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PhD Thesis

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Sexual rehabilitation in male patients with heart disease

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Papers included in this thesis:

Paper 1: High prevalence of sexual dysfunction among male patients with Implantable Cardioverter Defibrillator - a cross sectional questionnaire study. Manuscript

Pernille Palm Johansen, Ann-Dorthe Zwisler, Jesper Hastrup Svendsen, Annamaria Giraldi, Marianne Linnet Rasmussen, Selina Kikkenborg Berg

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Paper 3: Sexual rehabilitation improves sexual function in male cardiac patients with impaired sexual function – results from the randomised CopenHeart$_{SF}$, clinical trial. Manuscript

Pernille Palm Johansen, Ann-Dorthe Olsen Zwisler, Jesper Hastrup Svendsen, Lau Casper Thygesen, Annamaria Giraldi, Karina Gregersen Jensen, Jane Lindschou, Per Winkel, Christian Gluud, Elaine Steinke, Selina Kikkenborg Berg

Paper 4: A place of understanding: Patients' lived experiences of participation in a sexual rehabilitation programme after heart disease – CopenHeart $_{SF\text{-}QUAL}$.

Manuscript

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PREFACE

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Søllerød, September 2017

Pernille Palm

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ABBREVIATIONS

ATP: Antitachycardia pacing

cGMP: Cyclic guanosine monophosphate

CI: Confidence interval

CRT-D: Cardiac Resynchronization Therapy Defibrillator

EQ-5D-3L: The Euro Quality of Life (EuroQoL)

HADS: Hospital Anxiety and Depression Scale

ICD: Implantable cardioverter defibrillator

IHD: Ischaemic heart disease

IIEF: International Index of Erectile Function

MCID: Minimal Clinically Important Difference

MI: Myocardial infarction

OR: Odds ratio

PAIS: Psychosocial Adjustment to Illness Scale

PDE5: Phosphodiesterase5

PROMs: Patient-reported outcome measures

RCT: Randomised controlled trial

SCD: Sudden cardiac death

SD: Standard deviation

Sexual Function (SF)

SF36-MCS: Short Form-36, Mental Component Score

SF36-PCS: Short Form-36, Physical Component Score

Qualitative data (Qual)

Quantitative data (QUAN)

BRIEF INTRODUCTION

The focus of this thesis is on sexual dysfunction in male patients with heart disease, the extent of sexual dysfunction and the treatment for it.

Sexual dysfunction is common in patients with heart disease and often it has a negative impact on quality of life and overall well-being. Evidence exists that patients with ischaemic heart disease (IHD) suffer from a high degree of sexual dysfunction. Further, it is evident that sexual problems are common in patients with implantable cardioverter defibrillator (ICD), though results need to be expanded. Systematic approaches for treatment of sexual dysfunction in the clinical setting are lacking and besides the efficient and safe treatment with PDE5 inhibitors, several non-pharmacological treatment options e.g. physical exercise, pelvic floor exercise, and sexual counselling have been tested as single components for improving sexual dysfunction but has not been evaluated combined.

The overall aim of the thesis was to expand and consolidate existing knowledge regarding sexual dysfunction and the treatment of sexual dysfunction in populations of patients with IHD or ICD.

In order to achieve the aim, the CopenHeart Sexual Function (SF) project was developed. The CopenHeart SF project consists of the CopenHeart SF trial, a randomised controlled trial plus supporting quantitative and qualitative data. The CopenHeart SF trial is the cornerstone of the CopenHeart SF project.

Our objectives were: to evaluate the prevalence of sexual dysfunction and it's associating factors in patients with ICD and to evaluate and describe the meaning of a sexual rehabilitation programme.

Three studies with different research methodologies were conducted in order to achieve the objectives: 1) a cross-sectional survey to describe the prevalence and distribution of sexual dysfunction among male patients with ICD (study 1), 2) a randomised controlled trial and 3) a qualitative interview study, both (Study 2 + 3) with the purpose of evaluate and describe the effect and meaning of a sexual rehabilitation programme.

BACKGROUND AND INTRODUCTION

The following section describes the definition of sexuality, the characteristics of sexual dysfunction in patients with heart disease including a description of the normal function of the erection. Further, this section contains a description of the treatment offered and the evidence supporting this, and finally a rationale for conducting this CopenHeart SF project.

Definition of sexuality

Sexuality is an important part of human life and being able to function sexually has a tremendous influence on quality of life and overall well-being. The most comprehensive definition of sexuality is the one given by the World Health Organization:

…..a central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious and spiritual factors.[1]

This definition illustrates that sexuality is expressed in a unique and personalized manner and furthermore, that sexuality is related, but not limited, to sexual intercourse. Moreover, it points out that being able to function sexually involves several factors, both internal and external. The definition also expresses how vulnerable a healthy sexuality is, and that the occurrence of problems and dysfunctions can negatively impact the quality of life and overall well-being.

Sexual dysfunction in patients with heart disease

It is well known that there is a strong association between heart disease and sexual dysfunction, reflected by either reduced sexual activity or reduced ability to perform sexual activity.[2-5] Male sexual dysfunctions is divided into disorders in relation to desire and ejaculation as well as orgasmic and erectile function.[6] The most common sexual disorders among men are premature ejaculation and erectile dysfunction, the latter defined as the persistent inability to obtain or maintain an erection which enables satisfying sexual activity.[6] The causes of erectile dysfunction

can be classified mainly as organic, with a vascular, hormonal or neurogenic etiology, or psychogenic with an etiology connected to psychiatric disorders, psychological problems, interpersonal problems or concerns related to somatic disease, or a combination of both. Furthermore, it may appear as a side effect of medication.[7] It has been hypothesized that the endothelial dysfunction caused by atherosclerosis contributes to erectile dysfunction.[8] In addition, factors such as age, smoking, hyperlipidemia and obesity are associated with a higher incidence of erectile dysfunction.[2-4]

To understand the rationale for our project the normal mechanism of the erection of the penis is described shortly. Erection of the penis is a hemodynamic phenomenon, which includes a complex interaction between the central nervous system and peripheral factors. As a result of sexual stimulation, nitric oxide is released locally from the endothelial cells and activates the cyclic guanosine monophosphate (cGMP), which leads to relaxation of the corpus cavernosa and the penile arteries. This results in, an increased blood flow, expansion of the corpus cavernosum, blocking of the venous return and activation of the erection.[9] The pelvic floor muscles are also activated during erection. Both the ischiocavernosus and bulbocavernosus muscles are superficial pelvic floor muscles that are active during erection and they enhance rigidity. The bulbocavernosus muscle encircles 33–50% of the base of the penis.[10]

Psychogenic factors are believed to be significant for 10% to 30% of patients in sexual dysfunction and include concerns, depression and anxiety, all mental states which are often seen in patients with heart disease.[11,12] One study has shown that male patients who have lost the ability to get an erection during the last year have a significantly lower quality of life than those with normal erectile function.[13] Partners of patients with cardiovascular disease often have considerable concerns and anxiety about sexual activity with a potential adverse impact on the sexual activity of the couple.[14-16] Various medications like spironolactone, thiazides and beta-blockers, as well as some antihypertensive medication have favorable prognostic effect in patients with heart disease, but also increase the risk of developing erectile dysfunction.[17] Furthermore drugs used to treat erectile dysfunction may adversely interact with drugs used to treat heart disease.[17]

Patients with ischaemic heart disease (IHD) and patients with implantable cardioverter defibrillator (ICD), which are two large and growing patient populations, are especially affected.[14,18,19]

Sexual function in patients with ischaemic heart disease

Ischaemic heart disease is the most common type of cardiovascular disease and covers three conditions: stable angina, unstable angina and myocardial infarction.[20] In Denmark the incidence is nearly 18.000 per year.[21] Typically, IHD occurs as a consequence of coronary atherosclerosis. Atherosclerosis begins with damage to the endothelium that leads to the formation of plaque causing symptoms of angina or myocardial infarction.

Epidemiological studies and reviews, estimate the prevalence of erectile dysfunction in patients with IHD to be between 39% and 74%.[18,22-24] A study comparing older men with and without IHD, observed an increased prevalence of erectile dysfunction of 85% in those with IHD compared to 72% in those without heart disease.[25] Montorsi et al.[18] found the prevalence of erectile dysfunction among 300 male patients with IHD to be 49 % and erectile dysfunction was scored as mild, mild to moderate, moderate and severe in 21 (14%), 31 (21%), 20 (14%), and 75 (51%) of patients, respectively. Anxiety, sexual fear, reduced desire, and overprotectiveness and sexual fear from partners are commonly described in patients with IHD.[12,26] Fear of chest pain, another myocardial infarction (MI) or death during sexual activity are also common concerns, all though the risk of having a MI during sexual activity is less than 1 percent in patients with a previous acute MI.[27]

Sexual function in patients with ICD

An ICD is an implanted device that detects and treats abnormal ventricular tachyarrhythmias by antitachycardia pacing (ATP) therapy or high voltage shock therapy. Left untreated these arrhythmias can lead to sudden cardiac death (SCD). In Denmark 1700 ICDs are implanted every year.[28] Over the last 20 years treatment with ICD has reduced mortality markedly and guidelines for the use of ICDs have been developed.[29] ICD recipients are a heterogeneous group. Their diagnostic and co-morbidity profiles differ a lot; from young people genetically at risk of SCD with no prior symptoms to elderly patients with a history of heart disease and a large symptom burden.

Indication for ICD implantation can be divided into primary prophylactic (e.g. if the patient not previously has suffered from cardiac arrest, but is expected to be at high risk for life-threatening arrhythmias) versus secondary prophylactic (e.g. if the patient had previously suffered from a cardiac arrest). The index event leading to an ICD may have important impact on patients' psychological well-being and this is especially so if a cardiac arrest is the initial experience. See Textbox 1. for descriptions of definitions of the different types of ICDs and treatment from the ICD.

In ICD patients several small studies have revealed long term abstinence from or a decrease in sexual activity after the ICD implantation.[14,19,30,31] Besides erectile dysfunction, sexual problems in ICD patients have been described as overprotectiveness from the partner, lack of sexual interest, fear of death if the ICD did not fire, or fear of the ICD shock therapy.[14,19,32] Shock during sexual activity is experienced in varying frequencies from less than 1% to 18%.[14,19,33] Although shocks are infrequent, fear of the ICD firing during sexual activity seems to have a more profound impact as this is experienced in almost 30%.[14,19] Moreover, studies show that therapy, such as ATP therapy or shock therapy from the ICD may predict a poor psychological outcome,[34-36] however, we do not know if this is reflected on sexual function as well.

The majority of data on the subject have been collected using the same questionnaire instrument "The sex after ICD questionnaire", that has been developed especially for ICD patients.[14] The instrument provides a thorough overview of the patient's potential sexual problems, however it has not been developed to detect trends over time and evaluate the results of an intervention. Moreover, the instrument does not reflect the clinical definition of male sexual dysfunction which allows for comparison between other diagnostic groups. Finally, it does not cover the severity of erectile dysfunction. Therefore new projects in the field should be expanded to include knowledge regarding potential association related to therapy from the ICD and a thorough description of sexual dysfunction with at validated instrument.

Textbox 1. Definitions of the different types of ICDs and treatment from the ICD

Primary Prophylactic Indication ICD: Primary prevention prophylaxis ICD implantation is indicated in populations at high risk of sudden cardiac death due to ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT).

Secondary Prophylactic Indication ICD: For secondary prophylaxis, ICD placement is indicated as initial therapy in survivors of cardiac arrest due to VF or hemodynamically unstable VT.

Appropriate antitachycardiapacing (ATP): Antitachycardiapacing on a malign arrhythmia e.g. ventricular tachycardia.

Inappropriate antitachycardiapacing (ATP): Antitachycardiapacing on a benign arrhythmia e.g. a fast atrial fibrillation or as a consequence of device problems.

Appropriate Shock: High voltage shocks targeted a malign arrhythmia.

Inappropriate Shock: High voltage shock targeted a benign arrhythmia or device problems.

Standard treatment of sexual problems in patients with heart disease

Despite the fact that several international guidelines recommend that healthcare professionals address sexuality and potential sexual problems in patients with heart disease[27,37] this is rarely done in practice.[38] Consensus or agreed 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.[27] The PDE5 inhibitors have an overall success rate of 50% to 80% of those treated in patients with cardiovascular disease.[27,39,40] 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[27,40] and PDE5 inhibitors are generally considered safe. In patients with heart disease and no effect of PDE5 inhibitors or where PDE5 inhibitors are contra-indicated because of treatment with nitrates, there seems to be no consensus on what treatment should be offered for sexual dysfunction.

Non-pharmacological treatment potentials

Non-pharmacological interventions possess potential for reducing sexual dysfunction. Lifestyle factors such as; cigarette smoking, hyperlipidemia, and a sedentary lifestyle all predict erectile dysfunction[2,4] and these are the same risk factors that predict IHD. A meta-analysis of six

randomised trials including 740 patients with no known heart disease showed that lifestyle modifications such as physical exercise and pharmacotherapy for cardiovascular risk factors were associated with a significant improvement in erectile function.[41] A systematic review and meta-analyses evaluating the effect of physical exercise on erectile function found that in 478 patients (7 trials included) physical exercise improved erectile function measured by the International Index of Erectile Function (IIEF) with a mean difference of 3.85, 95% CI: 2.3-5.37.[42] Only one of the included trials involved patients with heart disease, the only one which did not detect a statistically significant improvement. The risk of bias in this trial was assessed as medium to high mainly due to issues related to randomisation, blinding of patients, personnel and outcome assessment. Randomised trials that address the psychological aspects of sexual dysfunction are limited in patients with heart disease. A recent Cochrane systematic review identifies only three studies that include a sexual counselling intervention in patients with a history of myocardial infarction, and found a clear need for methodologically rigorous and adequately powered randomised controlled trials.[43] The role of pelvic floor exercises as a treatment of erectile dysfunction has not been tested on patients with heart disease, but in the general population 40% to 47% had regained normal erectile function after 3-4 month of training the pelvic floor muscles.[10,44]

Evidence summary and trial rationale

Overall, it is evident that a large proportion of patients with IHD and patients with ICD suffer from sexual dysfunction and that a systematic clinical approach to these patients is lacking.

Further, it is evident that sexual problems and dysfunction in ICD patients is present, however, research needs to be expanded to include more robust instruments, and potential associations with sexual dysfunction identified.

Besides the efficient and safe treatment with PDE5 inhibitors, the evidence points towards non-pharmacological treatment options. Studies have shown that it is important to establish therapy or counselling to address the psychosocial aspects of sexual dysfunction. Moreover, trials have shown that lifestyle changes and especially physical exercise may improve sexual function, however as the trials were poorly designed, the evidence supporting these interventions is still weak. It is crucial that the evidence base on sexual dysfunction be expanded and that a clinical

intervention program based on the evidence on potentially effective components is developed and tested in these patients. Physical training, pelvic floor exercise and sexual counselling have been tested as single components with positive outcomes in relation to sexual dysfunction. In general, comprehensive cardiac rehabilitation, combining physical and mental components have proved to be particularly effective.[45,46] An intervention aimed at both the organic and the psychogenic factors impairing sexual function has not been tested in a well-designed randomised clinical trial in patients with ICD and patients with IHD. We hypothesize that an intervention consisting of physical training, pelvic floor exercises and sexual counselling will improve sexual function in patients with sexual dysfunction and either IHD or ICD.

OBJECTIVES

The overall aim of the thesis was to expand and consolidate existing knowledge regarding sexual dysfunction and the treatment of sexual dysfunction in populations of patients with IHD or ICD.

In order to achieve the aim the CopenHeart SF project was developed (see Figure 1.). The CopenHeart SF project consists of the CopenHeart SF trial, a randomised clinical trial plus supporting quantitative and qualitative data. The CopenHeart SF trial is the cornerstone of the CopenHeart SF project.

Our objectives were: to evaluate the prevalence of sexual dysfunction and it's associating factors in patients with ICD and to evaluate and describe the effect and meaning of a sexual rehabilitation programme.

Three studies with different research methodologies were conducted in order to achieve the objectives:

STUDY 1: Cross-sectional survey study (Paper 1)

- To describe the prevalence and types of sexual dysfunction among ICD patients
- To evaluate whether implantation indication and therapy from the ICD is associated with sexual dysfunction in the population.

STUDY 2: The CopenHeart$_{SF,}$ randomised clinical trial (Paper 2+3)

- To investigate the effect of a comprehensive sexual rehabilitation programme, combining physical exercise training, pelvic floor exercises and psycho-education for male patients with erectile dysfunction and IHD and/or ICD.

STUDY 3: The CopenHeart$_{QUAL}$, a qualitative interview study (Paper 4)

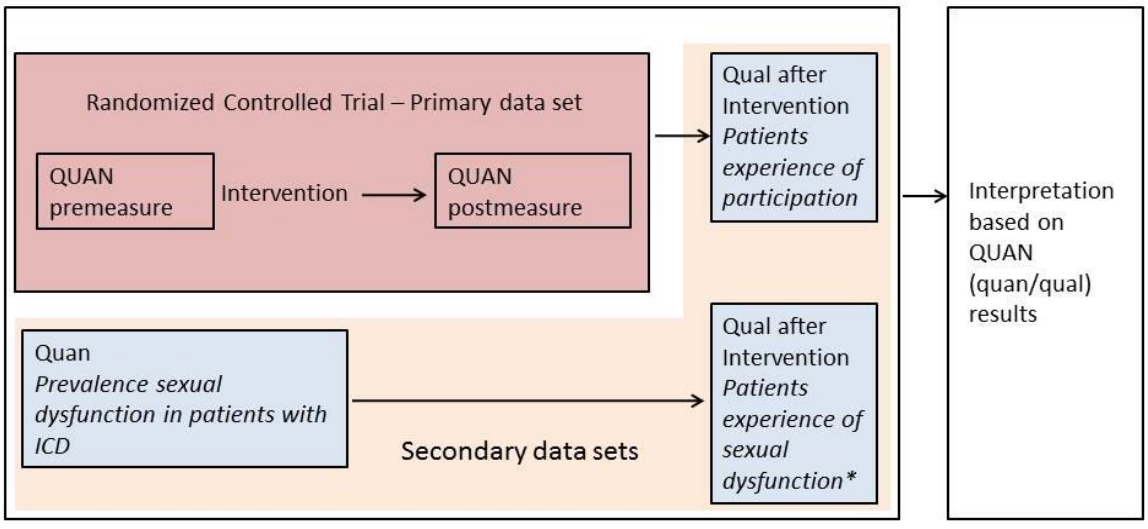
- To explore the lived experiences of participating in a non-pharmacological sexual rehabilitation intervention.

METHODS

The first part of this section presents and elaborates on the overall design, outcomes and data used in the thesis. The more specific methods used in the different studies are described in separate sections.

To describe the prevalence of sexual dysfunction and it's associating factors in patients with ICD and to evaluate and describe the effect and meaning of a sexual rehabilitation programme the mixed methods embedded experimental design was applied (Figure 1)[47]. The premise of the mixed methods design is that a single data set is not sufficient, and that different research questions require different approaches[47]. The embedded design consists of several distinct phases in which one type of data, secondary data qualitative data (Qual) and quantitative data (Quan), provides a supportive secondary role in a study based on primarily quantitative data (QUAN). In the CopenHeart SF trial we collected and analyzed the primary quantitative data (QUAN) in a RCT and the secondary qualitative data (Qual) and quantitative data (Quan) were collected and analyzed to support the findings, and thereby the secondary data helped explain the findings from the primary data. The rationale for this approach is that the combination of the two data sets provides a more general understanding of the research question. And thereby the results from the secondary qualitative data analysis and quantitative data supplement nuance and explain the statistical results from the RCT.

Figure 1. Trial design CopenHeart SF project



* These data are not included in the thesis

In the ideal academic world, the study regarding the prevalence of sexual dysfunction in patients with ICD and the qualitative study about patients experience (not included in this thesis) should be performed before beginning the trial, however; due to the three year timeframe of a PhD project the studies were performed simultaneously.

Quantitative outcomes

When assessing erectile function and dysfunction, objective clinical outcomes such as penile Doppler, endothelial function, maximum oxygen uptake and pelvic floor strength and endurance can be used[48-50]. These outcomes however are of little use if the desired outcome of interest is how satisfactory the sexual capacity is to a person. As sexuality is a very private domain, the sexual functioning of an individual can only be reported by the individual itself. Thus, measuring sexual function and dysfunction is predominantly performed by patient-reported outcome measures (PROMs)[51]. PROMs are characterized as being tools investigating patients' subjective perception of a phenomenon, e.g., disease specific symptoms or functional capacity. PROMs usually come in the form of standardized self-administered questionnaires, which can yield numerical scores and thus quantifiable results. When using PROMs it is important to choose ones documented to produce valid and reliable results that have ideally been tested in the language and the population in which they are intended to be used. The quality of a PROM is typically assessed by its validity and reliability and if measuring change over time, also its responsiveness. Validity refers to whether the questionnaire measures the phenomena it is designed to, reliability refers to the consistency with which the intended phenomena is measured and responsiveness is the PROM's ability to detect a change over time[52,53]. The PROMs most commonly used to measure sexual dysfunction have been developed for assessing male function across a variety of sexual domains (*e.g.* erectile function, desire, arousal, orgasm, and satisfaction).[54] Diaries and event-logs are other tools used.[54] In the clinical setting results from self-reported measures are supplemented with a thorough sexual history including external influencing factors, potential relationship issues, timeframe for the sexual problem, morbidities and co-morbidities.[55]

PROMs used in the thesis

The International Index of Erectile Function (IIEF) was chosen as the primary outcome in two of the manuscripts. The IIEF was developed in conjunction with the clinical trial program for

sildenafil, and has since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of erectile dysfunction. It has been linguistically validated in 32 languages and used as a primary endpoint in more than 50 clinical trials.[56,57] It consists of 15 items including five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, which are based on patients experiences during the last four weeks. Higher scores indicate a better sexual function. The total IIEF-15 summary score (minimum 5 points, maximum 75 points) is categorized as "good" (60–75), "fair" (44–59), and "poor" (5–43).[58] The erectile function domain has a cut-off score to diagnose and divide erectile dysfunction into four levels of severity: severe erectile dysfunction scores 6-10, moderate erectile dysfunction scores 11-16, moderate to mild erectile dysfunction scores 17-21, mild erectile dysfunction scores 22-25 and scores above 25 indicates no dysfunction. For the other domains a dysfunction was determined if scores were: 8 or less for the orgasmic function domain, the sexual desire domain, and the overall satisfaction domain and a score of 12 or less for the intercourse satisfaction domain.[59] The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of sensitivity and specificity, and has demonstrated consistent and robust treatment responsiveness.[57] A Minimal Clinically Important Difference (MCID) score has been evaluated for the erectile function domain to be 4.[57] The MCID is the smallest change in an outcome that patients would identify as important. MCIDs varied significantly according to baseline erectile dysfunction severity (mild erectile dysfunction: score of 2; moderate erectile dysfunction: score of 5; severe erectile dysfunction: score of 7).[60]

The sexual adjustment to illness was measured by the Psychosocial Adjustment to Illness Scale self-reported version (PAIS)[61] sexual relationship domain. The overall PAIS measures psychosocial adjustment to illness in terms of seven domains of adjustment: Health Care Orientation, Vocational Environment, Domestic Environment, Sexual Relationships, Extended Family Relationships, Social Environment and Psychological Distress. The PAIS meets psychometric criteria for test reliability and validity.[61] The sexual relationship domain evaluates shifts in the quality of sexual relationship due to the current illness; however, its responsiveness has not been tested. It consists of six items and the total score ranges from 0 to 18. Low score indicates good adjustment.

Qualitative data

Another widely applied method to access patients' views and experiences related to sexual health is qualitative research.[62] The most frequently used in health care research are qualitative research interviews. Interview studies can be performed within a variety of different scientific frameworks and methodologies, within which there are different approaches to data collection and analysis.[63] One of the most common approaches is the semi-structured interview, where a pre-prepared interview guide is used to acquire knowledge about a specific area of interest. The interview can be carried out in focus groups, family dyads, or with individuals face-to-face. After data-collection, interviews are analyzed and compiled into themes describing the patients' perspective of the phenomenon.[62] We performed ten individual face-to-face interviews and a thorough description of the method is described on page 24.

Methods used in study I: A Cross-sectional survey study (Paper 1)

This section describes the methods including, choice of design, population, outcome measures and statistical analysis in the study regarding prevalence of sexual dysfunction and associations in patients with ICD.

Design and population

To gain knowledge about the prevalence and distribution of sexual dysfunction in male patients with ICD, a cross-sectional postal survey was conducted. The questionnaires were collected when patients where approached for participation in the CopenHeart$_{SF}$ trial.[64] Male patients with an ICD were recruited from two University Hospitals in the Danish Capital Region. Inclusion criteria were males above the age of 18 with an ICD and minimum one year post-implantation. Exclusion criterion was no partner.

Outcome measures

Prevalence and distribution of sexual function was measured by the Danish version of the IIEF,[56] see page 18 for further information. In order to investigate whether implantation indication or ATP or shock from the ICD was associated with a poor sexual outcome, data on implantation indication (primary/secondary prevention) and therapy such as ATP and shock (both appropriate and inappropriate) was obtained from the Danish ICD Register.[65]

Statistical analysis

Data was tested for normality using the Kolmogorov-Smirnov test. Continuous data were presented as mean scores with corresponding standard deviation and compared using either Student's *t*-test or the Mann-Whitney depending on the normal distribution. Proportions were compared with the chi-square test. Responders were compared with non-responders according to demographic variables. For each analysis, persons with missing information on the included variables were excluded. Logistic regression was used to explore associations of ATP therapy and shock therapy, and whether primary or secondary prophylactic indication had the greatest implication. Age adjusted univariate analyses were performed with the four variables, ATP therapy, shock therapy, time since ICD and indication, and as a multivariate analysis with age, ATP therapy, and time since ICD and indication.

Methods used in study II: Randomised clinical trial: Study design and outcome (Paper 2+3)

This section describes the method, design and intervention in the CopenHeart SF trial.

Trial design and population

The CopenHeart$_{SF}$ trial was a two centre randomised clinical trial.[64] The randomised controlled design was applied and reported according to the CONSORT guidelines for non-pharmacological trials.[66] The CONSORT guidelines consist of a checklist and flow diagram that seek to address adequate reporting of randomised controlled trials, securing validity and applicability of the results.

The study complied with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (j.nr. 2007-58-0015) and has been approved by the Regional Ethics Committee (j.nr. H-4-2012-168). The CopenHeart$_{SF}$ trial is registered at ClinicalTrials.gov (NCT01796353).

Inclusion criteria: Male patients above 18 years of age with erectile dysfunction with implantable cardioverter defibrillator or with ischemic heart disease verified by coronary angiography, who had a partner, spoke and understood Danish, and provided a written informed consent were considered eligible for participation.

Exclusion criteria: cardiovascular status according to recommendations from the Princeton consensus group,[67,68] those with diseases of the urinary tract, those who performed intense exercise more than three hours per week, patients with neurological or orthopedic deficits which prevented training, patients with cognitive deficits which prevented consultations and patients who were included in on-going research prohibiting additional research participation.

Recruitment, randomisation and blinding

Patients received the IIEF questionnaire[56] by mail including a stamped return envelope. Patients with a score ≤ 25, the accepted cut-off score for erectile dysfunction[57] on the initial screening, were invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems.

Participants were randomised 1:1 to intervention or control by a computer-generated allocation sequence with a varying block size and were stratified according to patient group (IHD or ICD) and age (≤59 or ≥60 years). Randomisation allocation was performed centrally at the Copenhagen Trial Unit and revealed by telephone contact to the trial investigator.

All physical testing, data collection and statistical analyses was performed blinded to allocation group and participants were told not to reveal allocation group during visits. Questionnaires were completed electronically in the questionnaire system Enalyzer with 'single user', which meets the data legislation for logging. If patients did not complete the questionnaire electronically, the material was sent in paper form and independent trial personnel entered the responses into the database. Thus data management was handled independently from the researchers who interpreted the data.

