47 *Phys Med Rehabil* 2000; May-Jun;79(3):292-7.

48
49
50
51 63. Dorey G, Glazener C, Buckley B, Cochran C, Moore K. Developing a pelvic floor muscle
52
53 training regimen for use in a trial intervention. *Physiotherapy* 2009; Sep;95(3):199-209.

1
2
3
4 64. Parse RR. *The human becoming school of thought: a perspective for nurses and other health*
5
6 *professionals*. Thousand Oaks, Calif.: Sage; 1998.
7

8
9
10 65. Tibaek S, Klarskov P, Lund Hansen B, Thomsen H, Andresen H, Schmidt Jensen C, et al.
11
12 Pelvic floor muscle training before transurethral resection of the prostate: a randomized, controlled,
13
14 blinded study. *Scand J Urol Nephrol* 2007;41(4):329-34.
15

16
17 66. Schüssler B. *Pelvic floor re-education: principles and practice*. London: Springer; 1994.
18

19
20 67. Mezzani A, Agostoni P, Cohen-Solal A, Corra U, Jegier A, Kouidi E, et al. Standards for the
21
22 use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report
23
24 from the Exercise Physiology Section of the European Association for Cardiovascular Prevention
25
26 and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2009; Jun;16(3):249-67.
27
28

29
30 68. Ware JE, Kosinski M, Gandek B. SF-36 Health Survey.: Manual and Interpretation guide
31
32 2005;The Health Institute, New England Medical Center, Boston, Massachusetts.
33

34
35 69. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;
36
37 Jun;67(6):361-70.
38
39

40
41 70. Drummond MF. *Methods for the economic evaluation of health care programmes*. 3rd edition
42
43 ed. Oxford: Oxford University Press; 2005.
44
45

46
47 71. Rubio-Aurioles E, Sand M, Terrein-Roccatti N, Dean J, Longworth J, Eardley I, et al. Female
48
49 Assessment of Male Erectile dysfunction detection scale (FAME): development and validation. *J*
50
51 *Sex Med* 2009; Aug;6(8):2255-70.
52
53
54
55
56
57
58
59
60

1
2
3
4 72. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Extending the
5
6 CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and
7
8 elaboration. *Ann Intern Med* 2008; Feb 19;148(4):295-309.
9

10
11 73. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards
12
13 for testing and training: a statement for healthcare professionals from the American Heart
14
15 Association. *Circulation* 2001; Oct 2;104(14):1694-740.
16
17

18
19 74. Jugdutt BI, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave
20
21 myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll*
22
23 *Cardiol* 1988; Aug;12(2):362-72.
24
25

26
27 75. Giannuzzi P, Tavazzi L, Temporelli PL, Corra U, Imparato A, Gattone M, et al. Long-term
28
29 physical training and left ventricular remodeling after anterior myocardial infarction: results of the
30
31 Exercise in Anterior Myocardial Infarction (EAMI) trial. EAMI Study Group. *J Am Coll Cardiol*
32
33 1993; Dec;22(7):1821-9.
34
35

36
37 76. Otsuka Y, Takaki H, Okano Y, Satoh T, Aihara N, Matsumoto T, et al. Exercise training
38
39 without ventricular remodeling in patients with moderate to severe left ventricular dysfunction early
40
41 after acute myocardial infarction. *Int J Cardiol* 2003; Feb;87(2-3):237-44.
42
43

44
45 77. Pavy B, Iliou MC, Meurin P, Tabet JY, Corone S, Functional Evaluation and Cardiac
46
47 Rehabilitation Working Group of the French Society of Cardiology. Safety of exercise training for
48
49 cardiac patients: results of the French registry of complications during cardiac rehabilitation. *Arch*
50
51 *Intern Med* 2006; Nov 27;166(21):2329-34.
52
53

1
2
3
4 78. Savovic J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study
5 design characteristics on intervention effect estimates from randomized, controlled trials. *Ann*
6
7
8 *Intern Med* 2012; Sep 18;157(6):429-38.

