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PREFACE

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Charlottenlund, August 2017

Ida Elisabeth Højskov

Papers included in this thesis

Paper I

Højskov IE, Moons P, Hansen NV, Greve H, Olsen DB, La Cour S, Gluud C, Winkel P, Lindschou L, Egerod I, Christensen AV, Berg SK. Early physical training and psycho-educational intervention for patients undergoing coronary artery bypass grafting. The SheppHeart randomized 2 x 2 factorial clinical pilot trial. *Eur J Cardiovasc Nurs. 2016 Oct; 15(6):425-37. doi: 10.1177/1474515115594524. Epub 2015 Jul 17.*

Paper II

Højskov IE, Moons P, Hansen NV, La Cour S, Olsen PS, Gluud C, Winkel P, Lindschou J, Thygesen LC, Egerod I, Berg SK. SheppHeartCABG trial-comprehensive early rehabilitation after coronary artery bypass grafting: a protocol for a randomised clinical trial. *BMJ Open; 2017: 7:e013038, 2016-013038.*

Paper III

Højskov IE, Moons P., Egerod I, Olsen, PS, Thygesen LT, Hansen NV, La Cour S, Bech KH, Borregaard B, Gluud C, Winkel P, Lindschou J, Berg SK. Comprehensive phase one rehabilitation versus usual care in patients following coronary artery bypass grafting: Results from the SheppHeartCABG trial. Submission prepared.

Paper IV

Højskov IE, Thygesen LC, Moons P, Egerod I, Olsen PS, Berg SK. Non-adherence - a challenge for phase one rehabilitation after coronary artery bypass surgery: Secondary results from the SheppHeartCABG trial. Submission prepared.

The papers are referred to in the text by their Roman numerals.

TABLE OF CONTENTS

ABBREVIATIONS

AHA	American Heart Association
B-IPQ	The Brief Perception Questionnaire
BMI	Body Mass Index
Borg CR10	Borg Category Ratio scale 10
CABG	Coronary Artery Bypass Grafting
CPB	Cardio Pulmonary Bypass
CPET	Cardiopulmonary Exercise Testing
COPD	Chronic Obstructive Pulmonary Disease
ESC	European Society of Cardiology
EQ-5D	EuroQol five dimensions questionnaire
FRC	Functional Residual Capacity
HADS	The Hospital Anxiety Depression Scale
HADS-A	The Hospital Anxiety Depression Scale – Anxiety
HADS-D	The Hospital Anxiety Depression Scale - Depression
HeartQol	The Heart QoL (quality of life) questionnaire
IHD	Ischemic heart disease
IPAQ	The International Physical Activity Questionnaire
LVEF	Left Ventricular Ejection Fraction
MFI	Multidimensional Fatique Inventory
MCS	Mental Component Scale

MI	Myocardial infarction
MRC	The Medical Research Council
NYHA	New York Heart Association functional classification
ÔMSQ	Örebro Musculoskeletal Screening Questionnaire
OR	Odds ratio
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Scale
PEP	Positive Expiratory Pressure
PRO	Patient Reported Outcome
PSQI	The Pittsburgh Sleep Quality Index
RPE Borg	Ratings of Perceived Exertion Borg scale
SF-12:	The MOS 12 Item Short Form Health Survey
SF-36	The MOS 36 Item Short Form Health Survey
SheppHeart	**Sh**aping outcomes by **E**xercise training and **P**sycho-education in **P**hase 1 for **Heart** patients
STST	Sit to stand test
6MWT	6 minute walk test

DEFINITIONS

Exercise	Physical activity including planned, structured, repetitive boily movement[1]
Exercise training	Planned, structured and repetitive bodily movements performed to maintain or improve one or more attributes of physical fitness[2]
Exercise training programme	Single exercises gathered to a programme
Functional capacity	Person´s ability to perform physical activities[3]
In hospital training	Exercise training during hospitalization
Muscle endurance	Ability of a muscle group to execute repeated muscle functions sufficient to cause muscular fatigue[1]
Outpatient training	Exercise training after hospital discharge
Physical activity	Any bodily movement produced by contraction of skeletal muscles and resulting in energy expenditure above basal level and, as such, part of lifestyle intervention[2]
Physical capacity	Maximum physical extension that a person can sustain[1]
Physical function	Physical functioning can be divided into basic actions and complex activities; activities considered important for maintaining independence and those not required for independent living[4]
Phase one rehabilitation	In-hospital rehabilitation

INTRODUCTION

Inspiration for this thesis came from clinical practice in 2012. Patients discharged after coronary artery bypass grafting (CABG) surgery contacted the nurses with issues such as pain management, sleep disorders, limitations of lifting and when to start rehabilitation. The questions arose: should the treatment be organized differently? Should the approach to patients be changed? It was the starting point to examine previous research and patient experiences during admission for CABG and in the early postoperative period.

This thesis covers management of CABG patients during admission and in the first postoperative period after discharge with attention to developing a comprehensive phase one rehabilitation programme. In addition feasibility, acceptability and compliance to the programme and effect of the rehabilitation programme are examined. Few studies or randomised controlled trials have explored the early rehabilitation phase among CABG patients. Studies have investigated interventions including either a physical or a psychological component; no trial includes both components.

The objectives of the thesis were: (i) to develop a phase one rehabilitation programme from admission to four weeks following CABG surgery, (ii) to evaluate feasibility, acceptance and compliance to the phase one rehabilitation programme and (iii) to investigate the effect of a phase one rehabilitation programme including an intervention directed to both physical and psychological symptoms and problems related to CABG.

The thesis is divided in two parts. Part one includes the patients´ experiences, an introduction to the disease and treatment and arguments for phase one rehabilitation after CABG, followed by the objectives of the thesis and its design, results and evaluation of the pilot trial.

Part two includes changes in the design of the study based on findings from the pilot trial, results from the main randomized controlled trial and an explorative study of non-adherence followed by a discussion of the framework, findings and conclusion of the thesis.