Sexual rehabilitation

The experimental intervention was a comprehensive sexual rehabilitation program. Sexual rehabilitation in this trial was 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 intervention was a 12 week program including physical exercise, exercise training for the pelvic floor and psycho-educational consultations (see the timeline for the sexual rehabilitation and the outcome assessments in Figure 2).

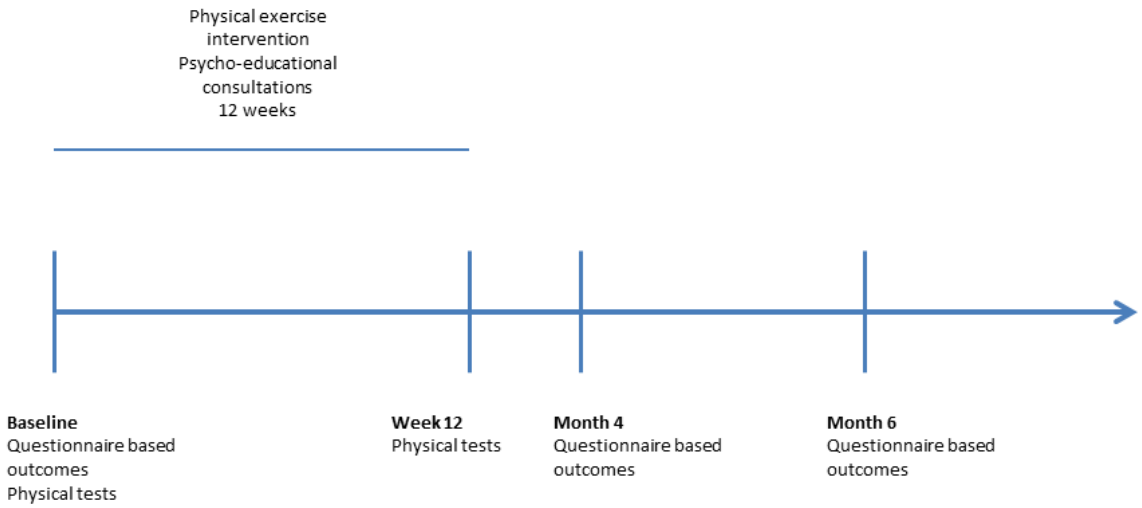


Figure 2. Timeline of the sexual rehabilitation programme including outcome assessment times

Physical exercise training

The aim of this part was to improve endothelia function, exercise capacity and to eliminate the fear and uncertainty the patient may feel in relation to sexual activity as a form of physical activity. Three weekly sessions were offered. A single training protocol was applied to all participants, but individualized when needed. The physical training intervention was initiated by the trial physiotherapists at hospital (The Heart Centre, Rigshospitalet) in accordance with relevant evidence[69], with 1-3 mandatory training sessions using t-shirts with wireless integrated ECG electrodes (Corus-Fit Cardio and Corus Exercise Assistant, CEA, V.2.0.16, Finland). For the continuing training program three options were available: 1) Supervised training at hospital; 2) Training at a local study-protocol certified supervised facility; and 3) Home-based training with contact with a physiotherapist when needed. The training program consisted of graduated cardiovascular training and strength exercises. The cardiovascular training was based on intensity on the Borg scale[70] and performed as interval training. The strength-related exercises primarily targeted the lower body muscles and comprised four exercises. See Table 1 for a description of the physical exercise program. The physical exercise programme in the CopenHeart$_{SF}$ trials meets the European[71] and the Danish guidelines[72] for physical exercise training in patients with heart disease. The physical exercise training consisted of 36 sessions, 3 weekly sessions for 12 weeks of 60 minutes. The sessions started with 10 min warm up bicycling followed by 20 min bicycling with

increasing intensity (interval training). This was followed by 20 min strength training and 10 min stretching exercises. To achieve cardiovascular adjustment and reduce the risk of cardiac arrhythmias and ischemia, the training sessions ended with a cool down period.

Table 1. The physical exercise program

Individual consultation with the physiotherapists Duration: 30 min	Introduction of the patient to the training diary and pulse watch Discussion of prior physical level Introduction to the training program Safety or co-morbidities issues Introduction to pelvic floor exercise program
Physical exercise program Duration and frequency: 12 weeks 60 min Three times per week In total 36 sessions	10 min warm up bicycling 20 min bicycling with increasing intensity (interval training) 20 min strength training 10 min stretching exercises

Pelvic floor exercise

The aim of the pelvic floor exercise intervention was to enhance the strength and endurance of the pelvic floor. Both the ischiocavernosus and bulbocavernosus muscles are superficial pelvic floor muscles that are active during erection and they enhance rigidity. The bulbocavernosus muscle encircles 33–50% of the base of the penis.[10] Patients were instructed to tighten their pelvic floor muscles as strongly as possible, two times a day: three times when lying, three times when sitting and three times when standing. The duration of the contraction was up to 10 seconds each, and patients were informed to have a 10 seconds break between each contraction.[73] The physiotherapist instructed the patients on how to contract the bulbocavernosus and ischiocavernosus muscles at the initial training session.

The psycho-educational consultations

The intervention took as its theoretical basis the patient-centered approach where the emphasis is on support and education. The consultations were based on a holistic view of the patient and the intervention was targeted at the modifiable parameters reported to affect sexual dysfunction. The psycho-educational intervention was inspired by RR Parse's 'Human Becoming Practice Methodologies' three dimensions,[74] which can be described as: 1. Discuss and give meaning to the

past, present and future, 2. Explore and discuss events and opportunities, and 3. Pursue imagined possibilities. According to this theory there are three ways to alter perceived health: Creative ideas, see, hear and feel how a situation could be if it was lived in a different way, recognizing personal patterns and value priorities and shedding light on the paradoxes by looking at incongruence in a situation and changing one's view of reality. The nurse is 'truly present' in the process through discussion, quiet contemplation and reflection. The psycho-educational intervention plus physical exercise was tested in COPE-ICD trial, with positive effects on psychological well-being (mental health) and general health sub-scale of the SF-36.[45] The nurse was trained in psycho-educational conversation through teaching and supervision of nurses who had experience with Parse's practice methodology from COPE-ICD trial. It is based on the theoretical literature that forms the basis for understanding the processes of practice methodology and existing specialty specific knowledge about heart disease, related symptoms and sexology. The supervisor observes and provides feedback in relation to the conversation's methods and goals. The emphasis is on openness in the interviews, and on the nurse's ability to: be silent presence, while the patient speaks, ask questions that encourage reflection, let the patient think of possibilities and to contribute with knowledge, advice and guidance when demanded and asked for. The training of the nurse took place prior to the intervention. The intervention in practice was handled by one nurse (PPJ) with several years of experience working with cardiac patients and trained in sexology. The sexology experience was gained in a two week intensive course on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist was available during the intervention. The nurse conducted consultations with patients individually, and patients were informed that they were welcome to bring partners. The consultation took place in a quiet room in an outpatient setting and lasted for 45-60 minutes. An inspirational guide formed the basis for the consultations (Table 2). The guide consists of several topics to address and works as inspiration and sets the base for information, intervention and goals to achieve between the consultations.

Table 2. Inspirational guide for the consultations

Areas of sexual assessment
Cause and type of sexual dysfunction
Address sexual concerns (psychological/physical)
Current level of sexual activity
Types of sexual activities
Sexual problems
Associated co-morbidity
Medication review
Safety recommendations

Usual care

Participants followed their usual outpatient visits according to treatment guidelines.[37,75] If sexual dysfunction was of physical origin both groups were encouraged to contact their general practitioner for prescription of PDE5 inhibitor treatment if not contraindicated.[27]

Outcomes

Both groups underwent outcome assessment at baseline, at 12 weeks (physical tests) and at 4 months and at 6 months (questionnaire based data).

Primary outcome

Sexual function was measured by the total IIEF score[56] at baseline, after 4 and 6 months.

Secondary outcome

Sexual adjustment to illness was measured by the Psychosocial Adjustment to Illness Scale (PAIS)[61] sexual relationship domain at baseline, and after 4 and 6 months.

For information about primary and secondary outcome see page 17-18 for further description.

Exploratory outcomes

The exploratory physical outcomes are pelvic floor strength and endurance measured by the Danish version of the Modified Oxford Grading Scheme[76] and peak VO2, heart rate (beats per minute), blood pressure, power at maximum exercise (watt max), Anaerobic Threshold, and VE/VCO2 slope measured by cardiopulmonary ergometer testing, at baseline and after 12 weeks.

The questionnaire based exploratory outcomes are the five subdomains of the IIEF,[56,57] with special attention to the erectile function domain, Short From-36 (SF-36),[77-80] the Hospital Anxiety and Depression Scale (HADS),[81,82] and The Euro Quality of Life (EuroQoL) (EQ-5D-3L)[83,84] at baseline and after 4 and 6 months. The questionnaire "Sex after ICD"[14] was evaluated in ICD patients at baseline and after 4 and 6 months.

Statistical analysis

Sample size and power calculations

We planned a trial of the continuous variable IIEF[56] 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.[85] If the true difference in the experimental and control means was 3.5 points, we needed to include 77 experimental participants and 77 control participants (a total of 154 participants) to obtain a power of 95% (β=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 PAIS[61] and a type 1 error probability of 5%, the corresponding power for the secondary outcome was found to be 87%.

Analysis

The analysis followed the intention-to-treat principle with a two-sided significance test at the 5% level using the SAS version 9.3 and R version 3.1.2 for the analyses. The primary model for assessing the effect of intervention was the univariate general linear model. This model assesses whether there is an effect of the intervention 4 months after randomisation. Since there was a statistically significant effect, tests was performed to evaluate whether there was a difference between the two patient groups regarding the size of the effect. The secondary model included follow-up data using a mixed model because of repeated outcome measures. Sub-group analyses of the primary outcome and all analyses of the secondary and exploratory outcomes were considered hypothesis generating if the effects were statistically significant ($P<0.05$). If missing values of the primary outcome were above 15% or the p-value of Little's test was below 5% multiple imputation techniques was used. The analysis was supplemented with a best/worst case analysis. Cohen's d[86] was calculated for all continuous outcomes to test the clinical effect.[86]

All analyses were performed blinded to allocation group by a trial-independent statistician. In the final analyses the intervention group and the usual care group were coded A and B. Results was presented to the CopenHeart research group as group A and group B and conclusions were drawn, one that A was the intervention group and B the usual care group and then the opposite. Afterwards group allocation was revealed to the research group.

Adherence and safety

To encourage adherence, and monitor compliance, training diaries and pulse watches were used (Polar Watch, Polar HR RS 400 monitors, Polar Electro, Finland).
Cardiopulmonary exercise testing was performed by experienced personnel, and instructions for completion and termination was established according to guidelines.[87] All events were registered and evaluated with the trial physician.

Methods used in study III: Qualitative interview study (Paper 4)

This section describes the choices made in the qualitative study with regards to study design, population, methodological and theoretical considerations, as well as a description of the analysis.

Study design, methods and population

To elucidate the lived experience of participation in a sexual rehabilitation programme, an interview study with a phenomenological-hermeneutical approach was chosen. The phenomenological-hermeneutical approach is widely accepted and often applied within qualitative nursing research, as methods within this framework allows for interpretation related to a specific field of interest or a specific phenomenon.[88-91] The method were inspired by the French philosopher Paul Ricoeur's phenomenological-hermeneutic approach.[92,93] This approach places the study in line with several other studies inspired by the abovementioned theory.[91,94] According to Ricoeur, human experiences are indirectly expressed through language and require interpretation. By expressing meaning as it manifests itself around an individual's experiences with sexuality and heart disease, and with participation in a rehabilitation programme it becomes possible to gain insight into patients' concerns and needs in order to plan proper after care for patients with heart disease and sexual dysfunction.

The theoretical framework for the study reflects aspects of behavioral theory of social cognitive theory developed by the American psychologist Bandura and his concept of self-efficacy.[95,96] The social cognitive theory emphasizes that we as humans can decide how to behave, which is considered a cognitive process. Self-efficacy should be understood as the individual's own competence to carry out a given behavior. The self-efficacy concept is based on the premise that individuals can control their own thought processes, motivation and actions and are therefore also able to change themselves and their situations. According to Bandura, the perception of efficacy is influenced by four factors: mastery experience, vicarious experience, verbal persuasion, and somatic and emotional state.[96] Mastery experience is related to prior success at having accomplished something that is similar to the new behavior whereas vicarious experience is gained by watching someone similar to self to have success. Verbal persuasion is related to encouragement by others and somatic and emotional states reflect the physical and emotional states caused by thinking about undertaken a new behaviour.[96]

A purposive sample of 10 males with erectile dysfunction and either IHD or ICD were interviewed. Patients were all participants in the CopenHeart$_{SF}$ trial. Articulate and knowledgeable interviewees were chosen and variation was sought in relation to age, type of patient group, origin of erectile dysfunction, and setting for exercise training.[62] Sample size in qualitative research has been debated, yet, no firm conclusion or consensus seems to have reached. [63,97] As the aim of a qualitative study is to gain in depth individual based knowledge about a phenomena or a research area the questions asked in relation to sample size is rather: " do you have the experience I am looking for" rather that the strategies used in quantitative research. Creswell[63] describe that in phenomenological hermeneutical studies 5 to 25 individual is recommended. We believed that 10 participants would provide good insight into how the intervention was experienced, knowing that including more participants might have added more details.

Patients were approached after completing the sexual rehabilitation programme and included if written consent was provided after they had received information orally and in writing about the study's purpose, anonymity and voluntary participation.

Data collection

All patients underwent interview in an undisturbed office room at the hospital. A researcher not involved in the randomized controlled trial conducted the interviews. To assure consistency and openness a semi-structured interview guide was developed and used. The interview guide served as a framework to ensure that all subjects of interest were covered (see Table 3. for Interview guide). With the aim of gathering the patients' in-depth accounts of their lived experiences of participating in the programme, open questions were used, such as: 'Could you please tell me about your intentions of signing up for the programme?' and 'Could you please tell me about your experiences from the programme?' To provide reflections on participants' sexuality, questions relating their earlier experience were also applied and therefor the guide also included questions on the experience with sexual function. Data regarding the exoerience of sexual dysfunction is not reported in the thesis.

Table 3. Interview guide
The following open-ended questions were explored: Can you tell me about your experiences with your sexual function in relation to your heart disease? Can you tell me about the information you have received in relation to your heart disease and any potential sexual problems? Can you tell me about your thoughts about participating in a study targeting sexual problems? Can you tell me about your experiences of participating in the rehabilitation programme? How did you experience the different parts of the intervention? How was your sexuality affected by the rehabilitation programme?

Participants were allowed to talk about experiences they found important, and only when narratives wandered too far from the research question, the interviewer gently guided them back. Interviews were carried out in August and September 2016 and lasted between 45 and 75 minutes. Interviews were recorded and subsequently transcribed.

Analysis

Two researchers carried out the analysis separately and thereafter discussed the findings with each other. The analysis consisted of three levels: naïve reading, structural analysis, and critical interpretation and discussion.[92,93] In naïve reading the text are read separately several times to grasp the meaning as a whole. The material was approached from a phenomenological viewpoint, meaning that reading sought to be open in order to gain an overall naïve understanding of the participants' experiences. The naïve reading guides the following structural analysis. .[92,93] The first reflections about what is said are noted here. Structural analysis moves from what is being said to what is talked about. First the whole text were read and divided it into units of meaning separately (what is said about sexuality and heart disease and participating in rehabilitation programme). Secondly, the units of meaning were reflected up upon the naïve reading. This validation process seeks to verify that the interpretation is in accordance with the original spoken words. Afterwards, the units of meaning are discussed and condensed jointly and significant units were constructed (what is talked about). Finally the significant units are condensed into themes. A theme is a thread of meaning that penetrates text parts and identifies the essential meaning of a lived experience.[92,93] The themes were reflected upon against the background of the naïve reading to seek for validation or invalidation of the naïve understanding. When the structural analysis invalidated the naïve understanding, the text was read again and a new naïve understanding was formulated. This process was repeated until a consensus was reached. In the discussion, themes were compared and contrasted to related research, and the meaning was discussed.

Example of the structural analysis is presented in the result section for the qualitative study.

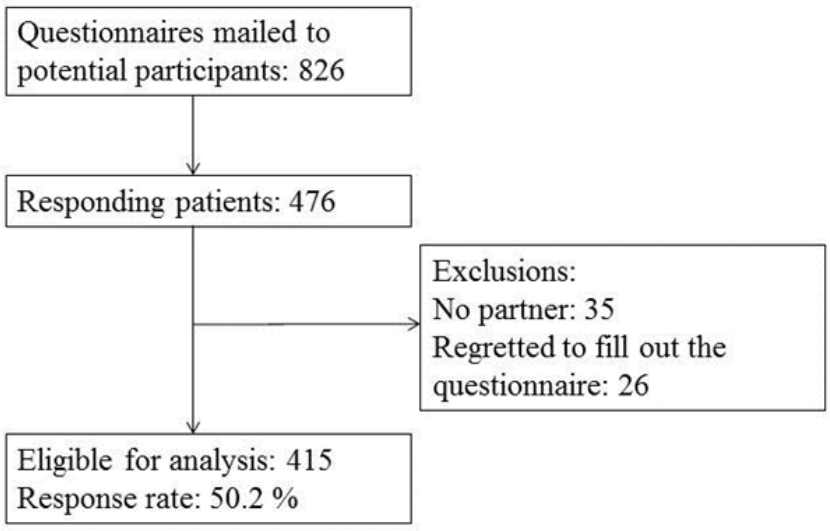
RESULTS

In the following section, results from each of the studies are presented separately. Results from the cross-sectional survey study are presented first followed by the RCT. Lastly the qualitative findings are presented.

Results from the cross-sectional survey study (Paper 1)

Of the 826 patients approached, 476 returned the questionnaire, 25 returned the questionnaire but regretted to fill it out and 35 did not have a partner. Thus, a sample of 415 valid (response rate 50.2%) questionnaires was analyzed (Figure 3. flowchart)

Figure 3. Flowchart



The population characteristics included: males with a mean age of 64 years (range 19 to 93), having their ICD for a mean of 5 years (range 1 to 21). Thirty eight patients had a cardiac resynchronization therapy defibrillator (CRT-D). Patients had a mean of 0.5±1.8 appropriate shocks (range 0 to 18), 0.2±1.4 inappropriate shocks (range 0 to 33), 5.1±42.4 appropriate ATP (range 0 to 1021), and 0.6±5.8 inappropriate ATP (range 0 to 110). No differences were seen between responders and non-responders.

The mean score on the Total IIEF scores was 39.6± 24.2 indicating a poor sexual function and only 31 % of the population had a good sexual function according to the total IIEF score. Mean scores on the other domains were as follows: 14.5±11.4 on the Erectile Function domain, 5.6±4.3 on the Orgasmic Function domain, 6.0±2.3 on the Sexual Desire domain, 5.6±5.6, on the Intercourse Satisfaction domain, and 6.1±2.7 on the Overall Satisfaction domain.

Erectile dysfunction of some degree was present in 70.5% of the patients. The distribution of erectile dysfunction was as follows: 29.6% normal erectile function, 7% mild erectile dysfunction, 7% mild to moderate erectile dysfunction, 7.5% moderate erectile dysfunction and 48.9% severe erectile dysfunction. Advancing age (continuous) was strongly associated with erectile dysfunction with an Odds Ratio (OR) 1.11 95% CI: 1.08-1.13. Stratifying by age groups, more than 90% of the patients above 70 year had erectile dysfunction (Table 4.).

Table 4. Prevalence and severity of erectile dysfunction in all and according to age group in ICD patients

Prevalence of Erectile dysfunction n (%)						
	19-40 y (n=18)	41-50 y (n=34)	51-60 y (n=66)	61-70 y (n=132)	71-80 y (n=109)	81-93 y (n=11)
ED severity						
No ED (IIEF score >25)	16 (88.9)	20 (58.8)	27 (40.9)	39 (29.5)	6 (5.5)	1 (9.1)
Mild (IIEF score 22-25)	2 (11.1)	2 (5.9)	8 (12.1)	9 (6.8)	5 (4.6)	0 (0)
Mild to moderate (IIEF score 17-21)	0 (0)	1 (2.9)	5 (7.6)	11 (8.3)	9 (8.3)	0 (0)
Moderate (IIEF score 11-16)	0 (0)	2 (5.9)	8 (12.1)	10 (7.6)	7 (6.4)	1 (9.1)
Severe (IIEF score 6-10)	0 (0)	9 (26.5)	18 (27.3)	63 (47.8)	82 (75.2)	9 (81.8)

When the other IIEF domains were investigated separately the prevalence of orgasmic dysfunction was present in 57.9% of patients, 82.8% had lowered sexual desire, 85.8% had intercourse satisfaction problems and 76.9% experienced problems related to overall satisfaction and when stratifying for primary versus secondary prophylactic indication, the erectile function domain and the total IIEF score differed significantly in the two groups (Figure 4). Age was not significantly different between the primary prophylactic indication group and the secondary prophylactic indication group (p=0.48).

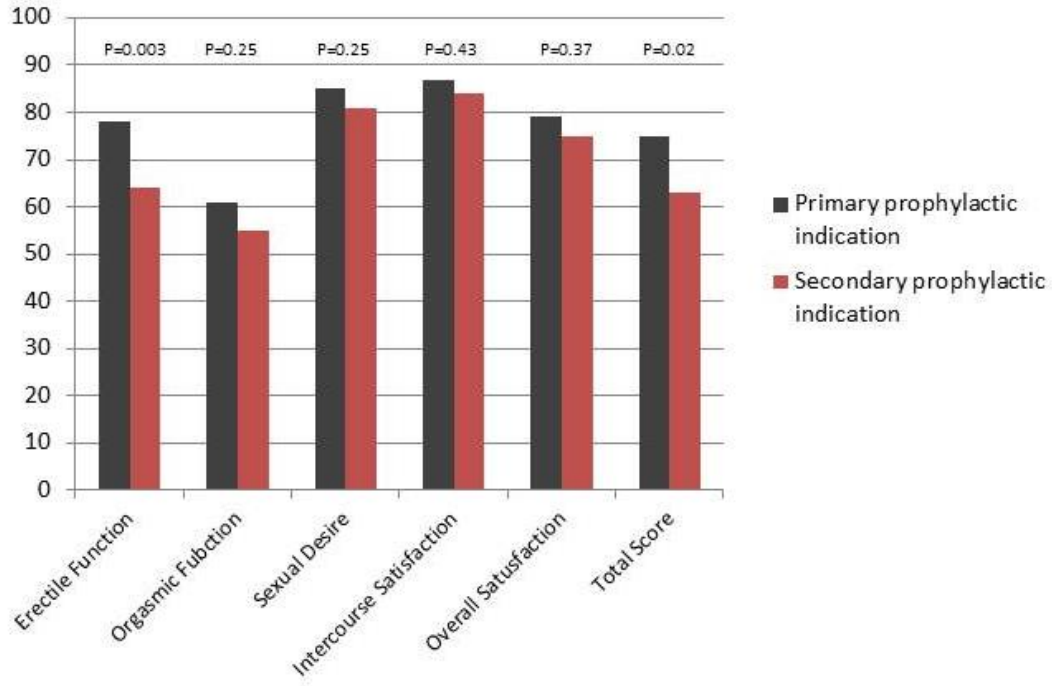


Figure 4. Percentage of patients with dysfunction or affected satisfaction by domain of the International Index of Erectile Function. Patients were subcategorized by primary or secondary prophylactic indication. For each domain, dysfunction and affected satisfaction is defined as follows: a score of 25 or less for erectile function domain, a score of 8 or less for the orgasmic function domain, the sexual desire domain, the overall satisfaction domain and a score of 12 or less for the intercourse satisfaction domain.

Analysis showed that mean intercourse satisfactions scores and mean overall satisfaction scores were significantly statistically related to the severity of erectile dysfunction ($p<0.001$). Lower scores were observed when erectile dysfunction severity increased. The mean satisfaction score in the intercourse satisfaction domain as well as the mean scores in the overall satisfaction domain revealed that only patients without erectile dysfunction had a mean score consistent with good satisfaction.

Further, results showed that patients with primary prophylactic prevention indication had a higher risk of having erectile dysfunction with an OR 2.06, 95% CI: 1.2-3.5 compared to patients having ICD on secondary prophylactic prevention indication. Receiving ATP therapy from the ICD

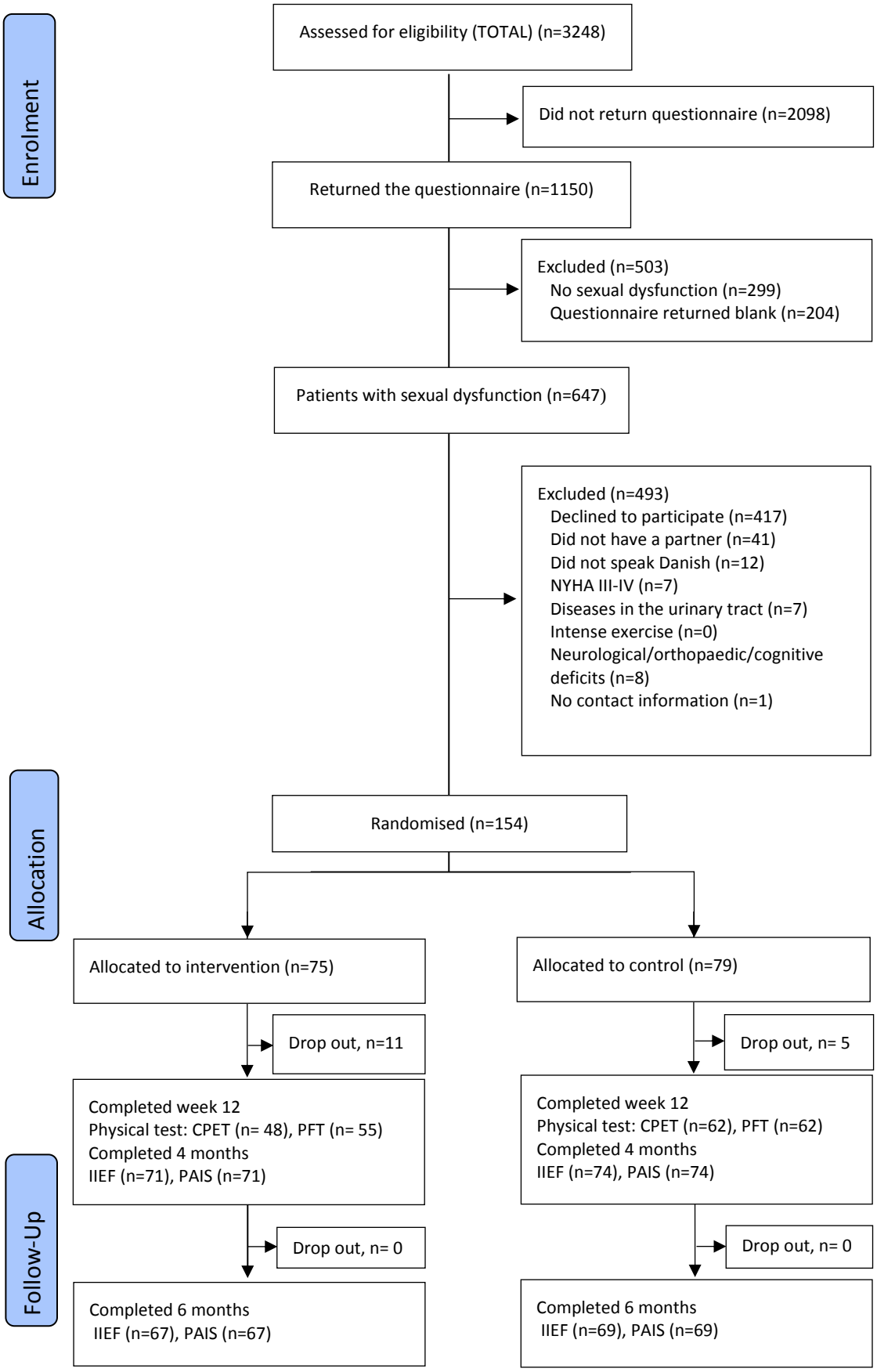
compared with not receiving ATP therapy was associated with erectile dysfunction OR 1.8, 95% CI: 1.1-3.2, orgasmic dysfunction OR 2.1, 95% CI: 1.3-3.5 and lowered intercourse satisfaction OR 1.9, 95% CI: 1.0-3.8, but not lowered sexual desire and overall satisfaction. We found no association with regard to shocks from the ICD, neither appropriate nor inappropriate and no association with time from the ICD. In the multivariate analysis ATP therapy remained associated with erectile dysfunction OR 2.1, 95% CI: 1.1-3.8, but not indication.