9
10
11 79. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias
12 in treatment effect estimates in controlled trials with different interventions and outcomes: meta-
13
14 epidemiological study. *BMJ* 2008; Mar 15;336(7644):601-5.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49**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

1				
2				
3	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
4				
5				
6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
7				

8 **Methods: Assignment of interventions (for controlled trials)**

9 Allocation:

10				
11				
12	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
13				
14				
15				
16				
17				
18	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
19				
20				
21				
22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15-16
23				
24				
25	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
26				
27				
28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Na
29				
30				
31				

32 **Methods: Data collection, management, and analysis**

33				
34	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
35				
36				
37				
38				
39		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
40				
41				
42				
43				
44				
45				

1				
2				
3	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
4				
5				
6				
7	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
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
11				
12		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
13				
14				
15				
16	Methods: Monitoring			
17				
18	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
19				
20				
21				
22				
23		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
24				
25				
26	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
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
30				
31				
32				
33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
36				
37				
38	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
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				



1				
2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Na
7				
8				
9	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
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
13				
14				
15	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
16				
17				
18	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
19				
20				
21	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
22				
23				
24				
25				
26		31b	Authorship eligibility guidelines and any intended use of professional writers	19
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Na
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Na
33				
34				
35	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
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

*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.

For peer review only

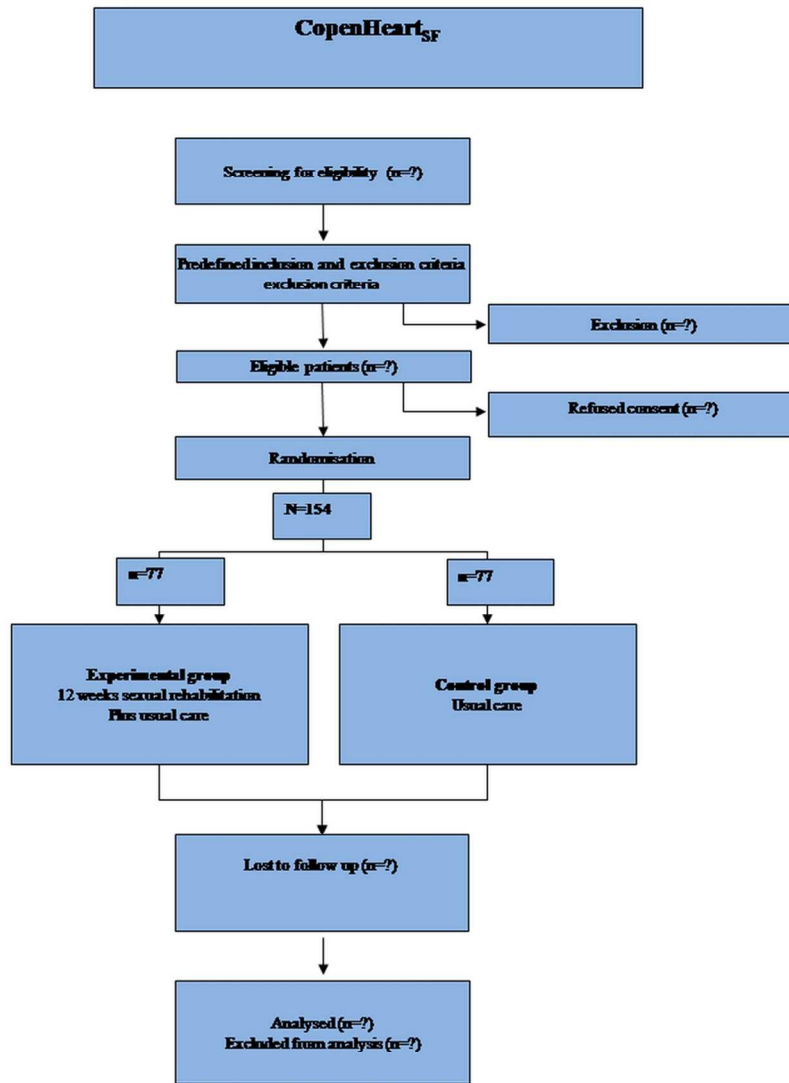


Figure 1. Flowchart

Flowchart
90x119mm (300 x 300 DPI)