BACKGROUND

The patient´s perspective for undergoing coronary artery bypass surgery

Patients undergoing CABG surgery experience symptoms and problems related to the underlying heart disease and the surgical procedure. The pre-operative expectations of patients waiting for open-heart surgery are related to quality of life, illness-related disability, physical activity, physical health status, and re-hospitalisation after surgery.[5]

Due to ischaemic heart disease (IHD), patients waiting for CABG are reduced in physical activity in their daily life leading to decreased lung volume and capacity.[6] Waiting time for surgery varies and can be extremely stressful[7-9] with symptoms of anxiety and depression related to increasing severity of chest pain and dyspnoea.[8] Symptoms of anxiety and depression peak before surgery with a decrease one week after surgery[10] and are the most frequent manifestations associated with impaired physical functioning after the operation.[9,11,12]

Pain, sleep disorders and fatigue are common patient-reported symptoms after CABG and may be partly due to a lack of post-operative physical activity.[7,13] Pain is primarily related to the surgical wound at the sternum and lower leg or forearm and secondary to the neck and shoulder area.[14] Sleeping problems are multiple; sleeplessness, poor sleep quality and lack of sleep continuity are common both before and after CABG.[15-17] Fatigue is also frequent in the early post-operatively period but decreases over time.[18]

In addition to these physical and psychological symptoms and problems, patients struggle with concerns about family, returning to work and everyday life following CABG surgery.[19] Patients undergoing CABG describe the treatment as difficult to handle, with physical and psychological changes and they seek support to handle not only the current situation, but also how to manage life in short- and long term.[15] Patients undergoing CABG need support from health professionals to cope with life including physical and emotional responses.

Ischemic heart disease

The IHD represents imbalance between myocardial oxygen supply and demand.[20] The most common reason for myocardial ischemia is atherosclerosis with plaque building up inside the

coronary arteries.[21] IHD continues to be the single largest cause of death in the world and causes more than 681,000 deaths across Europe each year; 15% among men and 13% among women.[22]

In Denmark approximately 200,000 people are living with IHD. Between 2007 and 2009 approximately 40,000 patients were hospitalised with cardiovascular disease of which 16,000 were diagnosed with IHD.[23] The incidence of IHD has decreased over time in developed countries[24] and IHD in females is a disease of the elderly, because women develop IHD 10 years later than men.[25]

CABG surgery, population and care pathways

The CABG has, since the late 1960s and the start of 1970s been an option for IHD, carried out by open-heart surgery[26,27] and is the most commonly and closely examined major surgical procedure worldwide.

In Denmark the surgical procedure is performed at four centres (Aalborg, Skejby, Odense and Copenhagen). The average yearly CABG surgery rate in Denmark is 740 per million inhabitants, but with a decreasing curve due to new treatment options. In Europe, this figure is 490 per million.[28] The epidemiological profile of CABG has changed in past decades. The population is now older and often in critical clinical conditions at time of surgery. The current mean age of patients undergoing CABG surgery for the first time is approximately 66 years for men and 68 years for women and the male-to-female ratio is 3:1.[29] As in other heart disease populations, the octogenarian population is increasing in the CABG population.[30] In-hospital mortality in CABG is around 1.8% and 30-day mortality is about 1.7 %.[29]

IHD is a complex disease with diabetes and chronic obstructive pulmonary disease (COPD) as frequent comorbidities. Sometimes the first symptoms of IHD are misread which results in a delayed surgery. The other end of the spectrum is that the first sign of IHD is sudden myocardial infarction followed by sub-acute CABG surgery. Treatment entails an average of five days of hospitalisation including preparation for surgery, surgical procedure, invasive procedures, medication, physical and mental recovery, and preparation for discharge.[31,32]

Cardiac rehabilitation

Cardiac rehabilitation has become recognized as a significant component in the continuum of care for cardiovascular disease patients. Cardiac rehabilitation programmes are divided into three main phases; 1) in-hospital rehabilitation (phase 1), 2) early outpatient rehabilitation (phase 2), and 3) long-term outpatient rehabilitation (phase 3).[33]

Cardiac rehabilitation is based on the idea of re-establishing a normal life, and ensuring the best possible physical, psychological and social level for individuals with heart disease.[34] Cardiac rehabilitation is the sum of interventions aimed at maintaining the patient´s social, psychological and physical skills after heart surgery and constitutes a comprehensive complex intervention[35]. Cardiac rehabilitation following cardiac surgery includes components such as patient assessment, physical activity counselling, exercise training, nutritional counselling, tobacco cessation, and psychosocial management including psycho-education.[34] The American College of Sports Medicine Guideline for CABG recommends mobilisation during hospitalisation, outpatient exercise training, and education after CABG.[1] In addition, the European Association of Cardiovascular Prevention and Rehabilitation recommends beginning exercise training with moderate intensity early during hospitalization.[34] Often the exercise training part of cardiac rehabilitation begins six to eight weeks following CABG due to post-surgical restriction on the upper body.[32]

Why phase one comprehensive cardiac rehabilitation after CABG?

Arguments for including exercise training in phase one rehabilitation after CABG

After surgery recovery is spontaneous, but physical activity is important to gain the best outcome, since it has positive effects on quality-of-life, exercise capacity, coronary blood vessels, the myocardium, endothelial function, and coagulation.[36] In addition, exercise training significantly decreases cardiovascular death and total mortality in patients with ischemic heart disease.[37] Safety of exercise training for heart patients has been thoroughly investigated and the risk of complications is minimal even in the early post-operative period.[38] Positive effects of exercise-based rehabilitation in phase two rehabilitation include mental, cognitive and/or social function, as well as reduction in morbidity, re-admission and mortality.[37,39,40] Based on these results, it

seems reasonable to apply exercise training with a systematic approach for phase one rehabilitation to patients who have undergone CABG surgery. It also seems reasonable to encourage exercise training early post-CABG to regain strength, although there is post-surgical upper body training restriction for six to eight weeks after surgery.[32]

Arguments for including psychological components in phase one rehabilitation after CABG

Psychological distress constitutes an independent risk factor for cardiac morbidity [41] and open heart surgery is a stressful event[42] associated with risk of depression and anxiety[43] which are associated with morbidity and mortality.[44] Cardiac rehabilitation with educational and psychological interventions impacts on psychological distress and disease management, by reducing symptoms and applying small to moderate effects on anxiety and depression in IHD.[45] These effect could be transferred to patients in the early rehabilitation phase, however, evidence is scarce.

In summary, there is evidence showing that exercise training improves outcomes after open heart surgery. Rehabilitation often begins two to four weeks after discharge, and the effect of early action is unknown. Patients undergoing CABG need psychological support and physical training to return to everyday life. However, there is a need to know how to handle the psychological impact related to IHD and CABG.