Results from The CopenHeart$_{SF}$ Trial – a randomised clinical trial (Paper 2+3)

This section reports the result from the CopenHeart SF trial.

Between March 2013 and June 2016, 3248 patients were identified for questionnaire pre-screening. Of these, 647 male patients were identified with erectile dysfunction of whom 154 (24%) were included (Figure 5). The baseline demographic data was balanced. Participants included had a mean age of 62 years, 64% were NYHA I, 79 had IHD, and 75 had an ICD. Of those with an ICD, 49 had IHD, 16 with heart failure, and 10 had inherited heart disease. Six per cent had high cholesterol. Erectile dysfunction of organic origin[7] was present in 95% of the participants. Nine per cent were treated with PDE5 inhibitors at baseline. Six partners (8 %) attended the psycho-educational intervention. Five drop outs in the control group and 11 in the intervention group were due to new onset of other diseases (e.g. cancer) or withdrawal of consent.

Figure 5. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.



NYHA, New York Heart Association; CPET, cardiopulmonary exercise testing; PFT, Pelvic Floor test; IIEF, International Index of Erectile Function; PAIS, Psychosocial Adjustment to Illness Scale.

Primary outcome

Sexual rehabilitation compared with usual care had a beneficial effect on sexual function with a mean difference IIEF score of 6.7, 95% CI: 3.1-10.4, p=0.0003 at 4 months after randomisation. The Cohen's d was 0.4, indicating a small clinical effect.[86] Results persisted at 6 months with a mean difference IIEF score of 6.7, 96% CI: 3.2-10.1, p=0.0002 (Table 4). No interaction between intervention group and disease group (IHD or ICD) was detected.

Secondary outcome

No statistically significant differences between groups were seen on the secondary outcome PAIS-SR sexual relationship domain after 4 months (Table 5).

Table 5. Primary and secondary outcomes; mean differences reported

	Follow up at 4 months†					Follow up at 6 months†				
	N	Estimate (95%CI)	P value	SD*	Cohen's d	N	Estimate (95%CI)	P value	SD*	Cohen's d
IIEF total score	145	6.7 (3.1-10.4)	**0.0003**	19	0.4	146	6.7 (3.2-10.1)	**0.0002**	19	0.4
PAIS SR score	145	-0.5 (-1.2; 0.2)	0.17	3	-0.2	146	-0.4 (-1.0-0.3)	0.26	3	0.1

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function; PAIS SR, Psychosocial Adjustment to Illness Scale Self-Reported version

† Main effect of intervention adjusted for age (binary), diagnosis group and baseline value

* Standard deviation of the unadjusted mean

Exploratory questionnaire-based outcomes

A statistically significant mean difference between groups on domains for erectile function of 3.9, 95% CI: 2.1-5.7, p<0.0001 and orgasmic function of 1.2, 95% CI: 0.3-2.2, p=0.01 was found at 4 months. No differences were seen in the other domains. In the mixed model including measures at 4 and 6 months, statistically significant mean differences were seen on four domains: erectile function, orgasmic function, sexual desire and intercourse satisfaction, only overall satisfaction remained statistically insignificant (Table 6). The effect of the intervention was not significant for self-reported health, anxiety and depression (Table 6 + 7). In the sexual rehabilitation group a 'within group difference' at month 4, on the IIEF total score and Erectile Function domain score of 4.2 and 3.3 respectively was detected (Table 8). On the "sex after ICD questionnaire" significantly fewer patients in the intervention group experienced problems with erectile function and overprotection from the partner compared with controls (Table 9). There were no differences

between groups with regard to PDE5 inhibitor intake at 4 months (p=0.09) and at 6 months (p=0.6).

Exploratory physical outcomes

The intervention showed an effect on the manual examination of pelvic floor strength (Table 10), but not on endurance. Results from the cardiopulmonary test showed a mean difference between groups on watt max of 10.3, 95% CI: 3.6-16.9, p=0.003 but no difference on VO2 peak (Table 11).

Sensitivity analysis

A best-worse-case scenario analysis showed a mean difference on 9.9, p<0.0001 for the best-worst-case scenario, and for the worst-best-case scenario, a mean difference of 2.5, p=0.28. Tests for interaction between intervention group and disease group, intervention group and time, intervention group, time and disease group were all non-significant.

Safety

One serious adverse event occurred in one patient in the intervention group. Due to angina pectoris during exercise training the patient was admitted to hospital, but discharged after 4 hours of observation and remained in the trial.

Adherence to intervention

A total of 64 (85%) patients participated in the exercise intervention with an average of 25.3 training sessions, and 64 (85%) participated in the sexual consultations with an average of 2.4 sessions during the trial. Of the participants returning their diary and pulse watch (52 participants), 29 (56%) conducted ≥ 26 exercise sessions (≥ 75%). When adherence was defined as participating in at least 50% of the sessions, 39 patients (75%) were adherent. Participants received from one to four psycho-educational consultations. The goal was set after each consultation and decided the number of consultations and was determined between the participant and the nurse.

Table 6. Exploratory outcomes at 4 and 6 months (questionnaire based data), Mean differences reported.

	Follow up at 4months [†]					Follow up at 6 months[†]				
	N	Estimate (95%CI) [†]	p-value	SD*	Cohen *d*	N	Estimate (95%CI) [†]	p-value	SD*	Cohen's *d*
Exploratory outcomes										
Erectile function domain	145	3.9 (2.1; 5.6)	**<0.0001**	9.1	0.4	146	3.5 (1.8-5.3)	**<.0001**	9.2	0.4
Orgasmic function domain	145	1.2 (0.3; 2.2)	**0.01**	4.0	0.3	146	1.2 (0.3-2.1)	**0.01**	3.9	0.3
Sexual desire domain	145	0.4 (-0.03; 0.8)	0.07	2.2	0.2	146	0.6 (0.2-1.0)	**0.002**	2.3	0.4
Intercourse satisfaction domain	145	0.9 (-0.1; 2.0)	0.08	4.8	0.2	146	1.0 (0.0-1.9)	**0.0499**	4.8	0.2
Overall satisfaction domain	145	0.2 (-0.3; 0.7)	0.38	2.1	0.1	146	0.2 (-0.3 - 0.6)	0.40	2.1	0.2
SF36-PCS	145	-0.5 (-2.4; 1.5)	0.64	9.2	-0.05	146	0.3 (-1.5 - 2.1)	0.74	8.8	0.03
SF36-MCS	145	-0.3 (-2.3; 2.3)	0.83	11.2	-0.02	146	0.0 (-2.3 - 2.3)	0.99	10.5	0.00
EQ-5D index	145	0.01 (-0.04; 0.1)	0.74	0.2	0.04	146	0.01 (-0.03 - 0.06)	0.54	0.2	0.06

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function, SF36-PCS, Short Form-36, Physical Component Score; SF36-MCS, Short Form-36 Mental Component Score

[†] Main effect of intervention adjusted for age (binary), diagnosis group and baseline value of the outcome

* Standard deviation of the unadjusted mean

Table 7. Results of logistic regression with binary explorative outcomes. The estimates are the odds ratio between sexual rehabilitation group and usual care group (reference group).

	N	OR (95%CI)	p-value
Binary outcomes			
HADS A (8+)	145	1.33 (0.70; 2.52)	0.38
HADS D (8+)	145	1.97 (0.64; 6.02)	0.24

Available cases adjusted for age (binary), diagnosis group and baseline value.

Table 8. Mean scores at all times

	Sexual rehabilitation group						Usual care group					
	Baseline		4 months		6 months		Baseline		4 months		6 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total IIEF	32.2	16.7	36.4	17.2	37.1	20.0	33.7	17.1	31.1	20.7	32.2	20.0
Erectile function domain	11.2	8.0	14.5	8.5	14.3	9.6	12.3	8.4	11.5	9.7	12.2	9.6
Orgasmic function domain	5.6	3.8	5.8	3.7	5.9	4.0	6.0	3.76	4.8	4.2	5.1	4.0
Sexual desire domain	6.1	2.3	6.1	2.1	6.4	2.3	5.9	2.1	5.6	2.3	5.4	2.3
Intercourse satisfaction domain	4.4	4.7	4.9	4.8	5.3	4.6	5.0	4.5	4.5	4.9	4.8	4.6
Overall satisfaction domain	4.9	2.1	5.2	2.0	5.2	2.0	4.6	1.8	4.7	3.1	4.8	2.0
PAIS	6.34	3.4	6.1	3.4	6.3	3.9	6.5	3.3	6.9	3.2	6.9	3.3
SF-36 Physical Component Scale	45.3	10.3	45.6	9.3	47.8	8.8	46.7	9.1	47.0	9.1	47.0	8.8
SF-36 Mental Component Scale	51.7	9.8	51.0	10.6	51.68	10.9	51.8	10.2	50.9	11.3	51.0	10.9
HADS A	3.8	3.8	4.3	4.3	3.9	4.0	4.2	3.8	4.0	4.0	4.0	4.0
HADS D	2.6	2.9	2.9	2.9	2.7	3.7	3.0	3.2	3.0	3.6	3.1	3.7
EQ5D Index	0.8	.2	0.8	0.8	0.8	0.2	0.8	0.2	0.8	0.2	0.8	0.2

SD, Standard Deviation; IIEF, International Index of Erectile Function; PAIS, Psychosocial Adjustment to Illness Scale; SF-36, Short Form-36; HADS A, Hospital Anxiety and Depression Scale Anxiety scores; HADS D, Hospital Anxiety and Depression Scale Depression scores; EQ5D, EuroQol

Table 9.Sex after ICD questionnaire

	Baseline		Months 4		Months 6	
	Sexual rehabilitation n=36	Usual care group n=39	Sexual rehabilitation n=36	Usual care group n=39	Sexual Rehabilitation n=36	Usual care group n=39
Lack of interest in sex after the ICD						
Never	9 (25)	15 (38)	8 (22)	11 (28)	11 (31)	8 (21)
Rarely	10 (28)	7 (18)	10 (28)	7 (18)	7 (19)	6 (15)
Occasionally	8 (22)	4 (10)	7 (19)	5 (13)	8 (22)	8 (21)
Frequently	8 (22)	10(26)	8 (22)	12 (31)	8 (22)	10 (26)
p-value (chi^2-test)	0.31		0.56		0.87	
Problems with erection after the ICD						
Never	4 (11)	11 28)	2 (6)	8 (21)	4 (11)	7 (18)
Rarely	6 (17)	4 (10)	9 (25)	1 (3)	8 (22)	1 (3)
Occasionally	9 (25)	6 (15)	8 (22)	9 (23)	7 (19)	11 (28)
Frequently	16 (44)	15(38)	14 (39)	17 (44)	15 (42)	13 (33)
p-value (chi^2-test)	0.23		**0.02**		0.06	
A partner that is overprotective						
Never	19 (53)	14(36)	17 (47)	14 (36)	22 (61)	14 (36)
Rarely	3 (8)	12 31)	3 (8)	13 (33)	4 (11)	8 (21)
Occasionally	5 (14)	6 (15)	8 (22)	4 (10)	4 (11)	7 (18)
Frequently	8 (22)	4 (10)	5 (14)	4 (10)	4 (11)	3 (8)
p-value (chi^2-test)	0.06		**0.047**		0.26	
Fear of the ICD firing during sex						
Never	28 (78)	24(62)	27 (72)	25 (64)	29 (81)	27 (69)
Rarely	6 (17)	9 (23)	5 (14)	5 (13)	3 (8)	3 (8)
Occasionally	0 (0)	3 (8)	1 (3)	5 (13)	0 (0)	2 (5)
Frequently	1 (3)	0 (0)	1 (3)	0 (0)	2 (6)	0 (0)
p-value (chi^2-test)	0.18		0.30		0.26	
Fear of cardiac arrest if the ICD does not fire						
Never	27 (75)	24(62)	25 (69)	23 (59)	29 (81)	23 (59)
Rarely	4 (11)	7 (18)	4 (11)	10 (26)	2 (6)	7 (18)
Occasionally	3 (8)	4 (10)	3 (8)	2 (5)	1 (3)	2 (5)
Frequently	1 (3)	1 (3)	1 (3)	0 (0)	2 (6)	0 (0)
p-value (chi^2-test)	0.77		0.28		0.12	

Table 10. Tabulation of pelvic strength measure (categorical) by intervention groups. Numbers are percentages.

Category*	Sexual rehabilitation	Usual care group	p-value
0	1%	0%	0.01**
1	9%	9%	
2	44%	68%	
3	45%	23%	

*Higher category means more strength

**Chi^2 test of all categories, multiple imputation dataset (n=154)

Table11. Exploratory outcomes at baseline and at week 12 (physical data), mean values and mean differences reported.

	Sexual rehabilitation				Usual care group							
Exploratory outcomes	N	Baseline ‡	N	Week 12 ‡	N	Baseline ‡	N	Week 12 ‡	N	Estimate † (95%CI)	p-value	SD*	Cohen's *d*
Pelvic floor endurance (sec)	73	9.3	55	12.1	72	11.2	62	11.5	154	1.5 (-0.5; 3.4)	0.13	7.5	0.2
Peak VO2	67	20.7	48	21.9	74	21.5	62	20.1	154	1.6 (-0.2; 3.4)	0.09	7.3	0.2
Heart rate – rest (bpm)	72	66.7	53	64.1	75	63.0	63	64.6	154	-1.0 (-4.2; 2.2)	0.53	11.7	-0.1
Heart rate – max (bpm)	72	131.4	53	134.8	75	152.5	63	130.0	154	6.3 (-1.8; 14.3)	0.12	11.7	0.5
Blood pressure – rest	72	135.6	53	137.3	75	138.9	63	136.7	154	2.1 (-3.6; 7.8)	0.46	11.7	0.2
Blood pressure – max	72	186.9	53	186.7	75	193.1	63	193.2	154	-1.9 (-8.5; 4.6)	0.56	32.0	-0.1
Watt max	72	149.6	**53**	160.4	75	159.5	63	154.3	154	10.3 (3.6; 16.9)	**0.003**	49.7	0.2
Anaerobic threshold	67	1.6	45	1.7	72	1.8	60	1.7	154	0.1 (-0.01; 0.3)	0.07	0.6	0.2
VE/VCO2 slope	67	27.8	45	28.1	72	26.8	60	26.6	154	0.2 (-0.8; 1.3)	0.66	5.4	0.04

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function, SF36-PCS, Short Form-36, Physical Component Score; SF36-MCS, Short Form-36 Mental Component Score
Where n= 154 multiple imputation was used, all others were available cases

* Standard deviation of the unadjusted mean

† Mean differences between groups at week 12

‡Mean values

Results from the qualitative interview study (Paper 4)

This section presents the results from the qualitative study.

Interviews were carried out in August and September 2016, lasted between 45 and 75 minutes and were recorded on tape and subsequently transcribed. Demographics and selected details are presented in Table 12.

Table 12. Demographic and clinical characteristics of participants

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10
Age	53	68	69	35	69	58	58	72	65	72
Patient group	IHD	IHD	IHD	IHD	IHD	IHD	ICD	ICD	IHD	IHD
Type of SD	Physical	Physical	Physical	Physical	Combined	Physical	Combined	Combined	Physical	Physical
Exercise location	Hospital	Hospital	Hospital	Combined	Hospital	Combined	Combined	Hospital	Combined	Home
No of sexual consultations	3	2	3	2	3	3	4	3	3	2

IHD = Ischaemic Heart Disease, ICD = Implantable Cardioverter Defibrillator, SD= Sexual Dysfunction, Combined= physical and psychological causes of sexual Dysfunction

Findings

The findings are presented as themes extracted from the structural analysis and interpreted in the critical interpretation and express the way in which patients with heart disease experience participating in a sexual rehabilitation programme. Three themes were identified reflecting the intervention to be a special place of understanding, describing the intervention as a supporting atmosphere and finally expressing the intervention as sexually empowering. A table of the structural analysis is placed at the end of the section (Table 13.).

Place of understanding

Discussing sex and sexual problems are reported to be taboo subjects [98] and when entering the intervention most participants described negative experiences from the established setting. They received no prior information or support in relation to their sexual challenges. In contrast, when participating in the CopenHeart$_{SF}$ trial, patients had a valuable experience and found themselves in a special place of understanding.

They experienced a context where professionalism was used to create a trustful and positive setting and how a professional interaction with the health professionals was important. This is exemplified by one participant when he described the consultations: *"What is the person sitting in front of you like? Are they saying things straight ahead? You can easily ask questions the wrong way, or the attitude when you ask. Are they "know it alls" or is it someone you can trust. Trust means a lot, and the team here has been good at this. I wouldn't be here if they weren't good".* This professional environment created dynamic interactions within the consultations, and promoted the development of individual emotional and practical skills as well as a new perception of self which had a positive impact on the patients' self-efficacy. Bandura has showed that people with high self-efficacy generally believe that they are in control of their own lives.[95] Thereby the intervention strengthened the patients' perception of being in control which empowered the patient to act on their own and prepared them to engage in their daily social life and sexual relationships.

Responses from the patients state how important it was that the environment was open to emotionally laden topics such as sexuality and sex. This was exemplified in the following quote, by one participant: "*it is a delicate subject, many professionals can't handle it. Here, they were really good at handling this. It was really okay".* This was in contrast to the participants' earlier experiences with the established system. The CopenHeart intervention created an environment in where emotionally difficult topics were met and embraced which provided affirmation of personal engagement for the patients.

Talking about sexuality often involves many metaphors and misunderstandings, and awkward situations tend to appear. Participants emphasized how a clear constructive communication was needed and how important is was that conversation was getting to heart of the matter. This was reflected upon their earlier experience in where participants experienced health professionals talking back and forth about sexuality and not really getting to the heart of the matter. One participant stated: "*She (the nurse) was just good, called a spade a spade, but in a good way. She was constructive and precise in her advice, and then it was up to me to grab the challenge (new way of communicating with his spouse)".* The perception is that patients receive constructive

advice and widen their competencies in communication and thereby might experience a higher degree of self-efficacy.

Overall, this place of understanding strongly influenced the capability of the patient in order to face the sexual challenges. According to Bandura's theory of self-efficacy this may be understood as the intervention supported the patient's ability to approach his sexual challenges and managed to change the way he saw himself. The intervention thus had an impact on the patient's social behavior and encouraged the patients to view the sexual challenges as something to be mastered rather than something to be avoided.

The supportive atmosphere

Participants expressed the view that team training motivated and encouraged them because it brought energy and fun. They talked about a special team spirit and some participants even gained new friendships, and a small group of patients started seeing each other privately after the training sessions. When describing the experience with the team training one participant stated: "*we yell and scream, we are old men yelling at each other, we have so much fun together".* The perception is that a certain supportive atmosphere or spirit is experienced which motivates and pushes the participants to move forward. According to Bandura, peers can act as a potential strength in the development of self-efficacy and self-assurance and might function as social validation for the patients.[99] Additionally these benefits might produce motivation to move on in life.

In contrast, some patients performed home-based exercise training, defined as exercise training either in their own home or at a local fitness centre. Most of these patients were characterized by being familiar with exercise training and performing weekly sessions. They all had a history with years of exercise training before entering the trial and found motivation and confidence in training in their usual environment which also was a practical and logistic advantage for these patients. This could illustrate that those familiar with exercise training do not necessarily need the support of peers and health professionals. According to Bandura, all people have mastery experiences, and mastery experiences are the most important way to boost self-efficacy.[96] People are more likely to do well in new things if they can relate it to former successful events. This could explain how

patients with good training routines have a lower degree of dependency of peers and health professionals.

Some participants were present when a man became ill during exercise training and was subsequently admitted to the emergency room. They didn't find this upsetting, rather it reassured them that they were close to help if needed and they experienced the team training to be safe. This is exemplified by a participant: *"During one of the sessions a guy became ill. The expertise was just nearby. It feels really safe to know that you are in the best hands".* And it appears that they did not feel anxious or uncertain of exercise training.

Participants explained how friendships developed beyond the training sessions. They started to meet up after training, having a beer or two. One participant described: "*the last time I was there, we agreed to go out for a beer and it was really cozy, and after that I started to drop by the training center to meet the other ones because we had this thing going on, that was after my sessions ended".* This quote illustrates how the participants can relate to other peers. Participants in the intervention suffered from the same problem, they were all aware that they were there because of their sexual problems and being in the same situation. According to Bandura relating to peers or social support can be a motivating and supporting factor and is probably why participants emphasized the importance of seeking each others company.[99]

Another supporting element experienced was technology. Many were comfortable with pulse watches, data from the bicycle, and apps on the phones reminding them of their exercise training three times a week, and some expressed a direct dependency on the technology to motivate themselves, and to be reminded. Technology clearly was a motivating and supporting factor. One participant stated: *"I had the pulse watch on so I couldn't skip training"* indicating that a need for motivation and if the pulse watch was not a part of the intervention it would have been easier to take shortcuts. A motivating emotional state is believed to positively impact self-efficacy, and support further engagement in the exercise training.[95]

Sexually empowered

Participants perceived a significant improvement in their sexual performance, experienced an increase in desire, an improvement in erectile function, as well as in overall sexual satisfaction

during the intervention. One participant stated: "*It works on the psyche as well. When the confidence arise the desire increases, much more – completely".* They expressed that participating in the intervention improved their quality of life and courage of life. One patient expressed: "*I mean... this is an important programme, it improves the quality of life for all and it is an area of taboo. You know... When you have been out of the game for a while…. then things change, and it can be really hard getting back on track. I would say go on with the programme".* This might indicate the importance of a comprehensive approach and that neither a sexual counselling intervention nor exercise training can stand alone. Some patients were specifically emphasizing the role of pelvic floor exercise as being efficient. It is highlighted by Bandura that the perceived difficulty of a task is of importance for perceived self-confidence.[95] For the patients the pelvic floor exercise was experienced as being a simple and easy task to implement in daily life suggesting that this specific performance had a positive impact on the patients perceived self-confidence. Whereas some participants experienced this positive change in their sexual performance as stated here: *"You know. It works so that you can hold more blood right. And you also shoot longer when it finally happens"*, others experienced no positive impact at all. One participant described: *"Not like I hoped. I was hoping it would be like old times"*. Patients thus might feel they are put outside of control of own performance regarding sexuality which may result in a low sense of self-efficacy impairing the patients well-being. Despite that fact, participants said that it was helpful to receive a comprehensive investigation of their sexual history, including a professional evaluation on the cause of the sexual problem, even though they didn't experience any positive impact on their sexual function. They gave the impression that participating was valuable which suggests that the intervention sustained hope and belief for the patients in their own capabilities lowering anger and guilt as stated by this participant: "*though my erection didn't get better it was still very good to be a part of the programme. I learned a lot about myself and got an idea of why I had my problem (sexual) and that it wasn't me that was the problem in our relationship".*

Several participants experienced severe relationship issues and described problems in relation to communication and differences in sexual needs. Some described how communication over years had developed to be more defensive in contrast to earlier in life where it used to be more constructive. The patients were encouraged to practice their wording in the consultations. During the intervention participants gained new communication skills and received counseling advice to

start a more helpful and fruitful conversation about sexuality and their individual sexual needs. This is illustrated in the following quote: "*It is important that you put the word right, you don't want to make accusations or attacks, but more: I feel that... you know, keep it on your own court. That works, you know".* This reveals how participants, by receiving advice on communication improved their self-efficacy. According to Bandura, verbal persuasion along with mastery experiences is important when you want to increase self-efficacy.[95] In this case the mastery experience was developed during the practice of their wording and their verbal persuasion from the nurse. This perceived efficacy might lead to developing confidence and strength in the patients to promote new self-generated strategies which may benefit their performance in their relationships. Viewed in this perspective, the intervention is suggested to empower the patient to self-help.

Participants was reflecting on their new skills and what they gained from the intervention on a more personal level which engendered courage and beliefs in one's own capabilities regarding sexuality. "*Then you can get some insight into yourself. About what really matters to me and what it means to have a good sexlife. And in that way have more courage to talk to my wife about it. I feel like….I know now that I can also do something myself".* This statement illustrates how the patient's self-confidence increased and how the patient gained the ability to actively control his own situation.

Table 13. Examples of the process in the structural analysis

Meaning unit (What the male says)	**Units of significance (What the male talks about)**	**Theme**
"What is the person sitting in front of you like? Are they saying things straight ahead? You can easily ask questions the wrong way, or the attitude when you ask'. 'Are they "know it alls" or is it someone you can trust. Trust means a lot, and the team here has been good at this. I wouldn't be here if they weren't good".	Professional environment created dynamic interactions	Place of understanding
"It is a delicate subject, many professionals can't handle it. Here, they were really good at handling this. It was really okay".	Environment was open to emotionally laden topics	
"She (the nurse) was just good, called a spade a spade, but in a good way. She was constructive and precise in her advice, and then it was up to me to grab the challenge (new way of communicating with his spouse)".	Getting to the heart of the matter	

"We yell and scream. We are all old men yelling at each other". *"We have so much fun together".*	Team training motivates	The supportive atmosphere
"During one of the sessions a guy became ill. The expertise was just nearby. It feels really safe to know that you are in the best hands".	Being around professionals during exercise training is safe	
"The last time I was there, we agreed to go out for a beer and it was really cozy, and after that I started to drop by the training center to meet the other ones because we had this thing going on, that was after my sessions ended".	Friendships developed	
"I had the pulse watch on so I couldn't skip training". *"I persuaded Signe (the physiotherapist) to get the diary when we finished. I put the information on my phone so that I have it. Then I can perform the exercise training programme at home whenever I like".*	Support by technology	
"You know. It works so that you can hold more blood right. And you also shoot longer when it finally happens". *'It is a small price for a good effect.'* *"Pelvic floor training programme it is so simple and it helps. So continue for God's sake, if you can".*	Pelvic floor exercise efficient and easy to perform	Sexually empowered
"Though my erections didn't get any better it was still very good to be a part of the programme. I learned a lot about myself and got an idea of why I had my problems (sexual) and that it wasn't me that was the problem in our relationship". *"It is important that you put the word right, you don't want to make accusations or attacks, but more: I feel that... you know, keep it on your own court. That works, you know".*	Helpful learning about themselves	
"It works on the psyche as well. When the confidence arise the desire increases, much more, completely".	Creates more desire	
"I mean... this is an important programme, it improves the quality of life for all and it is an area of taboo. You know... When you have been out of the game for a while…. then things change, and it can be really hard getting back on track. I would say go on with the programme".	Improves quality of life and helps you back on track.	

DISCUSSION

In this section findings are interpreted in light of existing knowledge. The section is divided into subsections regarding: (1) The prevalence of sexual dysfunction and associating factors for sexual dysfunction in ICD patients, (2) Discussion of the effect of sexual rehabilitation and the outcomes chosen, (3) Adherence to the intervention, (4) Methodological considerations with regard to choice of outcome, (5) Limitations in relation to self-reported outcomes and more specific in the different studies, (6) Generalizability/transferability.

In the following the findings from both the quantitative and qualitative data were interpreted separately and thereafter comparisons were made by examining similarities of the results in the discussion section in order to describe of the effects and meaning of a sexual rehabilitation programme.

The overall aim of the thesis was to expand and consolidate existing knowledge regarding sexual dysfunction and the treatment of sexual dysfunction in populations of patients with IHD or ICD.

A first objective was to describe the prevalence and distribution of sexual dysfunction among male patients with ICD. Our secondary objective was to evaluate and describe the effect and meaning of a sexual rehabilitation programme, the CopenHeart SF trial.