OBJECTIVES

The objectives of the thesis were: (i) to develop a phase one rehabilitation programme from admission to four weeks following CABG surgery, (ii) to evaluate feasibility, acceptance and compliance to the phase one rehabilitation programme, and (iii) to investigate the effect of a phase 1 rehabilitation programme that includes an intervention directed to both physical and psychological symptoms and problems related to CABG.

Two trials were undertaken to achieve these goals; a 2 x 2 factorial clinical randomized pilot trial and a randomized controlled trial. Below the specific objectives are highlighted.

Paper I: Randomized 2 × 2 factorial clinical randomized trial The SheppHeartCABG pilot trial

Objectives were i) to evaluate feasibility of patient recruitment, patient acceptance of the intervention, safety and tolerability of the intervention.

Paper II + III: Design and effect of phase one rehabilitation programme after coronary artery bypass surgery

Objectives were i) to present the protocol for the SheppHeartCABG trial (Paper II) and ii) to assess the effect of early rehabilitation (phase one), combining physical exercise and psycho-education for patients undergoing coronary artery bypass grafting using a randomized controlled trial (Paper III).

Paper IV: Non-adherence to phase one rehabilitation

Objective was to relate the non-adherence phase one rehabilitation after coronary artery bypass surgery to sociodemographic and clinical baseline data.

METHODS

Developing and evaluating a comprehensive phase one rehabilitation programme including a complex intervention is the purpose of this thesis. In order to succeed a structure was applied. The structure of this thesis is inspired by the framework from the Medical Research Council (MRC) [46] that in four phases describes the development and evaluation of complex interventions to improve health. The original framework from 2000 was updated in 2008[47] and again in 2013.[48] Complex interventions in this context are defined as interventions that include several interacting components.[48] Research involves different phases of investigation. This framework creates an overview and strategy of how to work through a sequential cyclical series of phases of

investigation. The thesis focused on three phases; development, feasibility, piloting and evaluation. The fourth phase "implementation" is beyond this thesis.

Developing phase of the rehabilitation programme

Similar interventions and methods used for evaluation were identified to establish an overview of current knowledge on physical and mental health, recovery and rehabilitation of patients undergoing CABG.

Understanding the likely process of physical changes expected was based on evidence and theory. In the process of developing the physical intervention, an understanding of physiological process in IHD and specifically by CABG surgery was ensured.[47] The few specific physical training recommendations for phase one rehabilitation[1,33] were included in the development of the physical component. Similarly in the process of developing a psycho-educational intervention decisions on theoretical basis was made. Outcomes were identified; outcome measures chosen with correspondence between outcome and outcome measures. The intervention components of the SheppHeartCABG clinical trial were designed and described in detail.[48]

Arguments for physical components

The use of each component in the physical intervention and psycho-educational intervention is described below. The set-up of the individual training components was decided based on recommendations in guidelines and statements for exercise-based rehabilitation and secondary prevention,[1,32,35] because the recommendations for phase one rehabilitation are sparse.

Deep breaths

Lung function decreases after open heart surgery.[49-51] General anaesthesia reduces functional residual capacity (FRC) by approximately 20% and cardiopulmonary bypass (CPB) impairs gas exchange resulting in pulmonary complications.[52] General anaesthesia, CPB and cardiac surgery can result in a decrease in vital capacity, lung compliance and respiratory depth.[53] Atelectasis increases FRC, even in uncomplicated open heart surgery, and atelectasis incidence has a range of

54-92%.[54] Basal ventilation and tidal volume decrease after anaesthesia and cardiac surgery. Respiration is insufficient due to low FRC and low compliance. Deep breaths can improve basal ventilation, tidal volume, diaphragm displacement and facilitate secretion elimination.[55-57]

Incentive spirometry

A PEP flute (Positive Expiratory Pressure) can be used during the first post-operative days to expand FRC by ventilating collapsed lung tissue.[58,59]

Neck and shoulder exercises

Patients are placed with a protruding rib cage during surgery and because they protect their sternum they tighten their neck and shoulder muscles which provoke pains.[60]

Cycling exercise

Muscle mass and condition need to recover following surgery. Cardio training involves, e.g. cycling during the early post-operative period as an alternative to walking.[61] In the early post-operative phase it is recommended that cycling intensity is moderate and equal to 3-4 on the Borg Category Ratio 10 Scale (BORG CR 10)[1,62,63] or equal to 11-13 (6-20) Rating of Perceived Exertion Scale also by Borg (RPE BORG).[64] RPE is based on a subjective rating and is suggested to be used in most cardiac rehabilitation guidelines.[33,34]

Walking and muscle endurance

Recovery of muscle and conditioning continues after discharge. Frequency of physical activity is important and it is recommended to take place at least five times a week at a moderate intensity.[1] Physical activity with light to moderate intensity has a positive influence on the patient´s condition compared with activity at low intensity.[65] Also resistance exercise training and walking can improve muscle strength and physical capacity.[66]

Arguments for exercise testing

Evaluation of patients' functional exercise capacity is important in cardiac rehabilitation.

Cardiopulmonary Exercise Testing

Cardiopulmonary Exercise Testing (CPET) is used to evaluate exercise capacity in many chronic diseases. In cardiac rehabilitation CPET is used after hospital discharge following surgery. A concern by using CPET early after surgery is the sternotomy. However, during CPET the patient can be placed in a position that fixes the sternum. CPET is well tolerated two weeks after open heart surgery.[67]

6-minute Walk test

The 6-Minute Walk test (6MWT)[68] determines the maximum walking distance (in meters) within 6 minutes using standardised instructions, while subjective exhaustion of fatique and dyspnoe before and after is recorded as well as the Borg CR-10[63] scale is utilised. The 6MWT is used widely to assess functional exercise capacity in cardiac rehabilitation settings and is measuring improvement in physical function over time which is important for patients' everyday life.[69] The 6MWT can be performed early after myocardial infarction (MI) and surgery.[70] 6MWT is reproducible and well tolerated.[71]

Sit-To-Stand-Test

The Sit-To-Stand test (STST) [72] is the maximum number of times a patient can sit and rise from a normal chair within 30 sec. Rate of perceived exertion is measured before and after using the Borg CR-10 scale.[63]. The STS test is performed to assess muscle endurance relevant to every day activity.[73]

Arguments for psycho-education

Patients undergoing CABG struggle with concerns related to themselves, to the family and to work and how and when the everyday life returns.[19] Life is multifaceted with perspectives that

for many even without disease can be difficult to manage. Patients undergoing CABG often need support from health professionals to cope with life in relation to surgery and their recovery.

Psycho-educational consultation

To assist the patient, a psycho-educational intervention was planned to improve disease coping by applying a patient-centred approach. The conceptual foundation for the dialogue (consultation) with the patients was based on the Human Becoming Practice Methodology[74] of Rosemarie Rizzo Parse. The core of this methodology is a holistic view on the patient and his/her participation in experiences with health and the position that the quality of life achievable by better health, can be described only by the person living that life. According to this methodology, there are three overall ways to change health: 1) creative imagining, which is to see, hear and feel what a situation might be like if lived in a different way, 2) affirming personal becoming, that is thinking critically about one's personal patterns, preferences and values, and changing one´s attitude to change health and 3) glimpsing the paradoxical, looking at incongruence in a situation, changes the view often held. These steps are facilitated through discussion and giving meaning to the past, present and future, discussing events and possibilities and moving along with envisioned possibilities.[74] A nurse is present in the dialogue through discussions, silent immersion and shared reflections, allowing the patient time and space to explore, discover and decide their own health beliefs and behaviour.

Arguments for mindfulness

Mindfulness programs have been subject to a range of mechanistic and clinical studies that seem to confirm a general trend of non-specific psychological and physiological improvement across a spectrum of standardized mental health measures, including psychological and physiological well-being. Effects on sleep and pain have been observed in other contexts, [75,76] and found effective in reducing anxiety accompanying cardiovascular disease.[77-79] Mindfulness programs have been modified and adapted for special needs. In this trial, a brief mindfulness intervention focused on effective support during hospitalisation and surgical recovery was formulated in cooperation with the Center for Research in Existence and Society, University of Copenhagen. An audio mindfulness programme including three guided meditations was developed.

Feasibility and piloting phase

The value of feasibility testing is difficult measure. Pilot testing provides an opportunity to identify recruitment, acceptability, compliance and delivery of intervention on a minor scale and examine the key uncertainty identified during the development. The study design needs to be suitable for the intervention and should be chosen on the basis of specific characteristics of the study.[48] Randomization is considered to be robust for preventing selection bias and was used in the pilot trial. In the pilot trial, the feasibility of patient recruitment, acceptance of the intervention as well as safety and how tolerable of the intervention were tested.

The evaluation process exploring the way in which the intervention during the pilot trial is implemented can provide insights into why an intervention fails or has unexpected consequences. A pilot evaluation can assess the fidelity and quality of implementation and identify contextual factors associated with variation in outcome, but it is not a substitution for evaluation of outcome.[80]

Evaluation phase

The study design, intervention and outcome measures were evaluated. Based on the evaluation the intervention components were modified and the study design changed. Some outcomes were replaced and decision of primary and secondary outcomes was made.

Evaluation of the intervention in the randomized controlled trial was pre-planned to focus on the effect and the pilot test process. In that regard, an exploratory study of non-adherence/adherence was planned as a part of the evaluation.

Methodology and outcome data

The methodological approach for this thesis is quantitative in order to determine the relationship between complex rehabilitation intervention and outcomes in a CABG-population.

To evaluate complex intervention, different outcomes are required in terms of multifaceted perspectives. It is important to define and describe outcomes precisely. In addition it is important to decide how to measure and choose instruments or methods to measure them.

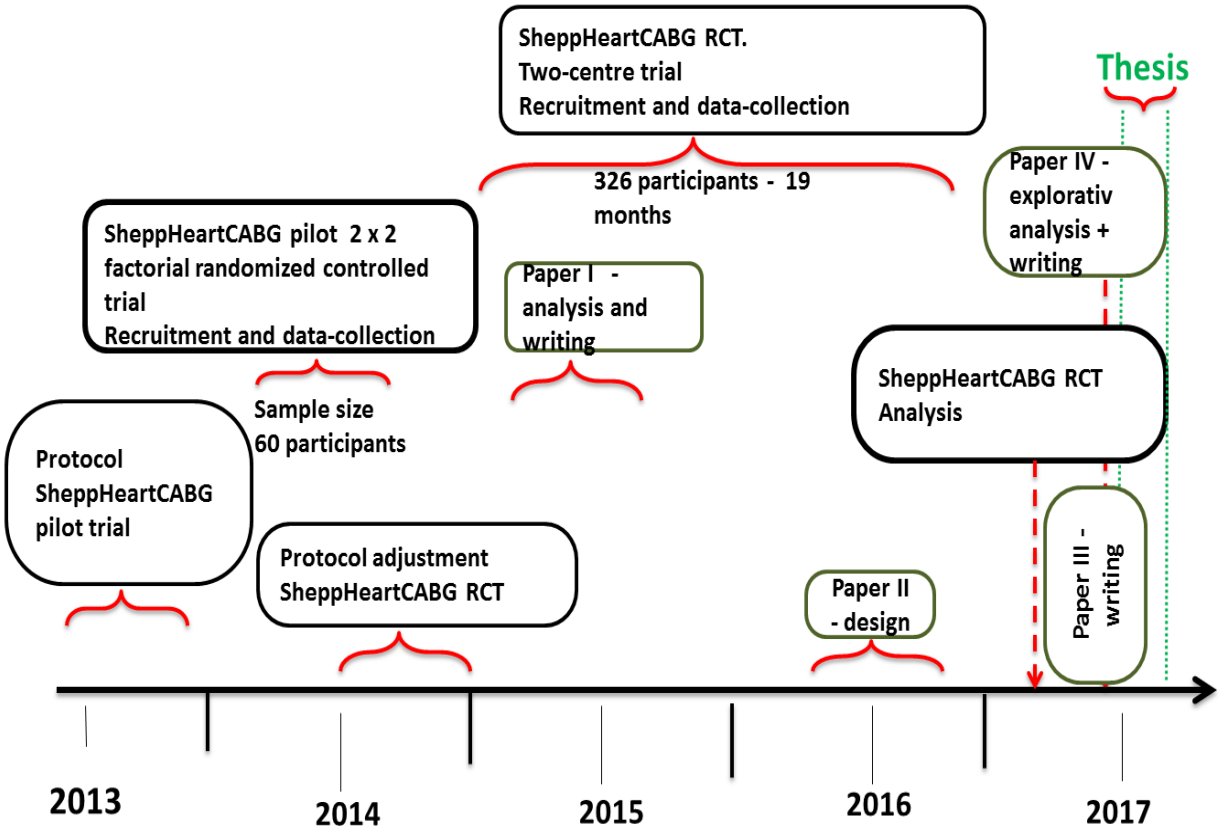


Figure 1. Timeline – the SheppHeartCABG pilot trial and the SheppHeartCABG.