Three studies with distinct research methodologies were undertaken in order to achieve this: a cross-sectional study, a randomised clinical trial and a qualitative study. The objectives explored produced the following results:

- Sexual dysfunction was common among patients with ICD and was not limited to erectile dysfunction. Orgasmic function, desire, intercourse and overall satisfaction were also affected. Primary prophylactic ICD indication and ATP therapy were associated with compromised sexual function, but not shock therapy.
- Comprehensive sexual rehabilitation compared with usual care significantly improved sexual function and physical capacity but not sexual adjustment to illness, self-rated health and mental health. Adherence was high and the intervention was safe.
- Three themes were identified: ‘a place of understanding’ where patients state a need for a respectful environment open for emotionally laden topics; a theme describing a

'supportive atmosphere' that encourage and support to persistently exercise training; and finally the intervention was experienced as 'sexually empowered' in where patients described how they developed new skills to help constructive communication with their spouses. Participating in the sexual rehabilitation programme was experienced as efficient, valuable, motivating and safe, but dependent on a professional setting. The intervention developed participants' self-efficacy with regards to their sexual performance and relationship.

Discussion of the prevalence of sexual dysfunction

To our knowledge, the results from the cross-sectional study are the first to address sexual dysfunction in a large male patient population with ICD using a validated generic instrument that reflects the definition of male sexual dysfunction. Sexual dysfunction was highly prevalent in ICD patients, with all domains affected. The overall presence of sexual dysfunction was 69% and more than 70% suffered from erectile dysfunction. The frequencies were higher than observed at the matching age in the general population (38%)[100], higher than in an atrial fibrillation population (57%)[59], similar to patients with IHD (75%)[22], though not as frequent as in patients with heart failure (89%).[101] A high proportion of patients experiencing erectile dysfunction were affected to an extent, which prevented them from enjoying sexual activity in the form of sexual intercourse.

Existing studies examining sexual problems in patients with ICD[14,19] are not directly comparable to our results as they use a different questionnaire instrument; however, problems with erection and desire have been reported previously and found to be less frequent compared with our results.[14,19] These previous study population samples had a similar mean age compared to our study, though they were smaller, and more patients had an ICD for primary prophylactic prevention indication. Differences in occurrence of problems with erection and desire between the studies may primarily be due to differences in the questionnaire instrument. Another reason for lower sexual desire in our study may be related to the larger burden of erectile dysfunction. It is well known that men with erectile problems tend to withdraw from their partner with a decrease in sexual response as a consequence[102] and men with low sexual response are more prone to have lack of sexual interest/lowered desire.[102]

Our results revealed that a decrease in erectile function was associated with a decrease in both intercourse satisfaction and overall satisfaction, and that it was only patients without erectile dysfunction who experienced good intercourse satisfaction and overall satisfaction. This implies that even patients with the mildest form of erectile dysfunction experience an adverse impact on sexual satisfaction. The same trend is described by Makarem et al.[103] in a group of hemodialysis patients. However, they found that it was only overall satisfaction that was affected by erectile dysfunction and also that patients with mild erectile dysfunction seemed to have a good overall satisfaction. In contrast, Giraldi et al.[104] found in a study that in a randomly chosen Danish population, only 11% of males suffering from erectile dysfunction were unsatisfied with their sexual life. Erectile dysfunction was measured by the same instrument, the IIEF, but with a lower cut-off score for erectile dysfunction of ≤21, probably resulting in a smaller sample with erectile dysfunction compared to ours.

Discussion of the associating factors to sexual dysfunction

Primary prophylactic indication for ICD was associated with more erectile dysfunction compared to patients having ICD on secondary prophylactic indication. It has been hypothesized that patients with secondary prophylactic indication would have a higher frequency of sexual dysfunction due to psychological distress from the index event (e.g. cardiac arrest) [105], however, our data did not confirm this. In our analyses we were not able to adjust for the presence of IHD, heart failure and reduced ejection fraction which, besides being the indication for primary prophylactic ICD, are also factors associated with sexual dysfunction.[27]

In our results, receiving ATP therapy from an ICD was associated with a higher degree of erectile dysfunction compared to not receiving ATP therapy; this was also true when adjusting for age, time since ICD, and indication. Many patients receiving ATP therapy do not experience the actual therapy, but feel the malign arrhythmia as palpitations and/or dizziness, which might remind them of being chronically ill and vulnerable, all psychological impacts associated with outcomes such as anxiety and concerns[106] which might have an effect on sexuality as well. In a study by Hoekstra et al.[107], patients with heart failure without sexual dysfunction reported a significantly higher emotional quality of life than those with sexual dysfunction, indicating a possible connection

between psychological outcomes and sexual dysfunction. Likewise, a psychological impact on sexuality was described in the qualitative data as patients experienced anxiety in relation to sexual activity and some simply stopped being sexually active. This is supported by previous findings where sexual concerns and anxiety were associated with sexual problems.[16,32,108]

Considering that a large number of patients with ICD in the cross-sectional study have IHD or heart failure, the overall results are not surprising; however, our results added knowledge to the existing evidence with data supporting a more robust conclusion and further associating factors to pay attention to.

Discussion of the effect of sexual rehabilitation

The CopenHeart$_{SF}$ trial was a randomised clinical trial with well-defined inclusion and exclusion criteria. Prevention of imbalance at baseline was secured by computer-generated allocation with varying block size. The CopenHeart$_{SF}$ trial is the largest randomised clinical trial investigating comprehensive sexual rehabilitation consisting of physical exercise, pelvic floor exercise and psycho-education in male with heart disease and erectile dysfunction. No trial has previously investigated the effect of a comprehensive intervention on sexual dysfunction, and only the individual components of the intervention have been evaluated previously, and in studies with a high risk of bias.

Primary outcome

In a randomised trial, Maio et al.[85] investigated the effect of physical exercise in addition to PDE5 inhibitors versus PDE5 inhibitor administration only; a total IIEF mean difference score of 5.5 and a mean difference score of 2.0 in the erectile function domain was detected in favor of the exercise compared to 6.7 and 3.9 in the present trial. Participants in the Maio trial consisted of a population of males with sexual dysfunction and no known cardiovascular disease, indicating a lesser cardiovascular burden on their sexual function, which is known to have a great impact. Our results are also partly supported by a more recent non-randomised controlled study from Kalka et al.[109] They found that in a population of patients with IHD, endurance training compared to a group not receiving endurance training erectile function did not improve between groups; however, a significant improvement was detected within the training group.

The Pelvic Floor Exercise intervention on top of lifestyle advice has been investigated previously and shown to significantly improve the erectile function domain of the IIEF.[10] This trial supports our findings but is not completely comparable as it includes a non-cardiovascular patient population which can be expected to have a lower level of cardiovascular induced erectile dysfunction. We found an improvement in the strength of the pelvic floor muscles, but not on endurance. This is in accordance with findings from a randomised trial in post stroke patients which also evaluated a 12 week pelvic floor training intervention.[76] Results from that trial showed no differences in endurance after 12 weeks between groups but found a late response after follow up (6 months) indicating that the effect on endurance might be delayed compared with strength. However we did not evaluate physical results at 6 months.

A recent Cochrane systematic review investigating the effect of sexual counselling on sexual function in cardiovascular patients,[43] revealed three randomised trials with a total of 381 participants. The trials included were of very low quality according to the GRADE criteria, and the conclusion was that no high quality evidence to support the effectiveness of sexual counselling for sexual problems in cardiovascular patients exists.

Secondary outcome

We did not find any effect on the secondary outcome in the sexual relationship domain of the overall validated PAIS-SR.[61] This might be due to the fact that we did not measure the whole PAIS, but only a part which may have compromised validity and responsiveness. In the light of that, choosing the sexual relationship domain might have been a poor choice. Another reason for the lack of effect could be that the intervention was not fully adopted into the patients' relationship.

Exploratory outcomes

A minimal clinically important difference (MCID) score on the erectile function domain has been established and found to be 4 points, with variation ranging according to baseline severity (mild: 2; moderate: 5; severe: 7 points).[60] The mean difference found in our study of 3.9 on the erectile function domain therefore indicates a clinically relevant effect. This is supported by a calculation of the Cohen's d effect size on 0.4, indicating a small effect.[86] In the qualitative findings the clinical effect on erectile function is expressed in various ways. Some indicated a significant improvement

in erectile function and also in sexual desire, which supports previous findings.[110] Whereas some patients described positive changes with regard to sexuality, others experienced no effect. Despite that, patients expressed gratitude for receiving a comprehensive investigation of their sexual history including a professional evaluation of their sexual problem and they indicated that the intervention was meaningful.

We did not find the expected effect on self-reported health and mental health in the questionnaire-based data. In the qualitative findings patients expressed that the changes in sexual function were improving their quality of life. This could indicate that the impact of the increase in sexual function was not large enough to be detected in the outcomes chosen, or perhaps the outcome was a poor choice. Another reason could be that the patients had a relatively high self-reported health with baseline scores in the intervention group and in the control group of 51.7 and 51.8 on the Mental Component Scale of the SF-36, and of 45.3 and 46.7 on the Physical Component Scale, which are higher compared with other heart populations entering a comprehensive rehabilitation intervention.[111,112] The same trends are seen in regards to anxiety, where the intervention group and the control group had mean scores of 3.8 and 4.2, and in relation to depression with scores of 2.6 and 3.0, reflecting a relative small burden of anxiety and depression compared to other rehabilitation studies[111,112] and in a large epidemiological study.[113]

The changes over time in the different domains on the IIEF revealed that after 6 months every domain significantly increased except overall satisfaction, and so a question is raised as to whether overall satisfaction might be driven by something else. Patients were a mean age of 62, and their partners probably the same age. Sexual problems in women exists in approximately 40% to 50% irrespective of age[114] and sexual desire problems are the most frequently reported,[114] and our results might reflect that patients' partners did not seem to adapt to a new sexual life. Results from the qualitative findings supported that patients had partner difficulties in relation to sexuality, which is in line with previous findings.[16] Moreover, it illustrates that sexuality is more than just being able to achieve an erection, to have intercourse and enjoy an orgasm but it also consists of and depends on several interpersonal factors. In the qualitative findings patients express how communicating with their partner was difficult and that openness about sexuality and good communication skills were important factors. According to Litzinger et al.[115] good

communication skills along with sexual satisfaction are the two most important factors for having a good overall relationship satisfaction. This emphasizes the importance of including partners in sexual rehabilitation programmes. In the CopenHeart$_{SF}$ trial partners were invited to co-participate in the psycho-educational intervention. However, few patients chose to include partners, which may have compromised the potential effect on overall satisfaction.

Adherence to the intervention

Adherence in the randomised clinical trial was high, 75% of participants completed more than 50% of sessions. Adherence to cardiac rehabilitation in general has proven to be a challenge and several studies show that only around 30% of eligible patients continue in these programs[116,117], indicating a meaningful and workable set-up in the CopenHeart$_{SF}$ trial. The qualitative findings emphasized the role of team training and technology as supporting and motivating factors. Patients expressed how being supervised by qualified staff was safe and being around peers joyful and motivating. Simonÿ et al.[118] found a similar trend, where a mutually supportive team spirit was important and encouraging, and some even depended on peers for support. These factors might have contributed to the relative high adherence rate.

Methodological considerations with regard to choice of outcome

We choose to include patients in the randomised clinical trial according to the established criterion for erectile dysfunction of a cut-off score ≤ 25 on the IIEF erectile function domain. We chose the total IIEF score to evaluate the effect of the intervention. Our considerations for choosing the erectile function domain cut-off score was that this had been established as a criterion through comprehensive statistical evaluation (sensitivity = 0.97; specificity=0.88), whereas the cut-off score for the total IIEF to our knowledge has not been systematically evaluated. Our considerations for choosing the total IIEF as our primary outcome was that we wanted to benefit from the complete description of sexual function including the different domains, and not limit results to just erectile function. We have been as explicit as possible in our reporting of the different terms used.

Limitations

Self-reported outcomes (Study 1 + 2)

Self-reported outcomes are by nature subjective and non-responder bias may hide important information. The response rate was 50% in the cross-sectional study, which is relatively high compared to other studies dealing with sexual matters.[11,14] Responders seemed to be similar to the non-responders with regard to the demographic variables included. Nevertheless, it was not possible to analyze differences such as severity of heart disease, medication, and social factors. The study is of a considerable size and includes a consecutively recruited population of ICD patients. All questionnaires in both the cross-sectional study and the randomised clinical trial were answered independently of the researcher and were handled by CopenHeart personnel not involved in the analysis. In general, none of the questionnaires applied addressed ejaculation problems which are known to be highly prevalent. The IIEF assess ejaculation in relation to orgasm, however it does not evaluate it as a single subject. When planning the trial the intention was to include results from the 'Female Assessment of Male Erectile Function' questionnaire. Because less than 5% of partners answered the questionnaire results are not reported and the potential validation from partners is missing.

Limitations in the cross sectional study (study 1)

The research method was exploratory which allows for investigation of associations in areas of interest, but cannot provide conclusions about cause-effect relations.[119] This should be taken into account when interpreting the results from the cross-sectional study.

Bias in the CopenHeart$_{SF}$ trial (study 2)

The physical exploratory outcomes, pelvic floor strength and endurance as well as physical capacity were obtained by manual digital examination and cardiopulmonary exercise testing, which implies a possible day to day variation. However, these conditions were the same for both groups. Consistency in the method was secured as only two dedicated persons performed all the physical tests and a manual was developed to secure consistency in the way they performed them. Furthermore, they was blinded to allocation group and patients were asked not to say which group they belonged to, however, in some cases they revealed the information which might have introduced bias.

The risk of reporting bias was low as groups were balanced at baseline, all the planned outcome have been reported and intention-to-treat analysis were used.

Limitations in general

This thesis is limited to males. In women with heart disease sexual dysfunction is also highly prevalent,[5,114] and female sexual function should be taken into account in the clinical setting as well as in future research.

Generalizability/transferability

(Study I)

It is well established that erectile dysfunction is highly prevalent in both patients suffering from IHD and heart failure, which are the major patient groups receiving an ICD. The causes are primarily related to atherosclerosis but also anxiety and side effects from medication are known to have a substantial negative impact.[27] In this cross-sectional study we were not able to adjust for any of the potential causes in this cohort due to limitations of the data, which was a major concern. However, the sample was large and no demographic differences were found between responders and non-responders, which supports a high degree of generalizability. However, due to our choice of outcome instrument and inclusion criteria in the RCT we excluded patients without partners, representing more than 7 % of the population, which might have compromised the generalizability.

(Study 2)

Although inclusion rate were almost similar to other cardiac rehabilitation trials[14,120,121], only 24% were included which may have compromised the generalizability, and only a non-responder analysis or interviews with non-responders would have revealed if the study population was similar to the target population. However, when contacted during the inclusion process, several patients expressed that their sexual problems existed for so long that they either got used to it or didn't believe they could be relieved.

Concerns when doing a rehabilitation trial include that the usual care group may seek help in other places during the trial period. Both groups were encouraged to contact their general practitioner for PDE5 inhibitors if indicated. More patients in the usual care group did so compared with the

sexual rehabilitation group, though the difference was not significant. We did not record if an intervention such as pelvic floor exercise was performed, but since our physical data finds no increase in the control group it indicates that no such interventions were performed.

With regards to generalizability it is evident that participants in rehabilitation trials are highly selected regarding personal resources and competences. The most frequently reported barriers of attendance in cardiac rehabilitation are; gender, high age, living alone, low income and accessibility[122,123] and some of these factors might have compromised the generalizability. We included patients from two different hospitals, in order to include a broader and more diverse population.

(Study 3)

Within the hermeneutical qualitative methodology credibility, transferability, dependability and conformability can be used to assess a study's trustworthiness[124]. Credibility refers to the congruence between the realities of the interviewees and the results and is a parallel to internal validity, securing a match between the realities of the results and the interviewees. The person conducting the interview was a skilled interviewer; however, she had limited experience in cardiovascular disease, as well as in sexual problems. This secured a natural curiosity for pursuing the underlying truth. Only two of ten participants had an ICD in comparison to patients with ischemic heart disease. This may be reflected in the results, and should be taken into account when considering transferability of findings. However, relevant information regarding demographic data, exercise location, number of consultations, and time and place of the interview were presented. To ensure the dependability criteria, we sought to be as traceable and documentable in the research process as possible. Therefore we have presented the background, methodology, methods, processes and analysis. Conformability is related to the integrity of the findings that are rooted in the data. Thus, we presented the process of analysis, quotes, and meaning units leading back to the interviewees that support each finding. The interview study was conducted after the participants finished their intervention, but before the outcome analysis was performed, securing that the interviews was not guided by the results.

CONCLUSIONS

Conclusion based on the findings of this thesis:

Results from a cross-sectional study of sexual function in a large population of male patients with ICD showed that sexual dysfunction was common. Furthermore, primary prophylactic ICD indication and ATP therapy, but not shock therapy, were associated with a compromised sexual function

In a randomised controlled trial, comprehensive sexual rehabilitation significantly improved sexual function compared with usual care with a mean difference between groups of 6.7 points on the IIEF total score. Moreover pelvic floor strength and physical capacity improved significantly, but no effect was detected in relation to sexual adjustment to illness, self-rated health and mental health. Adherence was high and the intervention was safe.

From a qualitative interview study three themes reflected the lived experience of participation in a sexual rehabilitation program: 'a place of understanding' where patients state a need for a respectful environment open for emotionally laden topics; a theme describing a 'supportive atmosphere' that encourage and support to persistently exercise training; and finally the intervention was experienced as 'sexually empowering' in where patients described how they developed new skills to help constructive communication with their spouses and experienced the effect of the intervention. Participating in the sexual rehabilitation programme was experienced as efficient, meaningful, motivating and safe, but dependent on a professional setting. The intervention developed participants self-efficacy with regards to their sexual performance and relationship.

Clinical implications

This thesis highlights the need for rethinking sexual problems in the traditional cardiac rehabilitation and the outpatient setting, as the existing set-up does not consider patients' sexual problems in a systematic way.

We found a high prevalence of sexual dysfunction in patients with ICD, not limited to erectile dysfunction, but also orgasmic function, desire, intercourse and overall satisfaction are affected.

Furthermore, previous studies examining sexual function in patients with ICD applying a disease specific instrument reveal device-related concerns in addition. The IIEF and the disease-specific 'sex after ICD' questionnaire are easy self-administrable validated instruments that provide valuable information on patients' sexual function and can easily be used in a clinical setting. From previous studies it is evident that a large number of patients with IHD are suffering from sexual dysfunction. Screening instruments for patients with IHD should capture both the general sexual dysfunctions but also the more disease specific e.g. sexual fear and overprotectiveness from the partner. In the light of that, the routine use of questionnaires for diagnosing sexual dysfunction, both disease-specific and generic, should be considered in the outpatient setting for patients with IHD and/or ICD.

Findings from this thesis suggest that a comprehensive sexual rehabilitation programme could be adopted in an aftercare plan for patients with IHD and ICD to improve sexual function. The set-up of the intervention could be implemented in the general cardiovascular rehabilitation setting after proper instruction and further training of nurses and physiotherapists. It would appear that interviewed patients were happy with the different parts of the rehabilitation programme and that they gained an effect and new and useable knowledge. Considering that sexuality is a delicate subject and taboo for many the relatively high inclusion rate indicates that the programme is needed, and the high adherence rate suggested that the programme is feasible. Results from the CopenHeart$_{SF}$ trial added further treatment options to the choice of treatment for patients with heart disease and sexual dysfunction.

When planning after-care or rehabilitation programmes for patients with heart disease and sexual dysfunction, the themes identified from the qualitative study should be integrated to ensure that patients can return to a satisfying sexual life when having a heart disease. The findings of this study, as well as previous research, highlight the importance of a professional setting including certain competencies when handling the after-care of patients with heart disease and sexual problems. These specific competencies are not mandatory in most rehabilitation settings today, and might lead to patients not being met and helped with their sexual problems. This emphasizes a need for rethinking cardiac rehabilitation. As the sexual dysfunction is often multifaceted, the optimal approach should include a thorough investigation of the origin of the sexual problem and

subsequently an individualized strategy. Some patients might benefit from pelvic floor exercise as a single intervention, whereas others might need a more comprehensive approach including physical exercise training, sexual counselling, medication and couples therapy. Patients described physical limitations in relation to their heart disease and a corresponding fear of sexual activity. This is important to identify e.g. if an ergometer cycle test can establish patients' exercise capacity, which is often much higher that the amount of energy used on sexual activity. Sexual activity can be performed by cardiac patients who can exercise >3 to 5 METS without angina, excessive dyspnea, ischemic ST-segment changes, cyanosis, hypotension, or arrhythmia.[27] This is the same amount of energy used when e.g. mowing the lawn and can be reassuring information when patients are afraid of physical activity such as sexual activity. Sexual activity often includes a partner and since some of the identified themes involved interactions between participants and their partner it seems obvious to focus on including partners.

The amount of evidence pointing towards non-pharmacological interventions as a treatment option in patients with heart disease and sexual dysfunction is growing. The overall focus in the future should be on implementing these results in the clinical practice, to explore barriers in the health care system as well as in health professionals, and also to include women.

Future research

This PhD thesis adds important findings to current evidence on patients with heart disease and sexual dysfunction, and suggests that implementation is warranted. Nevertheless, there are still implications for future research that should be considered.

During the planning of this trial we considered the 2x2 factorial design in order to investigate the separate effects of psycho-education and physical exercise plus a combination. Nevertheless, as sexual dysfunction in patients with heart disease often contains multiple components, it was our belief that the combined intervention would provide the best outcome. However, during this study data revealed that some patients emphasized the role of pelvic floor exercise as the most important part, whereas others embraced the whole comprehensive approach and future research should focus on more individually tailored interventions based on the origin of the sexual dysfunction and the individual person, but also looking in to the dose-response relationship.

The longest follow-up was at 6 months. The possible long-term positive or negative effect of comprehensive sexual rehabilitation has not been established, and longer follow-up data are still needed.

ENGLISH SUMMARY

Evidence exists that patients with ischaemic heart disease (IHD) suffer from a high degree of sexual dysfunction. Further, it is evident that sexual problems are common in patients with implantable cardioverter defibrillator (ICD), though results need to be expanded. Systematic approaches for treatment of sexual dysfunction in the clinical setting are lacking. Besides the efficient and safe treatment with PDE5 inhibitors, several non-pharmacological treatment options e.g. physical exercise, pelvic floor exercise, life style changes and sexual counselling have been tested as single components for improving sexual dysfunction in patients with heart disease. The causes of sexual dysfunction are related to organic and psychological changes or it may appear as a side effect to medication and often it is a combination of factors. Therefore, it is hypothesized that an intervention consisting of physical exercise, pelvic floor exercise and psycho-education would be the most beneficial.

The overall aim of the thesis was to expand and consolidate existing knowledge regarding sexual dysfunction and the treatment of sexual dysfunction in populations of patients with IHD or ICD.

In order to achieve the aim the CopenHeart Sexual Function (SF) project was developed. The CopenHeart SF project consists of the CopenHeart SF trial, a randomised controlled trial plus supporting quantitative and qualitative data. The CopenHeart SF trial is the cornerstone of the CopenHeart SF project.

Our objectives were: to evaluate the prevalence of sexual dysfunction and it's associating factors in patients with ICD and to evaluate and describe the effect and meaning of a sexual rehabilitation programme.

A cross-sectional questionnaire survey was conducted to describe prevalence and distribution of sexual dysfunction, and to explore whether primary or secondary prophylactic ICD indication and antitachycardia pacing (ATP) therapy or shock therapy had an impact on erectile function (Paper 1). A randomised clinical trial investigating the effect of a comprehensive sexual rehabilitation programme, combining physical exercise, pelvic floor exercise and psycho-education for male patients with sexual dysfunction and IHD or ICD (Paper 2+3). Finally, a qualitative interview study was conducted to describe the lived experiences of participation in sexual rehabilitation (Paper 4).

The main findings were that, sexual dysfunction was highly prevalent in patients with ICD and was not limited to erectile dysfunction, but also orgasmic function, desire, intercourse and overall satisfaction are affected. Primary prophylactic ICD indication and ATP were associated with compromised sexual function, but not shock therapy.

Comprehensive sexual rehabilitation compared with usual care significantly improved sexual function and physical capacity but not sexual adjustment to illness, self-rated health and mental health. The adherence was high and the intervention was safe. Three themes were identified: ‘a place of understanding’ where patients state a need for a respectful environment open for emotionally laden topics; a theme describing a ‘supportive atmosphere’ that encourage and support to persistently exercise training; and finally the intervention was described as ‘sexually empowering’ by developing new skills to help constructive communication with their spouses. Participating in the sexual rehabilitation programme was experienced as efficient, meaningful, motivating and safe, but dependent on a professional setting. The intervention developed participants’ self-efficacy with regards to their sexual performance and relationship.

DANISH SUMMARY

Patienter med iskæmisk hjertesygdom (IHS) har en høj forekomst af seksuel dysfunktion. Det er endvidere klart, at seksuel dysfunktion er hyppigt forekommende hos patienter med implanterbar cardioverter defibrillator (ICD), men resultaterne bør uddybes yderligere. Systematiske behandlingsstrategier af seksuel dysfunktion hos patienter med hjertesygdom mangler. Udover effektiv og sikker behandling med PDE5 hæmmere, har flere non-farmakologiske behandlingsmuligheder som eksempelvis fysisk træning, bækkenbundstræning, livsstilsændringer og seksuel rådgivning, vist et potentiale i forhold til at forbedre seksuel funktion hos patienter med hjertesygdomme, men de er alle testet som enkelte komponenter og flere undersøgelser udført i svage designs.

Årsagen til seksuel dysfunktion er relateret til fysiske og psykologiske forandringer eller kan opstå som bivirkning til medicin, og det optræder ofte i kombination. Vores hypotese, var at en intervention bestående af fysisk træning, bækkenbunden træning og psykoedukation kan bedre seksuel dysfunktion hos patienter med hjertesygdom.

De overordnede mål for denne afhandling var: 1) at beskrive forekomsten og fordelingen af seksuel dysfunktion hos mandlige patienter med ICD, 2) at vurdere og beskrive effekten af og meningen med seksuel rehabilitering af mandlige patienter med IHS og / eller ICD og seksuel dysfunktion.

En tværsnitsundersøgelse blev gennemført for at beskrive forekomst og fordeling af seksuel dysfunktion, og for at undersøge om primær eller sekundær profylaktisk indikation for anlæggelse af ICD'en samt om antitachycardiapacing (ATP) eller stød kan påvirke seksuelle funktion (Artikel 1). En randomiseret klinisk forsøg, der undersøger effekten af seksuel rehabilitering indeholdende fysisk træning, bækkenbundstræning samt psykoedukation for mandlige patienter med seksuel dysfunktion og IHS eller ICD blev gennemført (Artikel 2 + 3). Endelig blev der foretaget en kvalitativ interviewundersøgelse med henblik på at beskrive levede erfaringer deltagelse i et seksuel rehabiliterings program (Paper 4).

De vigtigste konklusioner:

Hos patienter med ICD er seksuel dysfunktion hyppigt forekommende. Ikke kun erektil dysfunktion, men også orgasme, lyst, samleje tilfredshed og samlet tilfredshed var påvirket. Primær profylaktisk ICD indikation og ATP, men ikke chokterapi var associeret til erektil dysfunktion.

Seksuel rehabilitering sammenlignet med vanlig behandling viste en signifikant forbedret seksuel funktion, styrket bækkenbundsmuskulatur samt fysisk kapacitet. Selvvurderet helbred, angst og depression blev ikke forbedret. Adherence til interventionen var høj

Tre temaer afspejler patienternes levede erfaringer med deltagelse i et seksuelt rehabiliteringsprogram: 'sted til forståelse', hvor patienterne angiver et behov for et respektfuldt miljø med plads til følelsesladede samtaler; et tema om vigtigheden af en 'støttende atmosfære'; og endelig et tema der beskriver den'sekeulle udvikling'. Interventionen opleves som effektiv, sikker, motiverende, og afhængig af et særligt professionelt set-up.

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APPENDICES

Paper 1

Paper 2

Paper 3

Paper 4

Paper 1

High prevalence of sexual dysfunction among male patients with Implantable Cardioverter Defibrillator - a cross sectional questionnaire study

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ABSTRACT

Aim

In patients with Implantable Cardioverter Defibrillator (ICD) sexual function is sparsely described. We aimed to determine the prevalence and distribution of sexual dysfunction, and to explore whether primary or secondary prophylactic ICD indication and antitachycardiapacing (ATP) or shock had an impact on sexual function.