Health professionals´ perception of a patient's health is often different from the patient's view, which can be a limitation for investigating an objective, clinical outcome. To minimize that discrepancy, patient-reported outcomes (PROs) have been increasingly highlighted in health care research, by both the American Heart Association (AHA) [81] and the European Society of Cardiology (ESC).[82]

PPROs are outcomes reported by the patient directly without interpretation by a health professional, relatives or others and can be assessed by self-report or by interview, provided that the interviewer records only the patient's answers.[83] PROs is an important mean of achieving an

independent outcome based on responses from validated questionnaires. The questionnaires are either generic (usable for all patients groups and the healthy population) or are disease specific (for a defined patient group).[84]

STUDY I: RANDOMIZED 2 × 2 FACTOR CLINICAL PILOT TRIAL (PAPER I)

Design and population

The SheppHeartCABG pilot trial was a 2 x 2 factor randomized controlled, single centre trial initiated with blinded assessment. The randomized controlled design was chosen because of the opportunity provided to test physical intervention and psycho-educational intervention separately and in combination.

The trial was conducted at Rigshospitalet, University Hospital of Copenhagen that conducts approximately 600 isolated CABG surgeries yearly. Inclusion criteria were first time elective isolated CABG, age ≥ 18 years, speak and understand Danish and giving informed written consent. Patients were excluded if diagnosed with a musculoskeletal or neurological disease precluding exercise testing and training or a lack of informed written consent.

Recruitment, randomization and blinding

The recruitment period was from September to December 2013. During that period all patients hospitalized for CABG surgery were consecutively screened for participation. The four intervention groups were; 1) physical training with different exercises plus usual care; 2) psycho-educational intervention plus usual care; 3) physical training with different exercises plus psycho-educational intervention plus usual care; and 4) usual care alone. The participants were randomly allocated 1:1:1:1 to the groups. The allocation concealment and allocation generation were conducted using central randomization by the Copenhagen Trial Unit and computer-generated using varying size blocks to avoid investigator bias.

Interventions

The rehabilitation programme was divided in two; physical training and psycho-educational consultations. All exercise components were initiated by a physiotherapist and documented in training diaries. Consultations were conducted by four trained nurses and the same nurse carried out all consultations for each patient. All patients received usual care according to guidelines.[31,32]

Exercise during hospitalization

The exercise training programme during hospitalization was initiated on the day of admission, and comprised the elements outlined in Figure 2. The components in the exercise training programme were:

- D*eep breaths* (7-10) four times daily from admission to hospital discharge

- *Incentive spirometry* was performed by breathing in a PEP-flute four times daily from post-operative day 1 until the end of day 4.

- *Neck and shoulder exercises* included rolling and lifting the shoulders, looking over one shoulder and moving the head in a semicircle in front of the body to the opposite shoulder. Each exercise was repeated 10 times twice daily from post-operative day 1 until hospital discharge.

- *Cycling exercise* included 10 min stationary cycling at an intensity of 11-13 (6 to 20 scale) on the RPE Borg scale® with a warm-up period before and cool-down period for five minutes each. [63] The translation between the Borg CR10 scale and the RPE was, unfortunately not correct and as a result the intensity level is lower than mentioned in Paper II. The intensity at warm-up and cool-down were ≤10 RPE and the cycling sessions were performed twice daily from post-operative day 3 until discharge.

Exercise from discharge to four weeks following surgery

From hospital discharge until four weeks after CABG, the physical training programme included daily walking of increasing duration, and muscle and endurance exercises including sit-to-stand[72] and heel lifting [85]with increasing number of repetitions. A physiotherapist introduced the exercises, enabling patients to perform the exercise sessions independently at home.