Methods

A cross-sectional survey of males with an implanted ICD was conducted at two University Hospitals in Denmark. Inclusion criteria were males above the age of 18 with an ICD. Exclusion criterion was no partner. Sexual function was assessed by the International Index of Erectile Function questionnaire and, data on implantation indication (primary/secondary prevention) and therapy such as ATP and shock (both appropriate and inappropriate) was obtained from the Danish ICD Register.

Results

Data from 415 questionnaires were analysed (response rate 50.2%). Patients had a mean age of 63.9± 12.1 years. Sexual dysfunction was present in 69% of patients, erectile dysfunction was present in 70% of patients, orgasmic dysfunction was present in 57.9% of patients, 82.8% had reduced sexual desire, 85.8% had intercourse satisfaction problems, and 76.9% experienced overall satisfaction problems. Patients with an ICD on primary prophylactic indication had more sexual dysfunction and erectile dysfunction compared to patients with an ICD on secondary prophylactic indication. ATP therapy, but not shock was associated to more erectile dysfunction.

Conclusion

Sexual dysfunction is common in patients with ICD and is not limited to erectile dysfunction, but also orgasmic function, desire, intercourse and overall satisfaction are affected. Primary prophylactic ICD indication and ATP, but not shock therapy is associated with compromised sexual function.

Introduction

Being able to function sexually is an important aspect of many peoples life and sexual problems and dysfunctions have a negative impact on quality of life and well-being[1-3]. In patients with implantable cardioverter defibrillators (ICD) sexual function is sparsely described and further information is warranted.

Background

Male sexual dysfunction is defined as problems in relation to erectile dysfunction, desire, orgasm, or ejaculation[4]. A common sexual disorder in cardiovascular disease patients is erectile dysfunction, defined as the inability to achieve and maintain an erection that enables satisfying sexual activity[4]. The underlying mechanism is often pathogenically related to cardiovascular disease, but may also be related to psychological issues or a side effect from medication[5,6]. Erectile dysfunction is highly associated with age[7]. In ICD patients several small studies reveal long term abstinence or a decrease in sexual activity after the ICD implantation [8-11]. Besides erectile dysfunction, sexual dysfunction reflecting the clinical definition of sexual dysfunction has not been investigated in ICD patients. Sexual problems, however, have been described as overprotectiveness from the partner, lack of sexual interest, fear of death if the ICD did not fire, or fear of ICD shock therapy[10-12]. Shock during sexual activity is experienced in varying degrees, from less than 1% to 18%[10,11,13]. Although shocks are infrequent, fear of the ICD firing during sexual activity seem to have a more profound impact as this is experienced in almost 30 %[10,11]. See Textbox .1 for definitions of the different types of ICD and treatments.

Moreover, studies show that therapy, such as antitachycardiapacing (ATP) or shock from the ICD may predict a poor psychological outcome[14-16] though they do not show if this outcome this is reflected on sexual function.

The majority of data on sexual health in ICD have all been collected using the same questionnaire instrument "The sex after ICD questionnaire", that has been developed especially for ICD patients[11]. The instrument provides a thorough overview of the specific sexual problems in an ICD population, however it does not possess the ability to detect trends over time and evaluate results of an intervention. Moreover, the instrument does not reflect the clinical definition of male sexual dysfunction which allows for comparison between other diagnostic groups. Finally, it does not cover the severity of erectile dysfunction.

The role of primary versus secondary prophylactic indication on psychological outcomes have been discussed previously, but no negative impact have been established in relation to patients quality of life and distress[17], although secondary prophylactic indication seem to affect partners level of anxiety[15]. The indications' influence on sexual function has not yet been evaluated.

Altogether, sexual problems are well established; however, sexual dysfunction reflecting the clinical definition and its associating factors in ICD patients are poorly described. Therefor the objective of this study was to describe (i) the distribution of sexual dysfunction among male ICD patients using a validated generic instrument, (ii) to evaluate if ATP and shock therapy from the ICD are associated with sexual dysfunction and, (iii) to investigate whether primary or secondary prophylactic indication adversely affect sexual function.

Methods and participants

Study design

This study was designed as a cross-sectional study. The study was a part of the recruitment process of the CopenHeart SF trial[18], a randomised controlled trial (RCT) which evaluates the effect of a

comprehensive rehabilitation programme to decrease sexual dysfunction in male cardiovascular disease patients. The present study was conducted as a postal survey and patients were contacted as a part of the recruitment for the RCT. Patients were recruited from two University Hospitals in the Danish Capital Region. The sample includes male patients with ICD.

Eligibility criteria and recruitment

Hospital records were screened consecutively according to date of ICD implantation in the period from March 2013 to June 2015. Inclusion criteria were males above the age of 18 with an ICD. Exclusion criterion was not to have a partner at time of answering the questionnaire. The partner exclusion criterion was applied as a consequence of the inclusion and exclusion criteria in the RCT trial and because the instrument, The International Index of Erectile Function questionnaire[19] used for measuring sexual dysfunction, covers partnered patients.

The following information was extracted from the hospital records: age and implantation date, as defined by the main CopenHeart SF trial[18].

Questionnaires were sent by mail to 826 patients. Participants filled out the International Index of Erectile Function (IIEF) questionnaire that concerns sexual function and consists of five domains[19].

Data sources

In order to investigate if implantation indication or therapy from the ICD was associated with a poor sexual outcome, data on implantation indication (primary/secondary prevention) and therapy such as ATP and shock (both appropriate and inappropriate) was obtained from the Danish ICD Register[20].

Prevalence and distribution of sexual function was measured by the Danish version of the IIEF [19]. The IIEF was developed in conjunction with the clinical trial programme for sildenafil, and has

since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of erectile dysfunction. It has been linguistically validated in 32 languages and used as a primary endpoint in more than 50 clinical trials[19,21]. It consists of 15 items including five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, which are based on patients experiences during the last four weeks. Higher scores indicate a better sexual function. The total IIEF-15 summary score (minimum 5 points, maximum 75 points) is categorized as "good" (60–75), "fair" (44–59), and "poor" (5–43) [22] The erectile function domain has a cut-off score to diagnose and divide erectile dysfunction into four levels of severity: severe erectile dysfunction score 6-10, moderate erectile dysfunction score 11-16, moderate to mild erectile dysfunction score 17-21, mild erectile dysfunction score 22-25 and score above 25 indicates no dysfunction. For the other domains a dysfunction was determined if scores were: 8 or less for the orgasmic function domain, the sexual desire domain, the overall satisfaction domain and a score of 12 or lees for the intercourse satisfaction domain[23]. The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of sensitivity and specificity[21].

Study size

The sample size has not been determined statistically, but was alone determined by the number of recruitment questionnaires generated in the CopenHeart SF RCT trial. Based on the already enrolled patients in the main trial the number of questionnaires distributed was 826.

Statistical methods

Data was tested for normality using the Kolmogorov-Smirnov test. Continuous data were presented as mean scores with corresponding standard deviation and compared using either the Student's *t*-test or the Mann-Whitney depending on the normal distribution. Proportions were compared with

the chi-square test. Responders were compared with non-responders according to demographic variables. For each analysis, persons with missing information on the included variables were excluded. Logistic regression was used to explore associations of ATP and shock, and whether primary or secondary prophylactic indication had the greatest implication. Analyses were performed as age adjusted univariate analyses with the three variables ATP, shock and indication, and a multivariate analysis with age, ATP, time from ICD and indication.

Ethics

The study was a sub study of the overall CopenHeart SF, which is approved by the regional ethics committee (no H-4-2012-168) and the Danish Data Protection Agency (no 2007-58-0015). The study was performed in accordance with good clinical practice and the Declaration of Helsinki. Clinicaltrials.gov identifier: NCT01796353.

Results

Of the 826 patients approached, 476 returned the questionnaire, 25 returned the questionnaire but regretted to fill it out and 35 did not have a partner. Thus, a sample of valid 415 (response rate 50.2%) questionnaires were analysed (Figure 1).

The mean age of the study population was 63.9±12.1 with a range from 19 to 93 years. Participants had their ICD for a mean of 4.9±3.8 years (range 1 to 21) and 38 patients had a cardiac resynchronization therapy defibrillator. Patients had a mean of 0.5±1.8 appropriate shocks (range 0 to 18), 0.2±1.4 inappropriate shocks (range 0 to 33), 5.1±42.4 appropriate ATP (range 0 to 1021), and 0.6±5.8 inappropriate ATP (range 0 to 110) (Table 1). The mean score on the Total IIEF scores was 39.6±24.2 indicating a poor sexual function, and only 31 % of the population had a good sexual

function according to the total IIEF score (score 60-75). Mean scores on the other domains were as follows: 14.5±11.4 on the Erectile Function domain, 5.6±4.3 on the Orgasmic Function domain, 6.0±2.3 on the Sexual Desire domain, 5.6±5.6, on the Intercourse Satisfaction domain, and 6.1±2.7 on the Overall Satisfaction domain.

In the total responder population the prevalence of erectile dysfunction of any degree as an erectile function domain score below 25, was present in 70.5% of the patients. The distribution of erectile dysfunction was as follows: 29.6% normal erectile function, 7% mild erectile dysfunction, 7% mild to moderate erectile dysfunction, 7.5% moderate erectile dysfunction and 48.9% severe erectile dysfunction. Advancing age (continuous) was highly associated with erectile dysfunction with an OR 1.11 95% CI: 1.08-1.13. When the age groups were stratified by decades (Table 2), more than 90% of the patients above 70 year had erectile dysfunction defined as an erectile function domain score below 25.

When the other IIEF domains were investigated separately the prevalence of orgasmic dysfunction was present in 57.9% of patients, 82.8% had lowered sexual desire, 85.8% had intercourse satisfaction problems and 76.9% experienced problems related to overall satisfaction and when stratifying for primary versus secondary prophylactic indication erectile function domain and the total IIEF score differed significantly in the two groups (Figure 2). Age was not significantly different between the primary prophylactic indication group and the secondary prophylactic indication group (p=0.48).

Analysis showed that mean intercourse satisfactions scores and mean overall satisfaction scores were statistically significant related to severity of erectile dysfunction ($p<0.001$). Lower scores were observed when erectile dysfunction severity increased (Table 3). The mean satisfaction score in the intercourse satisfaction domain as well as the mean scores in the overall satisfaction domain

revealed that only patients without erectile dysfunction had a mean score consistent with good satisfaction.

When investigating the associations with erectile dysfunction, age adjusted logistic regression showed that patients with primary prevention indication had a higher risk of having erectile dysfunction with an OR 2.06, 95% CI: 1.2-3.5 compared with patients having ICD on secondary prevention indication. Receiving ATP from the ICD compared with not receiving ATP was associated with erectile dysfunction OR 1.8, 95% CI: 1.1-3.2, orgasmic dysfunction OR 2.1, 95% CI: 1.3-3.5, lowered intercourse satisfaction OR 1.9, 95% CI: 1.0-3.8, but not lowered sexual desire and overall satisfaction. We found no association with regards to shocks from the ICD, neither appropriate nor inappropriate and no association with time from the ICD. In the multivariate analysis ATP remained associated to erectile dysfunction OR 2.1, 95% CI: 1.1-3.8, but not indication.

Discussion

To our knowledge, this study is the first to address sexual dysfunction in a large male patient population with ICD using a validated generic instrument that reflects the male definition of sexual dysfunction. We found that sexual dysfunction was highly prevalent in ICD patients, with all domains affected. Patients with primary prophylactic indication suffered from a higher amount of sexual dysfunction including erectile dysfunction compared with patients having an ICD on secondary prophylactic indication. Sexual dysfunction was adversely affected by ATP however shock did not seem to have an impact.

Our findings showed that more that 69% suffered from sexual dysfunction, and more than 70% from erectile dysfunction. Erectile dysfunction was increasing with increasing age. The prevalence is higher than observed at matching age in the general population (38%)[24], higher than in an atrial fibrillation population (57%)[23] similar to patients with ischaemic heart disease (75%)[25] though not

as frequent as patients with heart failure (89%)[26]. Existing studies examining sexual problems in patients with ICD are not directly comparable to this present study as they use another instrument; however problems with erection and desire have been reported in the studies by Berg et al. and Steinke et al. who found erectile problems, in 56% and 57% and desire problems in 29% and 38% respectively of their population[10,11]. This is in contrast to this study where erectile dysfunction was present in more than 70% of participants and sexual desire dysfunction in more than 82%. Previous study population samples were smaller, between 82 and up to 121 participants compared with 415 in this study. More patients in the Berg study had an ICD for primary prophylactic prevention indication 65% vs 45% in ours. Mean age in the two studies was 59 and 65 respectively not differing from our study. A plausible explanation might be due to the differences in the instrument. Another reason for low sexual desire can be related to erectile dysfunction. It is well known that men with erectile problems tend to withdraw from their partner with a decrease in sexual response as a consequence. Men with low sexual response are more prone to have lack of sexual interest/ lowered desire[27].

Of the 70 % of the patients experiencing erectile dysfunction, 50% had severe erectile dysfunction, which completely prevents sexual intercourse. This is a high proportion of patients not being able to enjoy sexual activity in the form of sexual intercourse. It is well established that erectile dysfunction is highly prevalent in both patients suffering from ischemic heart disease and heart failure, the major patient groups receiving an ICD, and that the causes are primarily related to atherosclerosis but also anxiety and side effects to medication is known to have a substantial negative impact[5]. We were not able to adjust for any of the potential causes in this cohort due to limited descriptive data and therefore the result must be interpreted as an overall prevalence in a relative large population sample of ICD patients.

The study revealed that a decrease in erectile function was associated with a decrease in both intercourse satisfaction and overall satisfaction, and that it was only patients without erectile dysfunction that experienced good intercourse and overall satisfaction. This implies that even patients with the mildest form of erectile dysfunction experience adverse impact on sexual satisfaction. The same trend is described by Makarem et al.[28] in a group of haemodialysis patients. However, in this study it was only overall satisfaction affected by erectile dysfunction and also patients with mild erectile dysfunction seemed to have a good overall satisfaction. In contrast, though not completely comparable, a study by Giraldi et al. [29] found that in a randomly chosen Danish population, 11% of males suffering from erectile dysfunction were unsatisfied with their sexual life. Erectile dysfunction was measured by the same instrument, the IIEF, but with a lower cut-off score for erectile dysfunction on $\leq$21, probably resulting in a smaller group with erectile dysfunction compared to ours.

Primary prophylactic prevention indication meaning that the patient has not had ventricular arrhythmia prior to ICD implantation was associated with more sexual dysfunction compared to patients having ICD on secondary prophylactic indication. It has been hypothesized that patients with secondary prophylactic indication would have a larger amount of psychological distress as a result of index event e.g. cardiac arrest, leading to the ICD implant[30], which could have influences sexual function, however our data could not confirm that. The majority of patients having an ICD for primary prophylactic indication are patients with ischaemic heart disease, heart failure symptoms corresponding to New York Heart Association (NYHA) function class II and III despite optimal medical treatment[31], reduced ejection fraction (EF), which are all factors known to be associated with sexual dysfunction[5]. We have not been able to adjust for these factors in our analysis.

We found that patients receiving ATP from the ICD experienced more sexual dysfunction compared with patients not experiencing ATP, also when adjusting for age and indication. Many patients receiving ATP will not experience the ATP it selves, but will feel the malign arrhythmia as palpitations and/or dizziness, which might remind them of being chronically ill and vulnerable, all psychological impacts associated to outcomes such as anxiety and concerns[32] which might reflect on sexuality as well. In a study by Hoektsra et al.[33], patients with heart failure without sexual dysfunction reported significantly higher emotional quality of life than those with sexual dysfunction, indicating a possible connection between psychological outcomes and sexual dysfunction.

Due to our choice of outcome instrument and inclusion and exclusion criteria in the RCT we excluded patients without partners, representing more than 7 % of the population, which might have compromised the generalizability.

Clinical implications

The IIEF is an easy self- administrable validated instrument that provides valuable information on patients' sexual function and it can easily be adopted in a clinical setting. Therefor the routine use of IIEF for diagnosing sexual dysfunction should be considered in the ICD clinic. However, since the IIEF only evaluates the level of different dysfunctions and not the underlying cause it should not serve as a single instrument. For patients with sexual dysfunction on the IIEF, a thorough sexual and medical history is important in order to plan the right treatment addressing sexual health. Treatment suggestions could include medical treatment with PDE5-inhibitors, adjusting cardiovascular medication, psychosocial support or risk factor reduction including physical exercise[5].

Strength and Limitations

Self-reported outcomes are by nature subjective. However, in this study we used the IIEF, which is recognized as the gold standard in evaluating sexual dysfunction. The response rate was 50%, which is relatively high compared to other studies dealing with sexual matters[2,11], however it might include some non-responder bias. However, the responders seemed to be similar to the non-responders although it was not possible to analyse differences such as severity of disease, medication, and social factors.

The study is of a considerable size and includes a consecutively recruited population of ICD patients.

Conclusion

Sexual dysfunction is highly prevalent in ICD patients, and it is not limited to erectile dysfunction, but also affects desire, orgasm, and satisfaction in a negative way. Primary prophylactic ICD indication and ATP, but not shock therapy is associated with compromised sexual function. Knowledge about ICD patients' sexual function is warranted and the present results may contribute to a better understanding of the subject. Further, this study highlights the need for a routine screening aiming at identification of patients with sexual dysfunction in the ICD clinic. Moreover, this study illustrates an unmet need for interventional studies to improve poor sexual outcome in this patient group.

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Textbox 1. Definitions of the different types of ICDs and treatment from the ICD

Primary Prophylactic indication ICD: Primary prevention prophylaxis ICD implantation is indicated in populations at high risk of sudden cardiac death due to VT/VF

Secondary Prophylactic Indication ICD: For secondary prophylaxis, ICD placement is indicated as initial therapy in survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT).

Appropriate antitachycardiapacing (ATP): Antitachycardiapacing on a malign arrhythmia e.g. ventricular tachycardia

Inappropriate antitachycardiapacing (ATP): Antitachycardiapacing on a benign arrhythmia e.g. a fast atrial fibrillation or as a consequence of device problems

Appropriate Shock: High voltage shocks targeted a malign arrhythmia

Inappropriate Shock: High voltage shock targeted a benign arrhythmia or device problems

Figure legends

Figure 1. Flowchart

Figure 2. Percentage of patients with dysfunction or affected satisfaction by domain of the International Index of Erectile Function. Patients were subcategorized by primary or secondary prophylactic indication. For each domain, dysfunction and affected satisfaction is defined as follows: a score of 25 or less for erectile function domain, a score of 8 or less for the orgasmic function domain, the sexual desire domain, the overall satisfaction domain and a score of 12 or lees for the intercourse satisfaction domain.

Figure 1 Flowchart

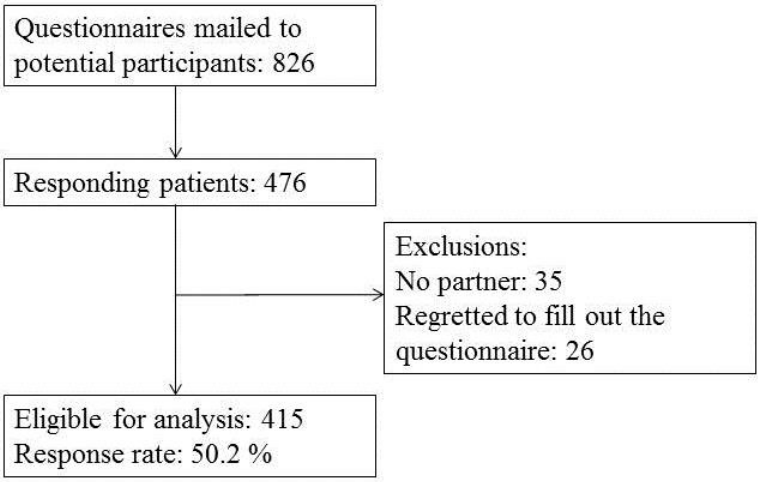

Figure 2

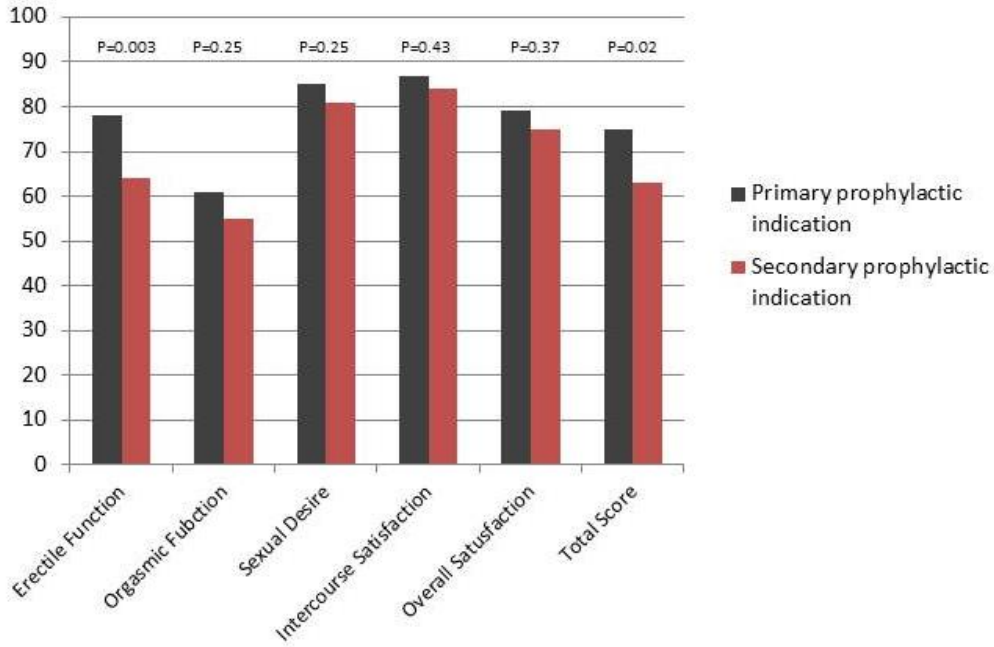

Table 1 Baseline variables for the participating ICD population

Variable	Responders	Non-responders	P^*
N	415	411	
Age	64.4±11.6	63.5 ±12.8	0.27
Time since ICD in years	5.1±3.8	4.7±3.7	0.11
CRTD	19	19	0.99
Number of appropriate ATP therapies	7.8±11.3	2.3±58.7	0.06
Number of Inappropriate ATP Therapies	0.6± 5.6	0.6±6.1	0.90
Number of appropriate high-voltage shock therapies	0.5 ±1.7	0.44 ±1.8	0.55
Number of inappropriate high-voltage shock therapies	0.2±1.8	0.2±1.1	0.98
Primary prophylactic indication	188	174	0.44
Secondary prophylactic indication	224	232	

Values are n or mean ± SD.

Abbreviations: CRTD, Cardiac Resynchronization Therapy Defibrillator; ATP, Anti Tachycardia Pacing; * Significance test for responders versus non-responders using *t* test for continuous variables and chi-square test for categorical variables.

Table 2 Prevalence and severity of erectile dysfunction in all and according to age group in ICD patients

Prevalence of Erectile dysfunction n (%)						
	19-40 y (n=18)	41-50 y (n=34)	51-60 y (n=66)	61-70 y (n=132)	71-80 y (n=109)	81-93 y (n=11)
ED severity						
No ED (IIEF score >25)	16 (88.9)	20 (58.8)	27 (40.9)	39 (29.5)	6 (5.5)	1 (9.1)
Mild (IIEF score 22-25)	2 (11.1)	2 (5.9)	8 (12.1)	9 (6.8)	5 (4.6)	0 (0)
Mild to moderate (IIEF score 17-21)	0 (0)	1 (2.9)	5 (7.6)	11 (8.3)	9 (8.3)	0 (0)
Moderate (IIEF score 11-16)	0 (0)	2 (5.9)	8 (12.1)	10 (7.6)	7 (6.4)	1 (9.1)

Severe (IIEF score 6-10)	0 (0)	9 (26.5)	18 (27.3)	63 (47.8)	82 (75.2)	9 (81.8)

ED, Erectile Dysfunction; y, years.

Table 3 Relationship between Satisfaction scores and Erectile Dysfunction (ED) severity

	ED severity				
	No ED	*Mild*	*Mild to moderate*	*Moderate*	*Severe*
Mean Intercourse Satisfaction Score*	12.2±2.1	9.3±2.4	8.7±2.7	4.8±4.1	0.9±2.3
Mean Overall Satisfaction Score*	8.4±1.5	7.1±1.6	6.4±1.6	5.6±2.0	4.4±2.4

* Significant on one way ANOVA. Trend across groups. Scores are mean ± SD.

Paper 2

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BMJ Open

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

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ABSTRACT

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

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

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

Strengths and limitations of this study

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

Registration: Clinicaltrials.gov identifier: NCT01796353.

BACKGROUND

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

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

Standard treatment

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

Non-pharmacological treatment potentials

Non-pharmacological interventions possess potential in reducing sexual dysfunction. Lifestyle factors such as cigarette smoking, hyperlipidaemia and a sedentary lifestyle all predict erectile dysfunction[4 5] and these are the same risk factors that predict coronary artery disease. A recent meta-analysis of six randomised trials with 740 patients with no known heart disease, showed that lifestyle modifications such as physical exercise and pharmacotherapy for cardiovascular risk factors were associated with a significant improvement in erectile function.[33] Furthermore, a randomised trial investigating the effect of exercise training 3 h/week or more in patients with no heart disease showed a significant result in improving the person's erectile function compared with controls with no exercise training.[34] We hypothesise that these lifestyle modifications can also improve sexual dysfunction in patients with already established heart disease. A systematic literature search showed five randomised clinical trials which examine the effect of physical exercise on sexual dysfunction.[35–39] Overall, 591 patients with heart disease were included and the effect was significant in three of the five trials.[37–39] However, the trials are characterised as being of small sample sizes, using non-validated tools and mainly focusing on the time before patients return to sexual activity and not on the ability and quality of the sexual performance. Randomised trials that address the psychological aspects of sexual dysfunction are limited in patients with heart disease. However, one randomised trial testing the effect of sexual therapy showed some promising trends when it comes to improving the frequency and quality of sexual activity in male patients post-cardiac event beyond the usual cardiac rehabilitation.[40] However, due to the limited power of the sample in this trial, it did not allow the detection of significant effects. The role of pelvic floor exercises as a treatment of erectile dysfunction is not tested on patients with heart disease, but in the general population 40–47% had regained normal erectile function after 3–4 months of training the pelvic floor muscles.[41 42] As the condition of sexual dysfunction often includes both physical and psychological components, it is plausible to believe that patients with heart disease and sexual dysfunction benefit from a comprehensive rehabilitation intervention[43 44]consisting of a psychoeducational component and an exercise training component including pelvic floor exercises.