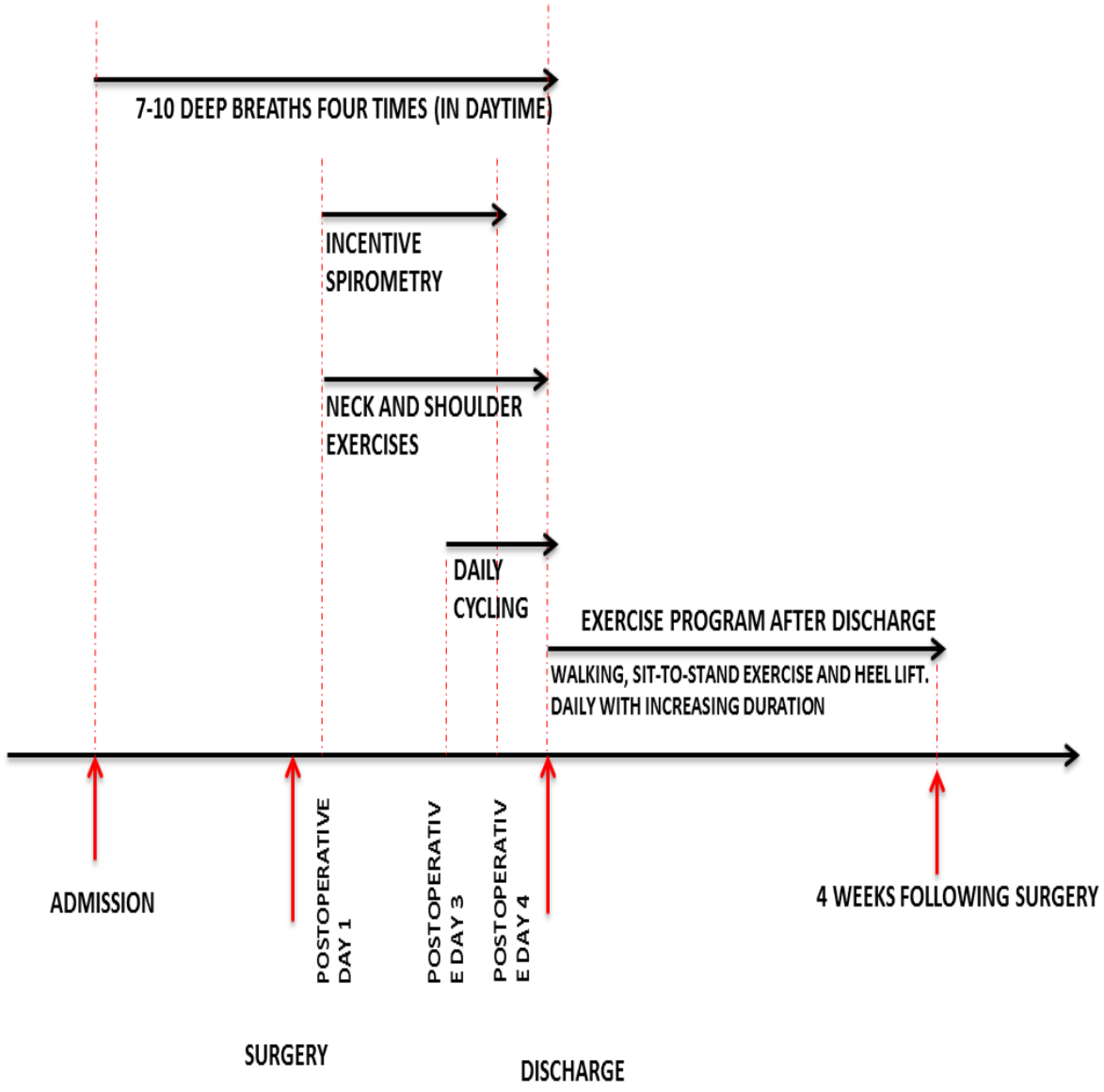


Figure 2. Physical exercise programme during hospitalisation and from discharge to four weeks post-CABG in the SheppHeartCABG pilot trial.

Psycho-educational consultation

The psycho-educational intervention was initiated on the day of admission and continued until four weeks after surgery, comprising four consultations of up to 60 min. The first three consultations were conducted in hospital; at admission, post-operative day 3, and at discharge. The fourth was conducted four weeks post-CABG.

To adopt a holistic approach to patient care, the primary aim of the consultations was to address well-being of each patient and, in doing so, improve coping strategies and help expedite the return to everyday life. Patients also received educational information that helped to improve their understanding of cardiac disease management. Topics for the consultation are outlined in Table 1.

	C_1	C_2	C_3	C_4
Discuss the events leading up the CABG surgery and experiences before admission	x			
Address present thoughts and questions	x	X	x	x
How have the heart disease and the pending CABG affected daily living?				
Are specific activities avoided?	x			
How has CABG surgery affected daily life? Are specific activities avoided?				x
Status of mobilization and activities				x
Discuss pain, fatigue and mobility		X	x	x
Discuss family, how do they tackle changing patterns in the family	x			x
Impact of CABG surgery on working conditions				x
Education about preparation and precautions for CABG surgery	x	X	x	x

Table 1. Guide to the psycho-educational consultations.

The foundation for the psycho-consultation was the Human Becoming Practice Mehodology.[74] This theory includes the following three dimensions within each consultation; I) discuss and give meaning to the past, present and future with regards to the disease and hospitalization; 2) explore and discuss events and future aspirations and; 3) encourage and facilitate achievement of these aspirations. According to the theory, it is possible to change health and health behaviour through: 1) creative imaging, i.e. see, hear and feel what a situation might be like if lived differently; 2) heightening awareness of personal patterns and value beliefs; 3) shedding light on paradoxes, i.e. looking at the discrepancy in a situation and changing the view of it. This theory has been found

useful for other patient groups with heart disease and been adopted successfully in a controlled trial.[86]

Mindfulness

Elements of mindfulness were integrated into the psycho-educational component as support for stress reduction and self-care through meditation-based exercises.[87] The delivery of the elements of mindfulness was adapted to fit into the clinical situation. Nurses were trained in introducing mindfulness exercises and in mindfulness supported communication skills. During the first session, the nurse would provide a brief introduction to mindfulness followed by an exercise. The mindfulness intervention included three guided meditation sessions on an mp3 player. Participants were encouraged to incorporate the mindfulness exercises into their daily life during hospitalization and after hospital discharge. A timeline for the psycho-educational consultations and mindfulness is presented in Figure 3.

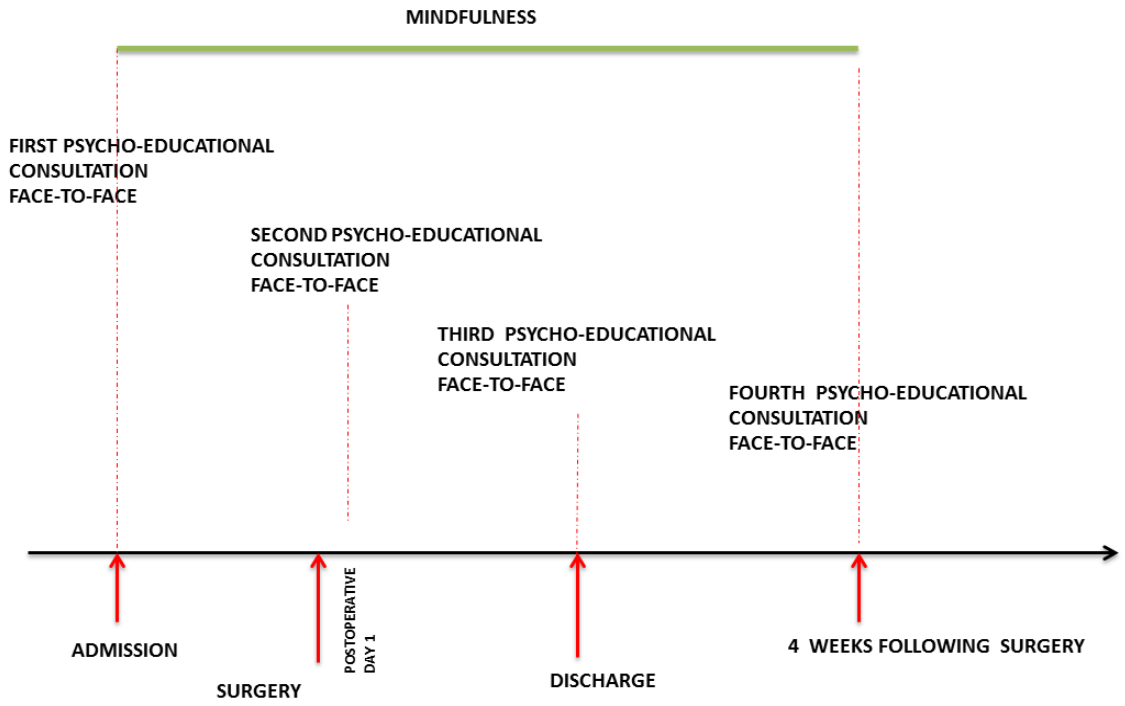


Figure 3. Timeline for psycho-educational consultation and mindfulness in the SheppHeartCABG pilot trial.

Usual care group

Both the usual care group and the intervention groups received usual care according to guidelines[31,32]

Outcome measurements

During the intervention period all participants were assessed three times; at admission (T1), at hospital discharge (T2), and four weeks post CABG (T3). Explorative outcomes were used.

Physical capacity was measured as peak oxygen uptake (VO_2 peak) and obtained with CPET using the breath-by-breath method on a cycle ergometer at Rigshospitalet (Ergo-SPIRO CS-200, Schiller, Switzerland) in accordance with guidelines[88] at discharge and four weeks post-CABG. The cardiopulmonary testing protocol included a four minute rest period followed by an increase in workload every minute until exhaustion. The exercise was a symptom limited maximal test and exhaustion was expressed by the patient. VO_2 was estimated from maximal workload achieved following standards for cardiopulmonary exercise testing.[89]

Functional capacity was measured by 6MWT[68], leg strength and *endurance* measured by the Sit-STST.[72] The participants walked up and down a 30 m distance for six minutes according to guidelines.[90] Also the STST was performed in accordance with guidelines:[91] the participants repeatedly sat in a chair and got to a full standing position as many times as possible in 30 sec in order to test leg strength and endurance. Physical tests were not done at baseline due to the risk of complication pre-CABG.

Patient-reported outcome

The patient-reported outcome measured in the pilot trial were all self-reported questionnaires, both generic and disease specific. The patient-reported outcomes were chosen (Table 2) to reflect the anticipated effect of the interaction components of the comprehensive intervention programme.

Perceived health – Medical Outcome Study Form

The *Medical Outcome Study Form (SF-36)* questionnaire is a generic instrument that includes 36 questions divided into 10 groups. Based on these questions the score is summarized in 8 domains: Bodily Pain Index, General Health Perception, Mental Health Index, Physical Functioning Index, Role Emotional Index, Role Physical Index, Social Functioning Index, Vital Index and two summary scores: Mental Component Scale (MCS) and Physical Component Scale (PCS). The score range is 0-100 with higher scores indicating better perceived health.[92,93] The standardized scores are calculated for each of the eight subscales and based on an American general population study. The scores of the subscales are summarized to the combined score. Finally, summary component scores are calculated on the combined scores. Reliability statistics exceeded Cronbach´s alpha minimum 0.90 for PCS and MCS and has shown a high internal consistency.[94]

Anxiety and depression - The Hospital Anxiety Depression Scale

The Hospital Anxiety Depression Scale (HADS) is a generic instrument used to identify symptoms of clinically relevant anxiety and/or depression, or psychological distress, but is not a diagnostic tool.[95] The instrument is extensively validated and recommended for use in cardiac patients.[96] HADS is a 14-item questionnaire with two subscales, one for anxiety and one for depression. Each subscale includes seven items rated on a four point scale (0-3). Higher levels indicate more symptoms. A score of 7 for either subscale is regarded as normal. A score of 8-10 suggests the presence of mood disorder and a value above 11 suggests probable presence of a mood disorder. The internal consistency is high, with a coefficient (Cronbach´s alpha) of 0.83 and 0.82 for HADS anxiety (HADS-A) and HADS depression (HADS-D), respectively.

Quality of life - HeartQol

HeartQol is a disease specific questionnaire on health-related quality of life including 10-items on physical and four on emotional subscales.[97] Scores range from 0-3 and are summarised in a HeartQol global score, a HeartQol physical score, and a HeartQol emotional score. Higher scores indicate high health-related quality of life. The coefficient of internal consistency is 0.81-0.91.[98]

Fatique – Multidimensional Fatigue Inventory

The Measurement by the Fatigue Instrument is a 20 item self-reported questionnaire designed to express fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity.[99] Each item is a statement and the respondent has to indicate to what extent the statement is true using a five level scale. Higher scores indicate a higher degree of fatigue.[100] A factor analysis has confirmed that the questions actually described five dimensions with a high Cronbach's alpha (mean 0.84). Comparisons between the different groups showed the expected differences.[101]

Illness-related knowledge – The Brief Illness Perception Questionnaire

Perception of illness is measured by The Brief perception Questionnaire (B-IPQ) [102] which is short and assesses cognitive and emotional representations of illness on the basis of eight items. B-IPQ uses a single-item scale approach to assess perceptions on a continuous linear scale. The scores range from 0 to 10 for each item. An overall score (0-80) can be computed and represents the degree to which the illness is perceived. A higher score reflects a more threatening view of illness.[102] Content validity and good test-retest reliability have been found.[102]

Physical activity –The International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ) questionnaire encompasses seven questions providing information on time within the last seven days spent walking, at vigorous- and moderate intensity, and sedentary activity.[103] The summary score was calculated to three levels of physical activity and the interpretation of the questionnaire is categorized in low, moderate and high, based on the stated time and Metabolic Equivalent of Task (METs min/week) used in different types of activities. Reliability correlations ranged from 0.34 to 0.89 with a median of about 0.80 and criterion validity correlations ranged from 0.14 to 0.53, with a median of about 0.30.[103]

Sleep – The Pittsburgh Sleep Quality Index

This is a self-rated questionnaire which assesses quality and disturbances of sleep over a one month period.[104] Nineteen items generate seven component scores. The sum of scores for seven components yields one global score. The scores range from 0 (better) to 21 (worse). A total of <5 is associated with good sleep quality and >5 indicates poor sleep quality. Content validity content and reliability statistics have exceeded Cronbach´s alpha minimum 0.83.[104]

Pain – Örebro Musculoskeletal Screening Questionnaire

Pain was measured by the Örebro Musculoskeletal Screening Questionnaire. This 25-item self-administered questionnaire addresses all musculoskeletal pains and assesses them in five categories.[105] The scores range from 1 to 200 with higher scores indicating increased risk of long-term disability. Construct validity and high reliability have been confirmed.[106]

Table 2. Timeline for patient-reported outcomes in the SheppHeartCABG pilot trial

Questionnaires	Baseline	Discharge	Four weeks post-CABG
Medical Outcome Study Form	x	x	x
The Hospital Anxiety Depression Scale	x	x	x
Heart Qol	x		x
Multidimensional Fatigue Inventory	x		x
The Brief Illness Perception Questionnaire			
The International Physical Activity Questionnaire	x		x
The Pittsburgh Sleep Quality Index	x		x
Örebro Musculoskeletal Screening Questionnaire	x		x