TRIAL OBJECTIVES

The objective of the CopenHeartSF is to investigate benefit and harm on the sexual function of male patients with ischaemic heart disease or patients with implantable cardioverter defibrillator of a comprehensive sexual rehabilitation programme, consisting of a psychoeducative component and a physical exercise component, including pelvic floor exercises. The primary hypothesis is that, a comprehensive sexual rehabilitation programme improves sexual function, as assessed by the International Index of Erectile Function (IIEF) questionnaire[45 46] in males with sexual dysfunction and ischaemic heart disease or patients with implantable cardioverter by 3.5 points in the experimental group compared with the control group after completion of the programme. The estimated increase in primary outcome is based on a study that examines the effect of a physical intervention in patients with cardiovascular disease taking PDE-5 inhibitors.[34] The secondary hypothesis is that sexual function, measured by the sexual domain in the Psychosocial Adjustment to Illness Scale (self-reported version; PAIS-SR) questionnaire[47] improves by two points in the experimental group compared with the control group after completing the programme. The estimated increase in secondary outcome is based on two studies that examine the prevalence of sexual dysfunction in patients with heart failure.[48 49]

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

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

METHODS

CopenHeartSF is an investigator-initiated randomised clinical superiority trial with blinded outcome assessment, with 1:1 central randomisation to a comprehensive sexual rehabilitation programme plus usual care or usual care alone. Based on sample-size calculations, 154 patients will be recruited from two university hospitals in Denmark. The CopenHeartSF trial is a part of the overall CopenHeart project, consisting of several randomised clinical trials (http://www.CopenHeart.org), designed to develop evidence-based knowledge of rehabilitation among patients with complex cardiac conditions. Major parts of the CopenHeartSF methods section and trial design in this article are similar to other randomised clinical trials, CopenHeartIE,[50] CopenHeartRFA[51] and CopenHeartVR.[52]

Study population and eligibility criteria

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

Experimental intervention

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

The physical components

Physical exercise

The goal of physical exercise is to achieve an improvement in the patient's physical work capacity, and to eliminate the fear and uncertainty the patient may feel in relation to sexual activity as a form of physical activity. The physical exercise intervention is based on The European Society of Cardiology recommendations for physical activity for cardiovascular patients.[54] The European Society of Cardiology recommends that all adults promote and maintain their fitness, muscle strength, flexibility and bone health several hours a week. Training must be of high intensity and of 30 min duration.[54] Furthermore, the intervention is supported by European recommendations for physical training in cardiac patients[55] and has been tested in two large rehabilitation trials, COPE-ICD and DANREHAB.[56 57] A professional physiotherapist with specific knowledge of cardiac rehabilitation initiates the physical exercise programme. Together with the patient, the physiotherapist plans and prepares a physical exercise protocol, taking into account the patient's clinical condition and physical abilities. Sixty minutes is allocated for the initial consultation and preparation of individual training protocol, including pelvic floor exercise instructions.

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

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

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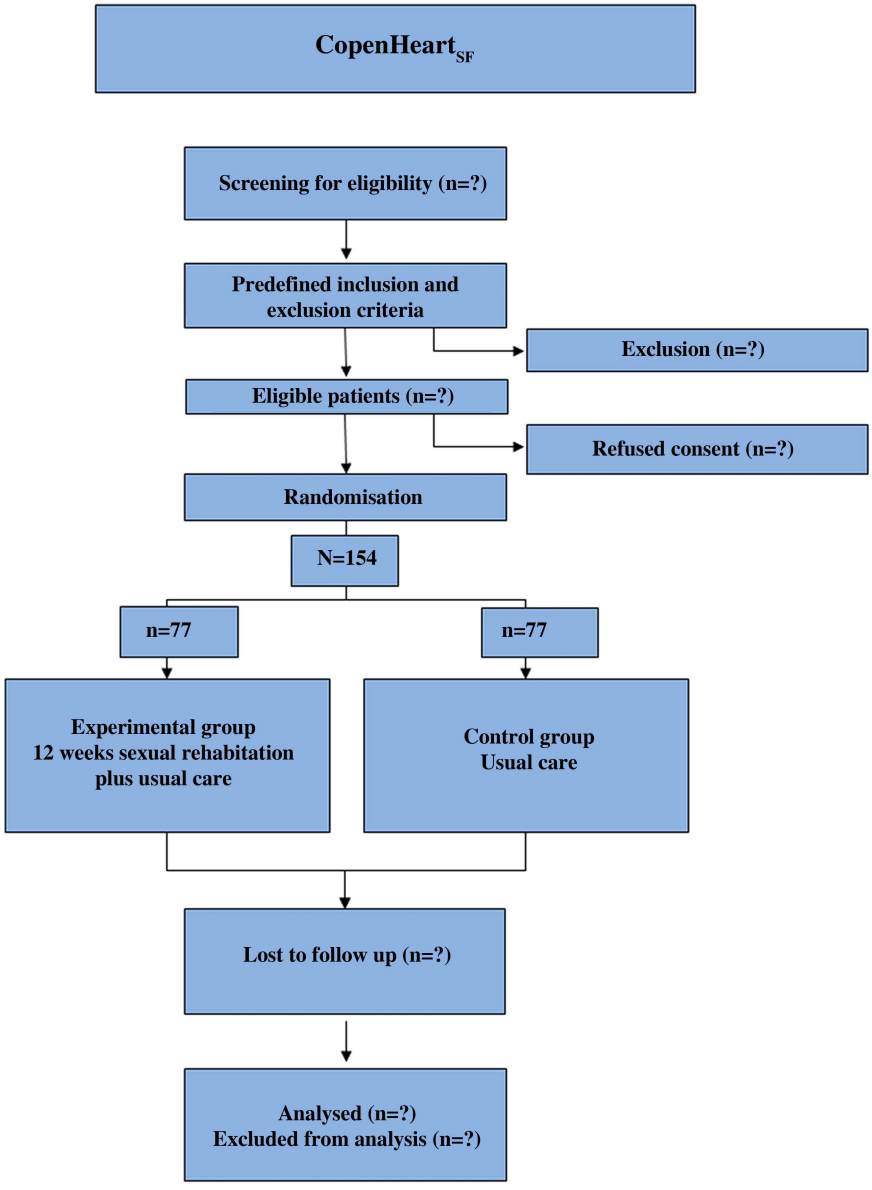

Figure 1 Flow chart.

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

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

Pelvic floor exercise

The bulbocavernosus muscle and the ischiocavernosus muscle, two superficial pelvic floor muscles, are active during erection and enhance rigidity. The bulbocavernosus muscle encircles 33–50% of the base of the penis.[41] The pelvic floor training regimen is inspired by Dorey *et al*,[63] who have developed a training regimen for male patients for use in randomised clinical trials. The regiment is developed and tested in a different patient population, and we have therefore modified it to fit cardiovascular patients. Patients are instructed in pelvic floor exercises by a skilled physiotherapist. Patients are instructed to perform their pelvic floor exercises twice daily. Studies showed that a few strong or maximum contractions are more effective when it comes to gaining muscle hypertrophy than several less strong contractions.[63] Patients are instructed to tighten their pelvic floor muscles as strongly as possible (as if to prevent flatus from escaping) three times when lying, three times when sitting and three times when standing. The duration of the contraction is up to 10 s each, and patients are informed to have a 10 s break between each contraction. The physiotherapist instructs the patients on how to contract the bulbocavernosus and ischiocavernosus muscles. In order to ensure that the right muscles are involved, attention is placed on the

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

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

The psychoeducational components

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

A specially trained nurse is responsible for the psychoeducative intervention. The intervention takes a theoretical basis of the patient-centred approach where the emphasis is on support and education. The conversations are based on a holistic view of the patient and focus on the handling of life and managing sexual dysfunction. The intervention is targeted at the modifiable parameters that are reported to affect sexual dysfunction. The psychoeducative intervention is inspired by RR Parse's[64] 'Human Becoming Practice Methodologies' three dimensions which can be described as (1) discuss and give meaning to the past, present and future; (2) explore and discuss events and opportunities and (3) pursue imagined possibilities. According to this theory, there are three ways to alter its perceived health: creative ideas, see, hear and feel how a situation could be if it was lived in a different way; recognising personal patterns and value priorities and shed light on the paradoxes by looking at incongruence in a situation and change the view of reality. The nurse is 'truly present' in the process through discussion, quiet contemplation and reflection. The psychoeducative intervention plus physical exercise was tested in the COPE-ICD trial, with positive effects on psychological well-being (mental health) and the general health subscale of the Short Form-36.[56] The nurse is trained in the psychoeducative conversation through teaching and supervision of nurses who have experience with the 'Human Becoming Practice Methodology' from the COPE-ICD trial. It is based on the theoretical literature that forms the basis for understanding the processes of practice methodology and existing specialty specific knowledge about heart disease, related symptoms and sexology. The supervisor observes and provides feedback in relation to the methods and goals of the conversation. The emphasis is on openness in the interviews and on the nurse's ability to: be silently present while the patient talks, ask questions that encourage reflection, let the patient find answers and solutions and contribute with knowledge, provide advice and guidance when requested and relevant. The training of the nurse takes place prior to the intervention. In practice the intervention will be handled by one nurse with several years of experience working with cardiac patients and trained in sexology. The sexology experience is gained in a 2-week intensive course on basic and clinical sexology including training in sexual therapy. Supervision from a sexologist is available during the intervention. The nurse will conduct consultations with patients individually, and patients are informed that they are welcome to bring spouses/relatives. The consultation will take place in a quiet room in an outpatient setting and last for 45 min. An inspirational guide will form the basis for the consultations. The guide consists of several elements and issues (medical, psychosocial, educational and sexual) that work as inspiration (see box 1).

Usual care

Participants in the experimental group and in the control group will receive the usual care according to current guidelines. Usual care is, for patients for whom it is not contraindicated, treatment with PDE-5 inhibitors. Patients who are candidates for PDE-5 inhibitors are encouraged to contact their general practitioner in order to establish the treatment. Use of PDE-5 inhibitors will be monitored in both intervention groups. To assess outcome measures, patients in the control group will be asked to complete questionnaires on equal terms with participants in the experimental group. In addition, they will be tested in the form of cardiopulmonary testing (peak VO_2) and pelvic floor muscle strength and endurance at baseline and at the end of the trial.

Outcomes and data collection

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

Primary outcome

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

Box 1 Inspiration guide for psychoeducational consultations

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

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

Secondary outcome

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

Exploratory outcomes

A more extensive evaluation of physical, psychological and demographic status over time will be performed. Physical examination will include pelvic floor strength and endurance assessed according to the Modified Oxford grading scheme which is a manual digital examination of the pelvic floor. It is tested and validated and used in several trials.[65 66] Furthermore, physical capacity will be measured by peak VO_2 using cardiopulmonary exercise testing (Ergo-Spiro CS-200, Schiller, Switzerland) with measurement of oxygen uptake (VO_2), heart rate (HR, bpm),ventilation rate (l/min), ventilation frequency (number/min), respiratory expiration ratio (CO_2/O_2 in %), blood pressure, physical activity level (METS) and gas exchange (VO_2 andVCO_2) during progressive loading and in the following recovery period. The test is conducted before the training programme initiates. Intensity performed as a ramp protocol (load gradually increases) with the initial work load of 25 W and increased by 12.5 W every minute until exhaustion, usually but not always, is where the patient's oxygen uptake reaches a steady state despite additional load. The test follows current standards for cardiopulmonary exercise testing.[67] The full test procedure is described by Rasmussen *et al*.[50] Additionally a series of questionnaires, regarding health-related quality of life, anxiety and depression and sexual dysfunction are administered (see table 1).

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

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

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

Blinding

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

Sample size and power calculations

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

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

Study procedure and randomisation

To achieve our estimated sample size of 154 participants, patients will be identified from the hospital databases. Patients will be selected consecutively. Patients with an implantable cardioverter defibrillator are required to have the device implanted more than 1 year prior to inclusion and patients with ischaemic heart disease 1 year from event and backward. The 1 year limit has been set so that patients are past their rehabilitation if any is provided. Patients will receive the IIEF questionnaire[45] by mail including a stamped return envelope. Patients with a score ≤25, the accepted cut-off score[46] on the initial screening, are invited to attend a preliminary interview with the offer to participate in a randomised clinical trial targeting sexual problems. The participant information is sent to the patient along with the invitation. This gives the patient an opportunity to read the material in advance and to prepare possible questions. At the initial interview/meeting it is determined whether the patient meets the criteria for participating in the trial. If patients are suited and want to participate they will be randomised to a comprehensive sexual rehabilitation programme plus usual care versus usual care alone. Stratification will be according to patient group (patients with ischaemic heart disease or implantable cardioverter defibrillator) and age (≤59 or ≥60 years) and randomised 1:1 to the experimental group or the control group. Randomisation will be performed centrally by the trial coordination centre, Copenhagen Trial Unit, according to a computer-generated allocation sequence with a variable block size concealed from the investigators. Allocation to the intervention groups is carried out when the investigator calls the Copenhagen Trial Unit. Relevant information (personal identification number, strata, etc) is typed into a computer system, and then the participant will be allocated to an intervention group and awarded a four-digit randomisation number. The investigator then informs the patient of the result and on how to proceed by letter. Thus, neither investigators nor patients or relatives can influence to which group the patients are allocated. For both groups, follow-up assessment will take place after 12 weeks (only physical evaluation), 16 weeks and 6 months. Questionnaires will be completed electronically in the questionnaire system 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 http://www.copenheart.org and enter with the login and password. If patients do not complete the questionnaire electronically, the material can be sent in paper form and an independent trial personnel then enters the responses into the database. Thus data management is handled independently from the researchers who interpret the data. All data are stored electronically in a coded database, and in an independent spread sheet, only accessible for the CopenHeart group. The recruitment process will continue until the number of 154 has been reached.

Statistical analysis

Analysis of primary and secondary outcomes

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

Models and analytical techniques

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

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

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

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

$$\begin{aligned} Y = &\text{intercept} + aY_{\text{baseline}} + bG + cI \\ &+ dI{:}G + eT + fI{:}T + gI{:}T{:}G \end{aligned} \qquad (2)$$

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

Missing values

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

ETHICS AND DISSEMINATION

The trial complies with the latest Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT01796353). Patients are informed about the trial in writing as well as verbally and only included if a written informed consent is obtained. Patients are assessed in accordance to whether it is safe for them to perform sexual activity. This is carried out according to recommendations from the Princeton consensus group.[32 53] If patients are suited and want to participate they will be enrolled in the trial. Trial participants are free to withdraw their informed consent at any time and be treated according to the departments' standard treatment procedures. A patient will be withdrawn from the trial if the trial participant withdraws his consent and will, in connection therewith, be informed that termination of the trial will have no implications for his future treatment. Patients who leave the trial will be politely asked for permission to continue to collect data and to use already collected data. If the patient gives permission, he will be included in the final analysis. Only if the patient refuses use of already collected data, will all data relating to him be destroyed. All patient data will be handled and stored in accordance with Danish Data Protection Agency rules and patients are ensured anonymity. The trial will be conducted according to the Act No. 593 of 14 June 2011 on Act on Research Ethics Review of Health Research Projects. The investigator will immediately notify the regional ethics committee if, within the interventions period, there occur serious adverse events, serious adverse reactions or suspected unexpected serious adverse reactions. The report will be accompanied by comments on possible implications for the trial, and notification will be made within 7 days after the investigator has knowledge of the event. The trial has no data monitoring committee however an internal monitor will perform random checks to see if the trial staff work according to the protocol. No risks are anticipated to occur during the sexual rehabilitation programme. As far as we know, there is no previous risk associated with nursing consultations. If the nurse, during the consultation, identifies a need for further consultations with professionals, she will encourage the participant to seek help from the general practitioner, psychologist or in their usual outpatient setting. Risks associated with exercise training and testing are sudden cardiac death associated with ventricular arrhythmias, acute myocardial infarction, and in patients with chronic heart failure, pulmonary oedema and deterioration in left ventricular function.[73] The last is only found in one study from 1988[74] and has not subsequently been demonstrated in larger studies.[75 76] In a recent French study of more than 25 000 patients with ischaemic heart disease, one-third with chronic heart failure found the risk of cardiac complications at 1:8500 exercise testing and 1:50 000 patient exercise hours.[77] Increasing exercise intensity and age are risk indicators. Therefore, the training intensity will be conducted as moderate high intensity (less than 80% of VO_2 max). To achieve cardiovascular adjustment exercise training as well as testing begins with a warming-up period and ends with a cool-down period, with a gradual downward adjustment of exercise intensity and HR, rather than an abrupt end. This cardiovascular adjustment has been shown to reduce the risk of ischaemia and arrhythmia in connection with physical exercise.[44 62] Participants must mainly exercise in an upright position to decrease left ventricular filling pressure and risk of ischaemia or heart failure triggered ventricular arrhythmias. When these precautions are respected, exercise training as well as exercise testing are considered to possess a low risk for the participants. There is, as far as we know, no previously known risk associated with pelvic floor exercise. Testing or examination of the pelvic floor may be associated with discomfort for the participants but is not considered to be associated with any risk. Staff members will be trained according to guidelines to handle any emergencies.

Dissemination plan

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

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

DISCUSSION

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

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

Trajectory

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

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

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Competing interests None.

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

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

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Paper 3

Sexual rehabilitation improves sexual function in male cardiac patients with impaired sexual function – results from the randomised CopenHeart$_{SF}$ trial

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ABSTRACT

Background Sexual dysfunction is common in patients with either ischemic heart disease (IHD) or implantable cardioverter defibrillator (ICD) and has a negative impact on quality of life. Non-pharmacological treatment options are lacking. The purpose of this trial was to assess the effect of sexual rehabilitation versus usual care for males with sexual dysfunction and either IHD and/ or ICD.

Methods Participants were randomized to a 12 weeks sexual rehabilitation program consisting of physical exercise training including pelvic floor exercise, and psychoeducational consultations, or usual care. Inclusion criteria: erectile dysfunction, IHD or ICD, and having a partner. Exclusion criteria: high risk patients (cardiovascular status), urinary tract diseases, intense exercise >3 times/week, neurological deficit. Primary outcome: sexual function as quantified by the golden standard International Index of Erectile Function (IIEF). Secondary outcome: sexual domain on the Psycho-social Adjustment to Illness Scale. Exploratory outcomes: exercise capacity (Watt max and VO2 peak), pelvic floor strength/endurance, self-reported health and mental health.

Results 154 male patients were included with a mean age at 61.6 years (standard deviation 6). Sexual rehabilitation compared with usual care improved sexual function with a mean difference IIEF score of 6.7(95% Confidence Interval: (CI) 3.1-10.4, (P<0.0003) at 4 months and a mean difference of 6.7, 95% CI: 3.2-10.1, (P< 0.0002) at 6 month. No effects were seen on the secondary outcome. Sexual rehabilitation also improved Watt max with a mean difference of 10.3, 95% CI: 3.6-16.9, (P<0.003), and Pelvic floor strength (P<0.01). No differences were seen on pelvic floor endurance, self-reported health and mental health.

Conclusion Sexual rehabilitation compared with usual care improves sexual function and physical exercise capacity.

Clinical Trial Registration The CopenHeart$_{SF}$ trial is registered at ClinicalTrials.gov (NCT01796353).

BACKGROUND

Sexuality is an important part of people's physical and mental health. Patients with cardiovascular disease have increased prevalence of sexual dysfunction[1,2], which has a negative impact on quality of life and well-being in men with cardiovascular disease. Sexual dysfunction is associated with an increase in anxiety and depression.[3-6] Disorders of male sexual function are categorized in relation to desire, ejaculation, orgasmic and erectile function.[7] The most common sexual disorders among men are premature ejaculation and erectile dysfunction, the latter defined as the persistent inability to obtain or maintain an erection which enables satisfying sexual activity.[8] The causes of erectile dysfunction can be classified mainly as organic, with a vascular, hormonal or neurogenic etiology, or psychogenic where the etiology is connected to psychiatric disorders, performance anxiety, interpersonal problems or concerns related to somatic disease, or a combination of both. Furthermore, erectile dysfunction can be due to an adverse effect from medications.[9]

In male patients with ischemic heart disease (IHD) erectile dysfunction is prevalent in up to 75% of patients[10-12], whereas for male patients with implantable cardioverter defibrillator (ICD), up to 57% are affected.[13,14] Despite the fact that several international guidelines recommend that health professionals address the topic of sexuality in patients with heart disease,[15,16] this is rarely done in clinical practice.[17] Guidelines and clinical practice on how and where patients with heart disease and sexual dysfunction should be treated are lacking, except for consensus about prescription of phosphodiesterase type 5 (PDE5) inhibitors.[16] Despite these recommendations, a study of 1455 males revealed that only 14% with erectile dysfunction report taking medications to improve sexual function.[18] Non-pharmacological interventions such as physical exercise including pelvic floor exercise possess a potential in reducing sexual dysfunction.[19-22] A systematic review and meta-analyses evaluating the effect of physical exercise on erectile function found that in 478 patients (7 trials included) physical exercise improved erectile function measured by the International Index of

Erectile Function (IIEF) with a mean difference of 3.85, 95% CI: 2.3-5.37.[23] Only one of the included trials involved patients with heart disease, the only one which did not detect a statistically significant improvement. The risk of bias in this trial was assessed as medium to high mainly due to issues related to randomisation, blinding of patients, personnel and outcome assessment. The role of pelvic floor exercises as a treatment of erectile dysfunction has not been tested on patients with heart disease, but in the general population 40% to 47% had regained normal erectile function after 3-4 month of training the pelvic floor muscles.[20,24] Psychological interventions, such as sexual therapy and counselling have shown a beneficial effect in males with erectile dysfunction[25], though a recent Cochrane systematic review identifies only 3 randomized clinical trials including a sexual counselling intervention in patients with a history of heart disease, and found a clear need for a methodological rigorous adequately powered randomized trials.[26] As the condition sexual dysfunction often includes both physical and psychological components[9] we hypothesized that, patients with IHD and patients with ICD suffering from sexual dysfunction would provide a solid base for knowledge regarding sexual dysfunction but also benefit from a comprehensive rehabilitation intervention consisting of both a psycho-educational counselling component and an exercise training component including pelvic floor exercises. The objective of the CopenHeart$_{SF}$ was to investigate the effects of a comprehensive sexual rehabilitation program, consisting of a physical exercise component, including pelvic floor exercises plus a psycho-educative component on sexual function of male patients with IHD or with ICDs.

METHODS

Our trial protocol has previously been published.[27] The CopenHeart$_{SF}$ trial is a randomized clinical trial comparing sexual rehabilitation versus usual care. The trial complies with the Declaration of Helsinki, was approved by the Danish Data Protection Agency (j.nr. 2007-58-0015), and has been

approved by the Regional Ethics Committee (j.nr. H-4-2012-168). The CopenHeart$_{SF}$ trial is registered at ClinicalTrials.gov (NCT01796353).

Participants, setting and recruitment

Male patients ≥18 years with erectile dysfunction and IHD verified by coronary angiography or an implanted ICD, had a partner, were Danish speaking and provided informed written consent were eligible for the trial. Patients were screened consecutively in hospital databases and had to be one year from their coronary angiography/ICD implantation. Exclusion criteria were: patients with intermediate or high risk in relation to their cardiovascular status according to the Princeton group[28], known urinary tract disease, performing intense exercise training more than three times weekly, known neurological or orthopedic deficits, or participated in other on-going research projects. Eligible patients were initially screened with the International Index of Erectile Function (IIEF) Questionnaire[29] along with an information letter regarding the RCT by mail. Responders indicating interest in the trial and with a score ≤ 25, the accepted cut off score indicating erectile dysfunction,[30] was contacted by telephone and provided with written information either by mail or email. Patients were contacted by telephone after a few days. This allowed for the patients to read the material in advance and to prepare possible questions. If the patients were interested, they were invited to an inclusion interview where written and oral consent was obtained from all participants.

Randomization and blinding

Participants were centrally randomized 1:1 to intervention plus usual care or to a control group receiving usual care by a computer-generated allocation sequence with varying blocks sized 4, 6, and 8, and were stratified according to patient group (IHD or ICD) and age (≤ 59 or ≥ 60 years). Allocation was performed by telephone contact to the Copenhagen Trial Unit. In rehabilitation intervention studies, it is not possible to blind participants and interventional staff;[31] however,

allocation of participants, all physical testing, data collection, statistical analyses, and drawing of conclusions were performed blinded to allocation group.

Intervention group

The experimental group was offered physical exercise, pelvic floor exercise, and psychoeducational consultations for 12 weeks and was urged to continue with the exercises hereafter.

Physical exercise

The aim of the physical exercise intervention was to improve endothelial function, exercise capacity, and to eliminate the fear and uncertainty the patient may feel in relation to sexual activity as a form of physical activity. Three weekly sessions of 60 minutes for twelve weeks were offered. A single training protocol was applied to all participants, but individualized when needed. The physical training intervention was initiated by trial physiotherapists at a hospital (The Heart Centre, Rigshospitalet) in accordance with relevant evidence,[32] with 1-3 mandatory training sessions using t-shirts with wireless integrated ECG electrodes (Corus-Fit Cardio and Corus Exercise Assistant, CEA, V.2.0.16, Finland). For the continuing training program three options were available: 1) supervised training at hospital; 2) training at a local study-protocol certified supervised facility; and 3) home-based training with contact to a physiotherapist when needed. The training program consisted of graduated cardiovascular training and strength exercises. The cardiovascular training was based on intensity of the Borg scale[33] and performed as interval training. The strength-related exercises primarily targeted the lower body muscles comprising four exercises. The sessions started with 10 min warm up bicycling followed by 20 min bicycling with increasing intensity (interval training. This was followed by 20 min strength training and 10 min stretching exercises. To achieve cardiovascular adjustment and reduce the risk of cardiac arrhythmias and ischemia, the training sessions ended with a cool down period.

Pelvic floor exercise

The aim of the pelvic floor exercise intervention was to enhance strength and endurance of the pelvic floor. Both the ischiocavernosus and bulbocavernosus muscles are superficial pelvic floor muscles that are active during erection and they enhance rigidity. The bulbocavernosus muscle encircles 33–50% of the base of the penis.[20] Patients were instructed to tighten their pelvic floor muscles as strongly as possible, two times a day: three times when lying, three times when sitting and three times when standing. The duration of the contraction was up to 10 seconds each, and patients were informed to have a 10 second break between each contraction.[34] The physiotherapist instructed the patients on how to contract the bulbocavernosus and ischiocavernosus muscles at the initial training session.

To encourage adherence, and monitor compliance, training diaries (physical exercise and pelvic floor exercise) and pulse watches were used (Polar Watch, Polar HR RS 400 monitors, Polar Electro, Finland).

The psychoeducational consultations

The aim of the consultations was to guide patients to interpret and react to relevant physical and psychological symptoms compromising participant's sexual health. A patient-centered approach inspired by RR Parse's Human Becoming Practice Methodologies[35] was applied. Consultations were carried out by a specially trained nurse, and were conducted as individualized sessions or including the participant's partner. An inspirational guide consisting of components such as: sexological and medical history, psychosocial and psychological concerns, was developed, and served as a basis for the consultations. The topics discussed were: causes of sexual dysfunction, sexual concerns, level of sexual activity, types of activities, relationship, sexual problems, co-morbidity and medication.

Usual care

Participants followed their usual outpatient visits according to treatment guidelines.[15,36] Besides usual care both groups were encouraged to contact their general practitioner for prescription of PDE5-inhibitor treatment if not contraindicated.[16]

Outcomes

Both groups underwent outcome assessment at baseline, after 12 weeks (physical tests), as well as at 4 months and 6 months (questionnaire based data).

Primary outcome

Sexual function was measured by the total IIEF score at baseline, at 4 months and at 6 month. The IIEF questionnaire consists of 15 items including five domains of sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. A high score indicates a better function. The total IIEF-15 summary score ranges from 5 to 75 points. On the erectile function domain a sum score of 25 or less indicated erectile dysfunction. The IIEF meets psychometric criteria for test reliability and validity, and has a high degree of sensitivity and specificity.[29] The IIEF is considered the gold standard instrument for efficacy assessment in clinical trials of sexual dysfunction.[29,30]

Secondary outcome

Sexual adjustment to illness was measured by the Psychosocial Adjustment to Illness Scale (PAIS), sexual relationship domain at baseline, and at 4months and 6 months. The PAIS meets psychometric criteria for test reliability and validity.[37] The sexual relationship domain evaluates shifts in the quality of sexual relations due to the current illness. It consists of six items and the total score ranges from 0 to 18 points. Low score indicates good adjustment. No cut off score exists.[37]

Exploratory outcomes

The explorative physical outcomes are, pelvic floor strength and endurance by the Danish version of the Modified Oxford Grading Scheme[38] and peak VO2, heart rate (beats per minute), blood pressure, power at maximum exercise (Watt max), anaerobic threshold, and VE/VCO2 slope measured by cardiopulmonary exercise testing, at baseline and at 12 weeks. The questionnaire-based exploratory outcomes are the different domains of the IIEF[29] representing erectile function, orgasmic function, desire, intercourse and overall satisfaction. Self-reported health by the Short Form-36(SF-36)[39], anxiety and depression by the Hospital Anxiety and Depression Scale (HADS)[40], and quality of life by the EQ-5D-5L[41] assessed at baseline and at 4 months and at 6 months. The 'Sex after ICD' questionnaire[13] was evaluated in ICD patients at the same time.

Safety

Cardiopulmonary exercise testing was performed by experienced personnel, and instructions for completion and termination was defined according to guidelines.[42] All events were registered and evaluated with the trial physician.

Statistical analyses

There has been an erratum to the statistical analyses plan published in the protocol paper.[27]

Sample size and power calculations

We planned a trial of the continuous variable IIEF[29] with one control per experimental participant. In a previous trial, the IIEF within each participant group was normally distributed with a SD of 6 points.[43] If the true difference in the experimental and control means was 3.5 points, we needed to include 77 experimental participants and 77 control participants (total 154 participants) to obtain a power of 95% (β=5%) and a type 1 error probability of 5%. Using this sample size, a standard deviation (SD) of 4 points and an alternative hypothesis of a mean difference of 2 points for the

secondary outcome[37] and a type 1 error probability of 5%, the corresponding power for the secondary outcome, the PAIS was found to be 87%.

Statistical analyses

The analyses followed the intention-to-treat principle with two-sided significance test at the 5% level using the SAS version 9.3 and R version 3.1.2 for the analyses. Continuous outcomes followed the same procedure as described in the following for the primary outcome. The primary model for assessing the effect of intervention was the univariate general linear model. This model assesses whether there is an effect of the intervention 16 weeks after randomization. Since there was a statistically significant effect, test was performed to evaluate whether there was a difference between the two patient groups regarding the size of the effect. The secondary model included follow-up data using a mixed model because of repeated outcome measures. In this model the baseline value of the outcome, intervention indicator (I), disease group indicator (G), the interaction between I and G and stratification variable (aged above and below 60 years) were included. Subgroup analyses of the primary outcome and all analyses of the secondary and exploratory outcomes were considered hypothesis generating if the effects are statistically significant ($P<0.05$). If missing values of the primary outcome was above 15% or the P-value of Little's test was below 5% multiple imputation techniques were used. As the intervention effect of the primary analysis in the univariate general linear model was significant, the analysis was supplemented with worst/best case analyses. The results of the multiple imputed dataset were considered the primary outcome analysis. Cohen's d was calculated for all continuous outcomes to test the clinical effect.[44] All statistical analyses were performed blinded to allocation group.

Results

Between March 2013 and June 2016, 3248 patients were identified for questionnaire pre-screening. Of these 647 male patients were identified with sexual dysfunction of whom 154 (24%) were included and randomized (Figure 1). The participants included had a mean age of 62 years, 64% were NYHA I, 79 had IHD and 75 had an ICD. Of those with an ICD, 49 had IHD, 16 with heart failure and 10 had inherited heart disease. Six percent had high cholesterol. Participants had mean BMI of 28 kg/m^2 and 95% had sexual dysfunction of a physical origin as defined by Vlachopoulos et al.[9] (Table 1). Nine percent were treated with PDE5 inhibitors at baseline.

Outcomes

Primary and secondary outcomes

Sexual rehabilitation compared with usual care had a beneficial effect on sexual function with a mean difference IIEF score of 6.7, 95% CI: 3.1-10.4, (P<0.0003) at 4 months after randomization in favor of the sexual rehabilitation group. The Cohen's d was 0.4, indicating a small clinical effect.[44] Results persisted at 6 months with a mean difference IIEF score of 6.7, 95% CI: 3.2-10.1, (P< 0.0002) at 6 month. To test if one of the disease groups carried a larger effect that the other interaction test was performed and no interaction between intervention group and disease group (IHD or ICD) was detected (Table 2). A best-worse-case scenario analysis showed a mean difference on 9.9, 95% CI: 5.7- 14.0, (P<0.0001) for best-worst- case scenario, and for worst-best case scenario a mean difference on 2.5, 95% CI: -2.0- 6.9, (P=0.28). Tests for interaction between intervention group and disease groups, intervention group and time, as well as intervention group, time and disease group were all non-significant.

No statistically significant differences between groups were found on the secondary outcome PAIS (Table 2).

Exploratory outcomes

Sexual rehabilitation group improved significantly erectile function 3.9, 95% CI: 2.1-5.7, (P<0.001) and orgasmic function 1.2, 0.3-2.2, (P=0.01) at 4 months and at 6 months as well as sexual desire 0.6, 95% CI: 0.2-1.0, (P=0.002) and intercourse satisfaction 1.0, 95% CI: 0.0-1.9, (P=0.0499) at 6 months (Table 3).

For the PDE5-inhibitor intake at 4 months, 7 (9%) participants in the intervention group reported taking PDE5-inhibitors, whereas there were 15 (19%) in the control group (P=0.09). At 6 months, the corresponding numbers were 7 (9%) and 9 (11%) respectively (p=0.6).

The P values of the effect of the intervention were not below 0.05 for self-reported health and mental health. On the physical outcomes, the intervention showed an effect on pelvic floor strength (categorical) between groups with a P value below 0.05 (Table 4), but no effect on pelvic floor strength (continuous) and endurance (Table 5).

Results from the cardiopulmonary test showed a mean difference between groups on maximum exercise capacity (Watt max) of 10.3, 95% CI: 3.6-16.9, (P=0.003) but no difference on VO2 peak (Table 4). Within groups a difference at 4 months on the IIEF total score and Erectile Function domain score of 4.2 and 3.3 respectively was detected (Table 6). On the "Sex after ICD questionnaire" statistically fewer patients in the sexual rehabilitation group experienced problems with erectile function (P=0.02) and overprotectiveness from the partner (P=0.047) compared with control.

Deviations from the protocol

The 'Female Assessment of Male Erectile Function' questionnaire was distributed for patients to have partners fill out. Since less than 5% of partners answered the questionnaire results are not reported.

Safety

One serious adverse event occurred in one patient in the intervention group. Due to angina pectoris during exercise training he was admitted to hospital, but discharged after 4 hours of observation and remained in the trial.

Adherence to intervention

A total of 64 (85%) patients participated in the exercise intervention with an average of 25.3 training sessions, and 64 (85%) participated in the sexual consultations with an average of 2.4 sessions during the trial. Of the participants returning their diary and pulse watch (52 participants), 29 (56%) conducted ≥ 26 exercise sessions (≥75%). When adherence was defined as participating in at least 50% of the sessions, 39 patients (75%) were adherent. Participants received between one to four psycho-educational consultations. The goal was set after each consultation and the number of consultations was determined between the participant and the nurse.

DISCUSSION

The CopenHeart$_{SF}$ trial is to our knowledge the largest randomized clinical trial investigating comprehensive sexual rehabilitation including physical exercise, pelvic floor exercise and psycho-education in male patients with heart disease and erectile dysfunction. The results show a beneficial effect of sexual rehabilitation on the primary outcome, the IIEF. Furthermore, beneficial effects on the exploratory outcomes: erectile function, orgasmic function, pelvic floor strength, and maximum exercise capacity were found. We found no effect on sexual adjustment to illness and mental outcomes. The intervention appeared safe with only one serious adverse event occurring.

No trials have previously investigated the effect of a comprehensive intervention on sexual dysfunction, and only the individual components of our intervention have been evaluated previously. In a randomized trial Maio et al.[43] investigated the effect of physical exercise in addition to PDE5 inhibitors versus PDE5 inhibitor administration alone, with, a total IIEF mean difference score of 5.5 and a mean difference score of 2.0 in the erectile function domain was detected in favor of the exercise compared to 6.7 and 3.9 in the present trial. Participants in the Maio trial consisted of a population of males with known sexual dysfunction and no cardiovascular disease, indicating less cardiovascular burden on their sexual function. Our results are also partly supported by a more recent non-randomized controlled study from Kalka et al.[45]They found that in a population of patients with IHD endurance training compared to a group not receiving endurance training did not improve erectile function significantly between groups, however a significantly improvement was detected within the training group.

We found a statistically significant improvement in maximum exercise capacity (watt max), but not measured by VO2 peak. All the physical test results however pointed in the same direction as the watt max, supporting the hypothesis that there is an improvement in overall physical capacity. Compared to other rehabilitation trials consisting of the same physical exercise intervention[46,47] results from our trial showed less improvement in both Watt max and VO2 peak. This might be due to recruitment of patients in a chronic stable phase, rather than in a discharge follow-up setting.

The Pelvic Floor Exercise intervention on top of lifestyle advice has been investigated previously and shown to significantly improve the erectile function domain of the IIEF.[20] This trial supports our findings but is not completely comparable as they include non-cardiovascular patient populations which can be expected to have a lower level of cardiovascular induced erectile dysfunction. We found an improvement in strength of the pelvic floor muscles, but not on endurance which is in accordance with findings from a randomized trial in post stroke patients also

evaluating a 12 weeks pelvic floor training intervention.[38] Results from that trial showed no differences on endurance after 12 weeks between groups but found a late response after follow up (6 months) indicating that the effect on endurance might be delayed compared with strength. However, it seems that even a small effect on physical capacity and few consultations are efficient in improving sexual function.

A recent Cochrane systematic review investigating the effect of sexual counselling on sexual function in cardiovascular patients [26] revealed three randomized trials with a total of 381 participants. The trials included were of very low quality according to the GRADE criteria, and the authors concluded that no high quality evidence to support the effectiveness of sexual counselling for sexual problems in cardiovascular patients exists.

We did not find the expected effect on self-reported health and mental health, probably because there is no such effect in our patients. However, in other patient groups results may be different. Thus, our patients had a relatively high self-reported health with baseline scores on 51.7 and 51.8 on the Mental Component Scale of the SF-36, and 45.3 and 46.7 on the Physical Component Scale, which are higher compared with other cardiac disease populations entering a comprehensive rehabilitation intervention.[46,47] The same trends are seen in regards to anxiety, where mean scores on 3.8 and 4.2, and in relation to depression with scores on 2.6 and 3.0 reflecting a relative small burden of anxiety and depression compared to other rehabilitation studies [46,47] and in a large epidemiological study.[48]

Within the screened patients, only 24% accepted participating in the present trial. This is similar to inclusion in a study by Steinke, a study concerning sexual matters[13], which included 21%, though a lower inclusion rate compared to the COPE-ICD trial[49] and the Danrehab trial[50], two comprehensive rehabilitation trials, which included 33% and 48% respectively. Both trials recruited

patients face-to-face, which is presumed to increase inclusion compared to patient recruitment by mail and questionnaires. We believe that 24% reflects that sexuality is a delicate subject, and that further sexual rehabilitation interventions are clearly needed. The inclusion rate on 24%, however; may have compromised the generalizability, and only a non-responder analysis or interviews with non-responders would have revealed if the study population was similar to the target population.

Adherence was high in our trial, 75% of participants completed more than 50% of the sessions. Adherence to cardiac rehabilitation has proven to be a challenge and several studies show that only around 30% of eligible patients continue in these programs[51,52] indicating a meaningful and workable design of the CopenHeart$_{SF}$ trial.

A Minimal Clinically Important Difference (MCID) score on the erectile function domain has been established and found to be 4, with variation ranging according to baseline severity (mild: 2; moderate: 5; severe: 7)[53] The mean difference found in our study of 3.8 on the Erectile Function domain indicates a clinically relevant effect, which is supported by a calculation of the Cohen's d effect size of 0.4 indicating a small, but clinical significant effect.

Half of the patients had an ICD, which in several studies are described as an extraordinary situation related to sexuality[13,14], as they experience problems related to the device. Furthermore partner problems have been described. The intervention was designed to address some of these factors, which was also the case in several patients. The Sex after ICD questionnaire, distributed only to the ICD group revealed a clear difference between groups in favor of the rehabilitation group with regards to a better erectile function and less overprotectiveness from the partner. Most patient had a sexual dysfunction of physical origin and no interactions was detected in the interaction test between disease groups indicating that none of the patient groups had a greater effect of the intervention that the other.

Strengths and limitations

In rehabilitation trials participants are not blinded, which might have led to bias, however, the trial was designed with central stratified randomization which secures against selection bias,[54,55] and all physical tests as well as statistical analysis was assessed blinded to intervention group, which reduced detection and interpretation bias.[54,55] Self-reported outcomes, such as questionnaires, are by nature subjective and potentially biased with a risk of recall bias. Nevertheless, questionnaires were distributed electronically and independently from the researchers. Questionnaires were all well recognized and validated instruments. All analyses were performed according to the intention to treat.

Conclusion

The CopenHeart$_{SF}$ trial demonstrated that compared with usual care, sexual rehabilitation improved sexual function significantly and results persisted over time, but did not seem to improve mental health and self-reported health. The intervention was associated with a relatively high adherence and appeared safe.

Perspectives and future studies

These data demonstrate that comprehensive sexual rehabilitation should be offered for patients with sexual dysfunction in relation to IHD and ICD. Even a small effect on physical capacity and few consultations seems to be beneficial in improving sexual function, so future studies should focus on investigating the association between duration and amount of intervention and response on sexual function.

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Disclosures:

None

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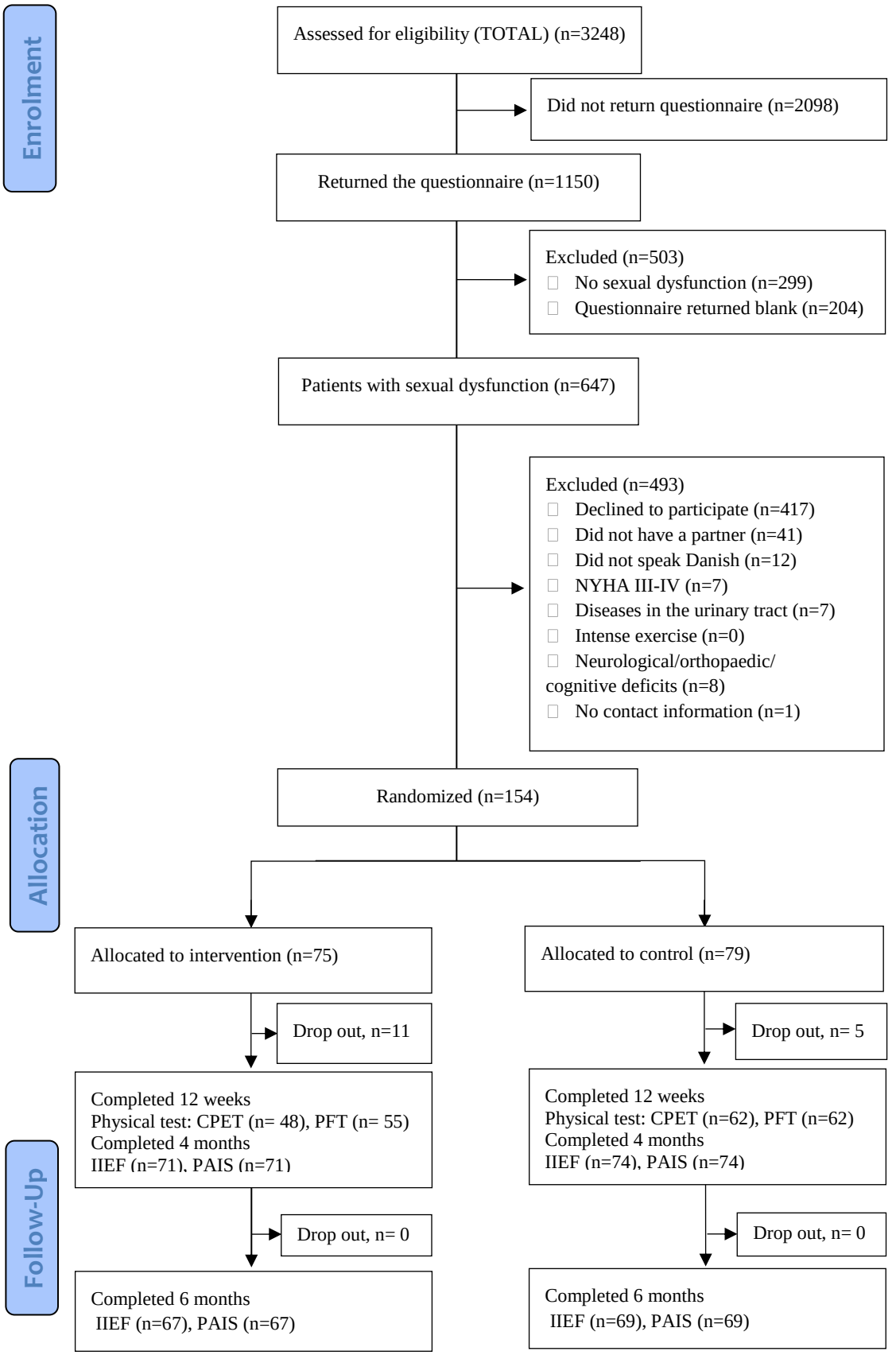
Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.



NYHA, New York Heart Association; CPET, cardiopulmonary exercise testing; PFT, Pelvic Floor test; IIEF, International Index of Erectile Function; PAIS, Psychosocial Adjustment to Illness Scale.
The 5 drop-outs in the control group, and 11 in the intervention group were due to new onset of other disease or withdrawal of consent.

Table 1. Baseline characteristics

	Sexual rehabilitation group (n=75)	Control group (n=79)
Age, mean (SD)	62.3 (9)	60.9 (9)
NYHA I, n (%)	50 (67)	49 (62)
NYHA II, n (%)	25 (33)	28 (38)
Stratification diagnosis		
Ischemic Heart Disease, n (%)	39 (49)	40 (51)
Implantable Cardioverter defibrillator, n (%)	36 (48)	39 (52)
□ Heart Failure, n (%)	7 (9)	9 (11)
□ Inherited Heart Disease*, n (%)	3 (4)	7 (9)
□ Ischemic Heart Disease, n (%)	26 (35)	23 (32)
Implantation indication ICD		
□ Primary prophylactic indication	23(64)	20(51)
□ Secondary prophylactic indication	13(36)	19(49)
Diabetes Mellitus, n (%)	15 (20)	16 (20)
Dyslipidemia, n (%)	5(7)	1(1)
Sexual dysfunction of physical origin n (%)	71 (95)	75 (95)
Current smoking, n (%)	9 (12)	12 (15)
Body Mass Index, mean (SD)	27.5 (3.8)	28.3 (4.1)
Longest educational level		
Primary school, n (%)	11 (14.7)	8 (10.1)
High School, n (%)	2 (2.7)	1 (1.3)
Vocational, n (%)	42 (56)	42 (53)
Short/medium higher education, n (%)	6 (8)	16 (15)
Long higher education, n (%)	14 (18)	12 (15)
Occupational status		
Retired, n (%)	42 (56)	43 (54)
Still working, n (%)	33 (44)	36 (46)
Physical activity		
Inactive, n (%)	37 (49)	42 (53)
Performing > 1 hour exercise per week	38 (52)	37 (47)
Medication		
PDE5 inhibitors, n (%)	6 (8)	8 (10)
Beta-blockers, n (%)	56 (75)	55 (70)
Amiodarone, n (%)	1 (1)	1 (1)
Calcium antagonists, n (%)	8 (11)	8 (11)
Ace inhibitors, n (%)	41 (55)	34 (43)
Nitrates, n (%)	3 (4)	10 (13)
Vitamin K antagonists, n (%)	5 (8)	4 (5)
Insulin, n (%)	1 (1)	2 (3)
Acetylsalicylic acid, n (%)	59 (79)	57 (72)
Statin, n (%)	64 (85)	66 (84)

* Inherited Heart Disease includes, long QT syndrome and cardiomyopathies

Table 2. Primary and secondary outcomes; mean differences reported

	Follow-up at 4 months[†]					Follow- up at 6 months[†]				
	N	Estimate (95%CI)	P value	SD*	Cohens d	N	Estimate (95%CI)	P value	SD*	Cohens d
IIEF total score	145	6.7 (3.1-10.4)	**0.0003**	19.0	0.4	146	6.7 (3.2-10.1)	**0.0002**	19	0.4
PAIS score	145	-0.49 (-1.2; 0.2)	0.17	3.3	-0.2	146	-0.4 (-1.0-0.3)	0.26	3	0.1

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function; PAIS, Psychosocial Adjustment to Illness Scale Self-Reported version

[†] Main effect of intervention adjusted for age (binary), diagnosis group and baseline value of the outcome

* Standard deviation of the unadjusted mean

Table 3. Exploratory outcomes at 4 and 6 months (questionnaire based data), Mean differences reported.

	Follow-up at 4 months†					Follow-up at 6 months†				
	N	Estimate (95%CI)	p-value	SD*	Cohen *d*	N	Estimate (95%CI)	p-value	SD*	Cohen *d*
Exploratory outcomes										
Erectile function domain	145	3.9 (2.1; 5.6)	**<0.0001**	9.21	NA	146	3.5 (1.8-5.3)	**<.0001**	9.2	0.38
Orgasmic function domain	145	1.2 (0.3; 2.2)	**0.01**	3.96	NA	146	1.2 (0.3-2.1)	**0.01**	3.9	0.31
Sexual desire domain	145	0.4 (-0.03; 0.8)	0.07	2.24	NA	146	0.6 (0.2-1.0)	**0.002**	2.3	0.28
Intercourse satisfaction domain	145	0.9 (-0.1; 2.0)	0.08	4.82	NA	146	1.0 (0.0-1.9)	**0.0499**	4.8	0.20
Overall satisfaction domain	145	0.2 (-0.3; 0.7)	0.38	2.06	NA	146	0.2 (-0.3 - 0.6)	0.40	2.1	0.09
SF36-PCS	154	-0.5 (-2.4; 1.5)	0.64	9.17	-0.05	146	0.3 (-1.5 - 2.1)	0.74	8.8	0.03
SF36-MCS	154	-0.3 (-2.3; 2.3)	0.83	11.15	-0.02	146	0.0 (-2.3 - 2.3)	0.99	10.5	0.00
EQ-5D index	154	0.01 (-0.04; 0.1)	0.74	0.23	0.04	146	0.01 (-0.03 - 0.06)	0.54	0.22	0.06

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function, SF36-PCS, Short Form-36, Physical Component Score; SF36-MCS, Short Form-36 Mental Component Score; EQ-5D, EuroQol.

Where n= 154 multiple imputation was used, all others were available cases

† Main effect of intervention adjusted for age (binary), diagnosis group and baseline value

* Standard deviation of the unadjusted mean

Table4. Tabulation of pelvic strength measure (categorical) by intervention groups. Numbers are percentages.

Category*	Sexual rehabilitation	Usual care group	p-value
0	1%	0%	0.01*
1	9%	9%	
2	44%	68%	
3	45%	23%	

*Higher category means more strength

**Chi2- test, multiple imputation dataset (n=154)

Table 5. Exploratory outcomes at baseline week 12 (physical data), mean values and mean differences reported.

	Sexual rehabilitation				Usual care group								
Exploratory outcomes	N	Baseline ‡	N	Week 12 ‡	N	Baseline ‡	N	Week 12 ‡	N	Estimate † (95%CI)	p-value	SD*	Cohen *d*
Pelvic floor endurance (sec)	73	9.3	55	12.1	72	11.2	62	11.5	154	1.5 (-0.5; 3.4)	0.13	7.47	0.19
Pelvic floor strength (cmH2O)	70	131.1	53	150.4	68	128.8	62	128.1	154	11.0 (-8.4; 30.4)	0.27	74.6	0.15
Peak VO2	67	20.7	48	21.9	74	21.5	62	20.1	154	1.6 (-0.2; 3.4)	0.09	7.30	0.22
Heart rate – rest (bpm)	72	66.7	53	64.1	75	63.0	63	64.6	154	-1.0 (-4.2; 2.2)	0.53	11.70	-0.09
Heart rate – max (bpm)	72	131.4	53	134.8	75	152.5	63	130.0	154	6.3 (-1.8; 14.3)	0.12	11.70	0.54
Blood pressure – rest	72	135.6	53	137.3	75	138.9	63	136.7	154	2.1 (-3.6; 7.8)	0.46	11.70	0.18
Blood pressure – max	72	186.9	53	186.7	75	193.1	63	193.2	154	-1.9 (-8.5; 4.6)	0.56	30.99	-0.06
Watt max	72	149.6	53	160.4	75	159.5	63	154.3	154	10.3 (3.6; 16.9)	**0.003**	49.7	0.21
Anaerobic threshold	67	1.6	45	1.7	72	1.8	60	1.7	154	0.1 (-0.01; 0.3)	0.07	0.59	0.23
VE/VCO2 slope	67	27.8	45	28.1	72	26.8	60	26.6	154	0.2 (-0.8; 1.3)	0.66	5.40	0.04

CI, confidence interval; SD, standard deviation; IIEF, International Index of Erectile Function, SF36-PCS, Short Form-36, Physical Component Score; SF36-MCS, Short Form-36 Mental Component Score

Where n= 154 multiple imputation was used, all others were available cases

* Standard deviation of the unadjusted mean

† mean differences between groups at week 12

‡Mean values

Table 6. Mean scores at all times

	Sexual rehabilitation group						Usual care group					
	Baseline		4 months		6 months		Baseline		4 months		6 months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total IIEF	32.2	16.7	36.4	17.2	37.1	20.0	33.7	17.1	31.1	20.7	32.2	20.0
Erectile function domain	11.2	8.0	14.5	8.5	14.3	9.6	12.3	8.4	11.5	9.7	12.2	9.6
Orgasmic function domain	5.6	3.8	5.8	3.7	5.9	4.0	6.0	3.76	4.8	4.2	5.1	4.0
Sexual desire domain	6.1	2.3	6.1	2.1	6.4	2.3	5.9	2.1	5.6	2.3	5.4	2.3
Intercourse satisfaction domain	4.4	4.7	4.9	4.8	5.3	4.6	5.0	4.5	4.5	4.9	4.8	4.6
Overall satisfaction domain	4.9	2.1	5.2	2.0	5.2	2.0	4.6	1.8	4.7	3.1	4.8	2.0
PAIS	6.34	3.4	6.1	3.4	6.3	3.9	6.5	3.3	6.9	3.2	6.9	3.3
SF-36 Physical Component Scale	45.3	10.3	45.6	9.3	47.8	8.8	46.7	9.1	47.0	9.1	47.0	8.8
SF-36 Mental Component Scale	51.7	9.8	51.0	10.6	51.68	10.9	51.8	10.2	50.9	11.3	51.0	10.9
HADS A	3.8	3.8	4.3	4.3	3.9	4.0	4.2	3.8	4.0	4.0	4.0	4.0
HADS D	2.6	2.9	2.9	2.9	2.7	3.7	3.0	3.2	3.0	3.6	3.1	3.7
EQ5D Index	0.8	.2	0.8	0.8	0.8	0.2	0.8	0.2	0.8	0.2	0.8	0.2

SD, Standard Deviation; IIEF, International Index of Erectile Function; PAIS, Psychosocial Adjustment to Illness Scale; SF-36, Short Form-36; HADS A, Hospital Anxiety and Depression Scale Anxiety scores; HADS D, Hospital Anxiety and Depression Scale Depression scores; EQ5D, EuroQol

Paper 4

A place of understanding: Patients' lived experiences of participating in a sexual rehabilitation programme after heart disease – CopenHeart SF-QUAL

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Abstract

Purpose:

As patients are important stakeholders in the health care system, their experience and knowledge is essential to include when evaluating rehabilitation programmes. The purpose of this paper is to explore the lived experience of participating in a non-pharmacological sexual rehabilitation programme.

Methods:

Qualitative interviews were conducted with 10 male patients representing participants from a randomised clinical trial investigating the effect of a 12 week sexual rehabilitation programme. The analysis was inspired by Poul Ricoeur's theory of interpretation. Analysis consisted of 3 levels: naive reading, structural analysis, and critical interpretation and discussion. The theoretical framework reflects aspects of behavioural theory of social cognitive theory developed by Albert Bandura, and his concept of self-efficacy.

Findings:

The findings are presented as themes extracted from the structural analysis and interpreted in the critical interpretation and express the way in which cardiovascular patients experience participating in a sexual rehabilitation programme. Three themes were identified reflecting the intervention to be a special place of understanding, describing the intervention as a supporting atmosphere and finally expressing the intervention as empowering sexuality.

Conclusion:

Participating in the sexual rehabilitation programme was experienced as efficient, valuable, motivating and safe, but dependent on a professional setting. The intervention developed participants self-efficacy with regards to their sexual performance and relationship.

Background

Sexual dysfunction is highly prevalent among patients with cardiovascular disease (1). Patients often experience a total loss of, or a decrease in their level of sexual activity as a consequence of cardiac disease(2). Sexual dysfunction has a negative impact on quality of life and well-being, and sexual dysfunction is associated with anxiety and depression(3,4). Sexual dysfunction in cardiovascular patients is caused by physical or psychological conditions, or as an adverse effect of the medical treatment(2), and often by both in combination(5). In male patients with cardiovascular disease, erectile dysfunction and ejaculation problems are the most common problems, but desire disorders and orgasmic dysfunction are also frequent(6,7). It is recommended that comprehensive cardiac rehabilitation should include sexual counselling (8), but this rarely happens in practice(9,10). Consensus and evidence on how or where patients with cardiovascular disease and sexual problems should be treated is lacking. Guidelines for medical treatment of physical erectile dysfunction exists(2) pointing to treatment with phosphodiesterase-5 (PDE-5) inhibitors, which are efficient and safe for most cardiovascular patients(2). However when medical treatment is contra-indicated or failing there seems to be no consensus on what treatment should be offered. Furthermore, PDE5-inhibitors are not helpful where a psychological aetiology exists. Studies indicate that non-pharmacological interventions such as exercise training and sexual therapy may be beneficial(11-13), however no interventional trials exist to guide practice. Therefor the CopenHeart$_{SF}$ trial was designed with the purpose of testing whether a non-pharmacological sexual rehabilitation intervention consisting of exercise training and psycho-education would improve male cardiovascular patient's sexual function(14). The primary outcome was the total score on the International Index of Erectile Function (IIEF), a questionnaire evaluating sexual function in five domains; erectile function, orgasmic function, sexual desire,

intercourse satisfaction and overall satisfaction(15). The trial showed that sexual rehabilitation, compared with the control group, had a statistical and clinical beneficial effect on sexual function measured by the IIEF questionnaire.

According to Porter(16), value should always be defined around the patients, and in a well-functioning health care system, this means that when setting up a rehabilitation programme, the meaning and fulfilment of patient needs should be evaluated. In the modern health care system patients are important stakeholders with subjective experiences and therefore it is mandatory that they are involved and heard, and that patients' experiences and needs should be included in the development of aftercare(17). The purpose of this study was therefore to explore the lived experience of participating in a non-pharmacological sexual rehabilitation programme (the CopenHeart$_{SF}$ trial).

Scientific and theoretical framework

Since the study focusses on human perception and the lived experiences of participation in a sexual rehabilitation programme, a phenomenological-hermeneutical approach was chosen. The phenomenological-hermeneutical approach is widely accepted and often applied within qualitative nursing research(18-20), as methods within this framework allow for interpretation related to a specific field of interest or a specific phenomenon. The collection of data, the analysis and interpretation were inspired by the French philosopher Paul Ricoeur's phenomenological-hermeneutical philosophy, his theory of interpretation, and his theory of time and narrative(21,22). This approach places the study in line with several other studies inspired by the above-mentioned philosophy (23-25). According to Ricoeur, human experiences are indirectly expressed through language and require interpretation, which is why he expanded

phenomenology to involve hermeneutics, which concerns understanding and interpretation of the written word(21). Ricoeur's theory of interpretation describes how we as human beings become aware of our participation in the world by expressing it. He states that by retelling an event, the past is brought into the present in order to shape the future, and by expressing meaning as it manifests around experiences with participation in a rehabilitation programme, it is possible to become aware of the meaning of the programme for the patients' in order to plan for proper rehabilitation that meets patients' sexual problems.

The theoretical framework for the study reflects aspects of behavioural theory of social cognitive theory developed by the American psychologist Albert Bandura and his concept of self-efficacy(26,27). The social cognitive theory emphasizes that we as humans can decide how to behave, which is considered a cognitive process. Self-efficacy should be understood as the individual's own competence to carry out a given behavior. The self-efficacy concept is based on the premise that individuals can control their own thought processes, motivation and actions and are therefore also able to change themselves and their situations. According to Bandura, the perception of efficacy is influenced by four factors: mastery experience, vicarious experience, verbal persuasion, and somatic and emotional state(27). Mastery experience is related to prior success at having accomplished something that is similar to the new behaviour whereas vicarious experience is gained by watching someone similar to self to have success. Verbal persuasion is related to encouragement by others and somatic and emotional states reflect the physical and emotional states caused by thinking about undertaken a new behaviour(27).

Methods

A qualitative research method with a phenomenological-hermeneutical approach was applied. According to the phenomenological-hermeneutical approach the aim is to explore how human beings perceive the world or in this case experience participation in a non-pharmacological sexual rehabilitation programme.

Setting and participants

Qualitative interviews were conducted with a purposive sample of 10 males with sexual dysfunction and either ischemic heart disease or patients treated with implantable cardioverter defibrillator (ICD). Patients were all participants from a randomized controlled trial (RCT) evaluating the effect of a sexual rehabilitation programme consisting of 12 weeks physical exercise training including daily pelvic floor exercise, and psycho-educational consultations. A trial protocol for the RCT was published(14) and therefore only a short summary of the intervention is given here.

Intervention:

The psycho-educational consultations were carried out in the hospital and were inspired by the three dimensions identified by Rosemary Parse in her methodologies of human becoming theory(28). These can be described as (1) discuss and give meaning to the past, present and future; (2) explore and discuss events and opportunities and (3) pursue imagined possibilities. The psycho-educational intervention was targeted at the modifiable parameters that are reported to affect sexuality, and was carried out by a specially trained nurse. Patients received two to four consultations. Though all patients had the possibility of inviting partners into the consultations,

only two of the patients' partners participated. A fundamental approach was based on the World Health Organizations definition of sexuality(29). This definition requires health professionals to perceive sexuality as a biological, psychological, social, economic, political, legal, historical, religious and spiritual phenomenon. Knowledge of sexual counseling was acquired by a two weeks intense course in sexology and by sexual counseling theories as described by Murray et al.(30).

Exercise training was either in-hospital in physiotherapy supervised group-based training; in the municipality setting; or home-based. It consisted of three weekly sessions with muscle-strength exercise plus cardiovascular training on an ergometer bicycle. One session was structured with 10 minutes (min) warm-up bicycling, 20 min bicycling with increased intensity (cardiovascular training), 20 min strength exercises (muscle-strength), and 10 min stretching and cool-down period. Furthermore patients performed pelvic floor exercise two times a day, three times when lying, three times when sitting, and three times when standing. The duration of the contraction was up to 10 seconds each, and patients were instructed to have a 10 second break between each contraction. Regardless of the setting for training, the exercise intervention was initiated by a project physiotherapist at the University Hospital hosting the trial.

Recruitment and participants

Articulate and knowledgeable interviewees were chosen and variation was sought through:

(1) age; representing both younger and older participants.

(2) type of heart disease; ischemic heart disease or ICD.

(3) type of sexual dysfunction; physical or a combination of physical and psychological.

(4) setting for exercise training; supervised in-hospital/municipality training, home training or a combination of both (31).

We found that these 10 patients would provide a good insight into how this intervention would be experienced, knowing that including more patients could potentially add to the insight(32).

A nurse involved in the RCT (PPJ) approached the patients after they had completed the sexual rehabilitation programme and a letter with written information was distributed. This was followed up by a telephone call providing additional information and, if needed, time to consider before consenting or declining. Patients were assured anonymity and informed that participation was voluntary and that they could withdraw their consent at any time. All ten of the identified participants consented and demographic details are presented in Table 1.

Data collection

All patients underwent interview in an undisturbed office room at the hospital. A researcher not involved in the randomized controlled trial (MM) conducted the interviews. To assure consistency and openness a semi-structured interview guide was developed and used. The interview guide served as a framework to ensure that all subjects of interest were covered. With the aim of gathering the patients' in-depth accounts of their lived experiences of participating in the programme, open questions were used, such as: 'Could you please tell me about your intentions of signing up for the programme?' and 'Could you please tell me about your experiences from the programme?' To provide reflections on participants sexuality, questions relating their earlier experience were also applied and therefor the guide also included questions on the experience with sexual function.

Participants were allowed to talk about experiences they found important, and only when narratives wandered too far from the research question, the interviewer gently guided them back. Interviews were carried out in August and September 2016 and lasted between 45 to 75 minutes. Interviews were recorded and subsequently transcribed.

Analysis

Two researchers (SKB,PPJ) carried out the analysis separately and thereafter discussed the findings with each other. Since the analysis and interpretation was inspired by Ricoeur, the analysis consisted of three levels: naïve reading, structural analysis, and critical interpretation and discussion(21). In naïve reading the text was read separately several times to grasp the meaning as a whole. The material was approached from a phenomenological view, meaning that reading sought to be open in order to gain an overall naïve understanding of the participants' experiences. The naïve reading guides the following structural analysis(21). The first reflections about what is said were noted here. Structural analysis moves from what is being said to what is talked about. First we read the whole text and divided it into units of meaning separately (what is said about participating in a sexual rehabilitation programme). Structural analysis deals with patterns in the text that can explain what the text is saying. Secondly, the units of meaning were reflected upon in relation to the naïve reading. Units of meaning could be in the form of part of a sentence, a whole sentence or several sentences, each of which, however, expressed 'only one meaning'. Explaining a text thus involves an objective approach to the text. Explaining what the text expresses means moving from what the text says to what the text is talking about. Therefore, the units of meaning were discussed and condensed jointly and significant units were constructed to identify what was talked about. Finally the significant units or the essence were condensed into three themes. A

theme is a thread of meaning that penetrates text parts and identifies essential meaning of a lived experience(21) . The themes are seen in relation to the whole interview transcript and in the analysis part as a hermeneutical spiral. The critical interpretation continues with a discussion of the themes that were identified in the structural analysis, the purpose being to reach a new understanding of the possible dimensions of the patients' lived experiences with participation in the programme. The deeper interpretation of the interviews concerns not what the patients wanted to say but what the interviews are about, and thus the movement between explanation and understanding in the interpretation process continues – from what the interviews say to what they talk about. Thus it is an understanding process, in which theoretical perspectives are drawn on to help clarify and understand phenomena in the patients' lives. Throughout the whole interpretation process the empirical data guided the selection of theoretical perspectives. Examples of the structural analysis are presented in table 3. The table show meaning units, units of significance and the theme.

Ethics

The study complies with the latest Declaration of Helsinki and was approved by the Danish Data Protection Agency (j.nr. 2007-58-0015) and has been approved by the Regional Ethics Committee (j.nr. H-4-2012-168). The CopenHeart$_{SF}$ trial is registered at ClinicalTrials.gov (NCT01796353).

Findings

The findings are presented as themes extracted from the structural analysis and interpreted in the critical interpretation and express the way in which cardiovascular patients experience participating in a sexual rehabilitation programme. Three themes were identified reflecting the

intervention to be a special place of understanding, describing the intervention as a supporting atmosphere and finally expressing the intervention as being sexually empowering.

Place of understanding

Discussing sex and sexual problems are reported to be taboo subjects (33) and when entering the intervention most participants described negative experiences from the established setting. They received no prior information or support in relation to their sexual challenges. In contrast, when participating in the CopenHeart$_{SF}$ trial, patients had a valuable experience and found themselves in a special place of understanding.

They experienced a context where professionalism was used to create a trustful and positive setting and how a professional interaction with the health professionals was important. This is exemplified by one participant when he described the consultations: "*What is the person sitting in front of you like? Are they saying things straight ahead? You can easily ask questions the wrong way, or the attitude when you ask. Are they "know it all' or is it someone you can trust. Trust means a lot, and the team here has been good at this. I wouldn't be here if they weren't good".* This professional environment created dynamic interactions within the consultations, and promoted the development of individual emotional and practical skills as well as a new perception of self which had a positive impact on the patients' self-efficacy. Bandura has showed that people with high self-efficacy generally believe that they are in control of their own lives(26). Thereby the intervention strengthened the patients' perception of being in control which empowered the patient to act on their own and prepared them to engage in their daily social life and sexual relationships.

Responses from the patients state how important it was that the environment was open to emotionally laden topics such as sexuality and sex. This was exemplified in the following quote, by one participant: "*it is a delicate subject, many professionals can't handle it. Here, they were really good at handling this. It was really okay".* This was in contrast to the participants' earlier experiences with the established system. The CopenHeart intervention created an environment in where emotionally difficult topics were met and embraced which provided affirmation of personal engagement for the patients.

Talking about sexuality often involves many metaphors and misunderstandings, and awkward situations tend to appear. Participants emphasized how a clear constructive communication was needed and how important is was that conversation was getting to heart of the matter. This was reflected upon their earlier experience in where participants experienced health professionals talking back and forth about sexuality and not really getting to the heart of the matter. One participant stated: "*She (the nurse) was just good, called a spade a spade, but in a good way. She was constructive and precise in her advice, and then it was up to me to grab the challenge (new way of communicating with his spouse)".* The perception is that patients receive constructive advice and widen their competencies in communication and thereby might experience a higher degree of self-efficacy.

Overall, this place of understanding strongly influenced the capability of the patient in order to face the sexual challenges. According to Bandura's theory of self-efficacy this may be understood as the intervention supported the patient's ability to approach his sexual challenges and managed to change the way he saw himself. The intervention thus had an impact on the patient's social

behavior and encouraged the patients to view the sexual challenges as something to be mastered rather than something to be avoided.

The supportive atmosphere

Participants expressed the view that team training motivated and encouraged them because it brought energy and fun. They talked about a special team spirit and some participants even gained new friendships, and a small group of patients started seeing each other privately after the training sessions. When describing the experience with the team training one participant stated: " *we yell and scream, we are old men yelling at each other, we have so much fun together".* The perception is that a certain supportive atmosphere or spirit is experienced which motivates and pushes the participants to move forward. According to Bandura, peers can act as a potential strength in the development of self-efficacy and self-assurance and might function as social validation for the patients (34). Additionally these benefits might produce motivation to move on in life.

In contrast, some patients performed home-based exercise training, defined as exercise training either in their own home or at a local fitness centre. Most of these patients were characterised by being familiar with exercise training and performing weekly sessions. They all had a history with years of exercise training before entering the trial and found motivation and confidence in training in their usual environment which also was a practical and logistic advantage for these patients. This could illustrate that those familiar with exercise training do not necessarily need the support of peers and health professionals. According to Bandura, all people have mastery experiences, and mastery experiences are the most important way to boost self-efficacy(27). People are more likely to do well in new things if they can relate it to former successful events. This could explain how

patients with good training routines have a lower degree of dependency of peers and health professionals.

Some participants were present when a man became ill during exercise training and was subsequently admitted to the emergency room. They didn't find this upsetting, rather it reassured them that they were close to help if needed and they experienced the team training to be safe. This is exemplified by a participant: "*During one of the sessions a guy became ill. The expertise was just nearby. It feels really safe to know that you are in the best hands".* and it appears that they did not feel anxious or uncertain of exercise training.

Particpiants explained how friendships developed beyond the training sessions. They started to meet up after training, having a beer or two. One participant described: "*the last time I was there, we agreed to go out for a beer and it was really cozy, and after that I started to drop by the training center to meet the other ones because we had this thing going on, that was after my sessions ended".* This quote illustrates how the participants can relate to other peers. Participants in the intervention suffered from the same problem, they were all aware that they were there because of their sexual problems and being in the same situation. According to Bandura relating to peers or social support can be a motivating and supporting factor and is probably why participants emphasized the importance of seeking each others company (34)

Another supporting element experienced was technology. Many were comfortable with pulse watches, data from the bicycle, and apps on the phones reminding them of their exercise training three times a week, and some expressed a direct dependency on the technology to motivate themselves, and to be reminded. Technology clearly was a motivating and supporting factor. One participant stated: "*I had the pulse watch on so I couldn't skip training"* indicating that a need for motivation and if the pulse watch was not a part of the intervention it would have been easier to

take shortcuts. A motivating emotional state is believed to positively impact self-efficacy, and support further engagement in the exercise training(26).

Sexually empowered

Participants perceived a significant improvement in their sexual performance, experienced an increase in desire, an improvement in erectile function, as well as in overall sexual satisfaction during the intervention. One participant stated: "*It works on the psyche as well. When the confidence arise the desire increases, much more – completely".* They expressed that participating in the intervention improved their quality of life and courage of life. One patient expressed: "*I mean... this is an important programme, it improves the quality of life for all and it is an area of taboo. You know... When you have been out of the game for a while…. then things change, and it can be really hard getting back on track. I would say go on with the programme".* This might indicate the importance of a comprehensive approach and that neither a sexual counselling intervention nor exercise training can stand alone. Patients were specifically emphasizing perceptions of the role of pelvic floor exercise as being efficient. It is highlighted by Bandura that the perceived difficulty of a task is of importance for perceived self-confidence(26). For the patients the pelvic floor exercise was experienced as being a simple and easy task to implement in daily life suggesting that this specific performance had a positive impact on the patients perceived self-confidence. Whereas some participants experienced this positive change in their sexual performance as stated here: "*You know. It works so that you can hold more blood right. And you also shoot longer when it finally happens"*, others experienced no positive impact at all. One participant described: "*Not like I hoped. I was hoping it would be like old times".* Patients thus might feel they are put outside of control of own performance regarding sexuality which may result in a low sense of self-efficacy impairing the patients well-being. Despite that fact,

participants said that it was helpful to receive a comprehensive investigation of their sexual history, including a professional evaluation on the cause of the sexual problem, even though they didn't experience any positive impact on their sexual function. They gave the impression that participating was valuable which suggests that the intervention sustained hope and belief for the patients in their own capabilities lowering anger and guilt as stated by this participant: "*though my erection didn't get better it was still very good to be a part of the programme. I learned a lot about myself and got an idea of why I had my problem (sexual) and that it wasn't me that was the problem in our relationship".*

Several participants experienced severe relationship issues and described problems in relation to communication and differences in sexual needs. Some described how communication over years had developed to be more defensive in contrast to earlier in life where it used to be more constructive. The patients were encouraged to practice their wording in the consultations. During the intervention participants gained new communication skills and received counseling advice to start a more helpful and fruitful conversation about sexuality and their individual sexual needs. This is illustrated in the following quote: "*It is important that you put the word right, you don't want to make accusations or attacks, but more: I feel that... you know, keep it on your own court. That works, you know".* This reveals how participants, by receiving advice on communication improved their self-efficacy. According to Bandura, verbal persuasion along with mastery experiences is important when you want to increase self-efficacy(26). In this case the mastery experience was developed during the practice of their wording and their verbal persuasion from the nurse. This perceived efficacy might lead to developing confidence and strength in the patients to promote new self-generated strategies which may benefit their performance in their

relationships. Viewed in this perspective, the intervention is suggested to empower the patient to self-help.

Participants was reflecting on their new skills and what they gained from the intervention on a more personal level which engendered courage and beliefs in one's own capabilities regarding sexuality. "*Then you can get some insight into yourself. About what really matters to me and what it means to have a good sexlife. And in that way have more courage to talk to my wife about it. I feel like….I know now that I can also do something myself".* This statement illustrates how the patient's self-confidence increased and how the patient gained the ability to actively control his own situation.

Discussion

This study describes patients' lived experience of participating in a sexual rehabilitation intervention. The first theme that was described was that patients found that the intervention created a special place of understanding.

Prior to the intervention patients received no information or support in relation to their sexual challenges. This might reflect the fact that health professionals still find it difficult discussing sex, as described in a study by Jaarsma et al.(10) which concludes that health-professionals find that discussing sex might upset or embarrass the patient, and that they feel a lack of knowledge in questions regarding sexual matters. In contrast, patients participating in the CopenHeart$_{SF}$ trial had a meaningful experience and found themselves in that special place of understanding. They experienced a context where humour and professionalism was used to create a respectful and positive setting. According to Steinke et al.(35) it is mandatory that a comprehensive sexual counselling consists of several factors, including competencies in exploring the patient's sexual

history; counseling and communication techniques for use within a specific sexual counseling consultation; delivery of accurate information to patients; follow-up education or counseling; referrals to other healthcare professionals; and discussion of sexual concerns in various populations and situations. The patient's perception of the provider's knowledge, maturity, and willingness to discuss sexual issues also plays a role in facilitating an appreciative discussion. Participants said that they experienced a place in which discussion of sexual problems was met in a professional way. The nurse who conducted the consultations had several years' experience in cardiology; was familiar with cardiac rehabilitation consultations; as well as being qualified in an intensive sexology course. All these factors created a professional setting for comprehensive sexual counselling. According to Lion et al.(36), six principles exist when counseling about sexuality. 1) Progress from the topics that are easy to discuss to the more difficult, 2) Discuss how patient acquired information and attitudes toward sex, 3) Initiate emotionally charged questions with an informational statement, 4) Assume the full range of sexual experience, as it decreases anxiety and reduces misinformation, 5) Keep your sense of humor, 6) Use the sexual words and phrases known by, and perceived comfortable for the patient. These principles formed the intervention conducted by the nurse and responses from the patients state how important these were to create an environment open to emotionally laden topics such as sexuality and sex.

Furthermore patients experienced a certain supportive atmosphere in which they found encouragement and support. Simonÿ et al.(37) found in a group of cardiac rehabilitation patients a similar tendency for a mutually supportive team spirit to encourage and cheer one another and for some participants they were depending directly on peer support. A review by Parry et al. (38) confirmed the positive experience with regards to peer support. They found that support from

peers had a positive effect on self-efficacy; however this was in heart patients in general and was not related to sexuality.

Patients described how participating in the programme helped gain more confidence in their erection and also how they experienced a better and more firm erection. This supports previous findings from studies evaluating single interventions consisting of either an exercise training component or a therapeutic component (11,12). These studies, however, measure on quantitative data.

Technology clearly was a motivating and supporting factor for the participants. This is in accordance with a study by Karmali et al.(39) who investigated factors for adherence in cardiac rehabilitation and found that monitoring of activity, action planning and tailored counselling by the cardiac rehabilitation team were all supportive and motivating for high adherence.

Participants described a secure and motivating environment and it appears that they did not feel anxious or uncertain of exercise training, which is in line with other research findings where team training is experienced as securing and supportive(40). However, in contrast other findings show that some cardiovascular patients are dealing with an existential anxiety regarding exercise training(37).

Patients described how the programme empowered them to communicate in a more constructive way. According to Litzinger et al.(41) good communicating skills are, along with sexual satisfaction, essential for having a good overall relationship satisfaction. Though, it seems that good communication skills are the most important factor in maintaining a good relationship satisfaction(41). This is also expressed by the participants, who speak about the importance of openness and constructive communication and how they, despite that their erection did not improve, had a positive experience of participating in the programme.

Within the hermeneutical qualitative methodology credibility, transferability, dependability and conformability can be used to assess a study's trustworthiness(42). Credibility refers to the congruence between the realities of the interviewees and the results. The person conducting the interview was a skilled interviewer with limited experience in cardiovascular disease, as well as sexual problems. This secured a natural curiosity for pursuing the underlying truth. Only two of ten participants had an ICD in comparison to patients with ischemic heart disease. This may be reflected in the results, and should be taken into account considering transferability of findings. However, relevant information regarding demographic data, exercise place, number of consultations, and time and place of the interview were presented. To ensure the dependability criteria, we sought to be as traceable and documentable in the research process as possible. Therefore we presented the background, methodology, methods, processes and analysis. Conformability is related to the integrity of the findings that are rooted in the data. Thus, we presented the process of analysis, quotes, and meaning units leading back to the interviewees that support each finding.

Clinical implications

When planning after-care or rehabilitation programmes for cardiovascular patients with sexual dysfunction, learning s from the themes identified on: a special place of understanding, supporting atmosphere and empowering self-help should be integrated as important focus areas to ensure that patients can return to a satisfying sexual life after a cardiac disease. The findings of this study, as well as previous research, highlight the importance of a professional setting including certain competencies when handling the after-care of cardiovascular patients with sexual problems. These specific competencies are not mandatory in most rehabilitation settings in

Denmark, and might lead to patients not being met and helped with their sexual problems. This emphasizes a need for rethinking cardiac rehabilitation. As the condition is often multifaceted, the optimal approach should include a thorough investigation of the origin of the sexual problem and a subsequently individualized strategy. Some patients might benefit from pelvic floor exercise as a single intervention, whereas others might need a more comprehensive approach including physical exercise training, sexual counselling, medication and couples therapy.

Conclusion

The purpose of this study was to explore patients lived experience with participation in a rehabilitation programme targeting sexual problems. Three themes were identified: 'a place of understanding' where patients state a need for a respectful environment open for emotionally laden topics; a theme describing a 'supportive atmosphere' that encourage and support to persistently exercise training; and finally the intervention was experienced as 'empowering sexuality' in where patients described how they developed new skills to help constructive communication with their spouses. Participating in the sexual rehabilitation programme was experienced as efficient, meaningful, motivating and safe, but dependent on a professional setting. The intervention developed participants self-efficacy with regards to their sexual performance and relationship.

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Tables

Table 1. Demographic and clinical characteristics of participants

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10
Age	53	68	69	35	69	58	58	72	65	72
Patient group	IHD	IHD	IHD	IHD	IHD	IHD	ICD	ICD	IHD	IHD
Type of SD	Physical	Physical	Physical	Physical	Combined	Physical	Combined	Combined	Physical	physical
Exercise place	Hospital	Hospital	Hospital	Combined	Hospital	Combined	Combined	Hospital	Combined	home
No of sexual consultations	3	2	3	2	3	3	4	3	3	2

IHD = Ischaemic Heart Disease, ICD = Implantable Cardioverter Defibrillator, SD= Sexual Dysfunction, Combined= physical and psychological causes of sexual Dysfunction

Table 2. Interview guide

The following open-ended questions were explored:

Can you tell me about your experiences with your sexual function in relation to your heart disease?

Can you tell me about the information you have received in relation to your heart disease and potential sexual problems? Can you tell me about your thoughts about participating in a study targeting sexual problems? Can you tell me about your experiences of participating in the rehabilitation programme?

How did you experience the different parts of the intervention?

How was your sexuality affected by the rehabilitation programme?

Table 3. Examples of the process in the structural analysis

Meaning unit (What the male says)	**Units of significance (What the male talks about)**	**Theme**
"What is the person sitting in front of you like? Are they saying things straight ahead? You can easily ask questions the wrong way, or the attitude when you ask". "Are they "know it alls" or is it someone you can trust. Trust means a lot, and the team here has been good at this. I wouldn't be here if they weren't good"	Professional environment created dynamic interactions	Place of understanding
"It is a delicate subject, many professionals can't handle it. Here, they were really good at handling this. It was really okay".	Environment was open to emotionally laden topics	

" She (the nurse) was just good, called a spade a spade, but in a good way. She was constructive and precise in her advice, and then it was up to me to grab the challenge (new way of communicating with his spouse)".	Getting to the heart of the matter	
"We yell and scream. We are all old men yelling at each other". *"We have so much fun together".*	Team training motivates	The supportive atmosphere
"During one of the sessions a guy became ill. The expertise was just nearby. It feels really safe to know that you are in the best hands".	Being around professionals during exercise training is safe	
" The last time I was there, we agreed to go out for a beer and it was really cozy, and after that I started to drop by the training center to meet the other ones because we had this thing going on, that was after my sessions ended".	Friendships developed	
"I had the pulse watch on so I couldn't skip training". *"I persuaded Signe (the physiotherapist) to get the diary when we finished. I put the information on my phone so that I have it. Then I can perform the exercise training programme at home whenever I like".*	Support by technology	
"You know. It works so that you can hold more blood right. And you also shoot longer when it finally happen".' *"It is a small price for a good effect".* *"'Pelvic floor training programme it is so simple and it helps. So continue for God's sake, if you can".*	Pelvic floor exercise efficient and easy to perform	Sexually empowered
"Though my erections didn't get any better it was still very good to be a part of the programme. I learned a lot about myself and got an idea of why I had my problems (sexual) and that it wasn't me that was the problem in our relationship". *'It is important that you put the word right, you don't want to make accusations or attacks, but more: I feel that... you know, keep it on your own court. That works, you know".* *"It works on the psyche as well. When the confidence arise the desire increases, much more, completely".*	Helpful learning about themselves Creates more desire	
"I mean... this is an important programme, it improves the quality of life for all and it is an area of taboo. You know... When you have been out of the game for a while…. then things change, and it can be really hard getting back on track. I would say go on with the programme".	Improves quality of life and helps you back on track.	