Data analysis

The estimates of means and standard deviations of PROs were calculated. Feasibility was evaluated in the terms of *acceptability, adherence and attrition*.[107]

Acceptability was measured by the percentage of eligible patients who agreed to participate in the trial. For each individual component in the programme, adherence to the intervention was

measured by calculating the percentage of recommended exercise sessions performed by the patient versus the number of prescribed sessions. *Adherence* calculations included only prescribed sessions. *Attrition* was calculated by the percentage of patients who did not complete the trial. Regarding s*afety and tolerability;* patients were taken off the intervention programme in case of high or low blood pressure (diastolic <50 or >120 mmHg and systolic <90 or >200 mmHg), fast or slow heart rate (<50 or >100 beats/min); hyperthermia (>38°C), or pulsoximetry determined arterial oxygen saturation <90%. The number of days the patients were off the programme was documented.

Data were analysed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) and SPSS V.21 (SPSS Inc. IPM), R version 3.1.2 (R Foundation for Statistical Computing, Vienna Austria).

Results from the randomized 2 × 2 factor pilot trial (Paper I)

Feasibility

During the inclusion period 104 patients were admitted for elective CABG surgery and 90 were found eligible to participate (87%). Sixty patients provided informed consent to participate in the trial, corresponding to 58% of all patients admitted and 67% of all eligible patients (Figure 7). Reasons for refusal to participate included a lack of interest in participation (40%; 12 of 30), fatigue (47%; 14 of 30), and apprehension regarding surgery (7%; 2 of 30). A flowchart indicating the progress of patients through the pilot trial is shown in Figure 7. Four patients, all of whom were assigned to the psycho-educational group dropped out of the pilot trial: one during the first session; one before and two after hospital discharge. The reasons were refusal to continue to participate due to the distance to the hospital; two participants did not provide an explanation, and one patient died.

Adherence

In the two intervention groups that included physical training, the patients carried out 59% (924/1565) of the expected training sessions during hospitalisation. One patient (3%) performed

all training sessions (52/52). Nine patients (30%) carried out 75% (348/447) and nine patients (30 %) performed 50% of the planned sessions (363/642). Regarding the psycho-educational intervention, 11 patients (42%) participated in ≥75% of the four consultations and six patients (23%) in 50%. Twelve patients (46%) indicated that they had used mindfulness during the psycho-educational programme.

Eight patients in the physical training group, four in the psycho-educational group, seven in the combined group, and five patients in the usual care group failed to complete the physical tests at discharge because of sudden discharge or transfer to the cardiology department at their regional hospital. In the psycho-educational groups, four patients in the single (psycho-education alone) group and seven in the combined group failed to complete the fourth session.

Self-reported outcomes

Table 3 shows the mean value and standard deviation over time for each of the PROs.

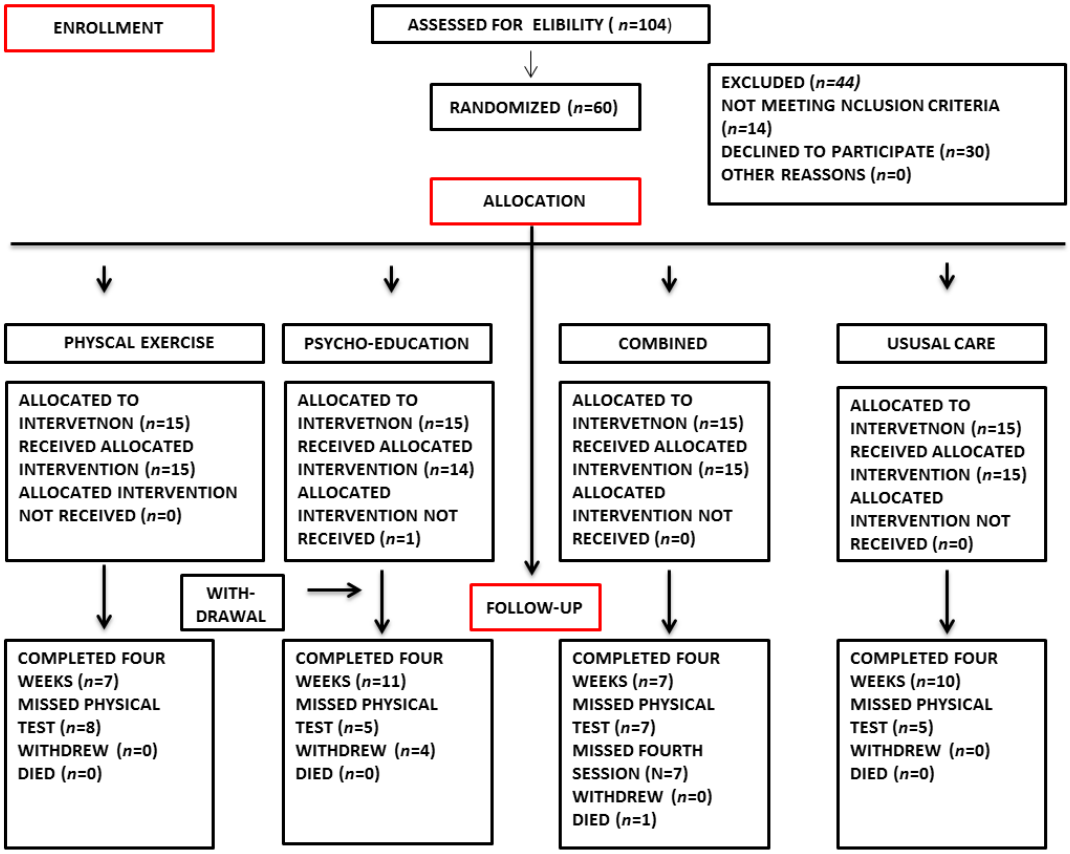


Figure 7. Flow chart of Study I. The SheppHeartCABG pilot trial.

Table 3. Mean values and standard deviation for PROs.

Quantity	Physical exercise			Psycho-education			Psycho-education/ physical exercise			Usual care		
	N (%)	Mean	SD	N (%)	Mean	SD	N (%)	Mean	SD	N (%)	Mean	SD
MCS[1]												
Baseline	11 (73)	48.0	14.9	11 (73)	51.4	10.6	9 (60)	50.9	11.3	8 (53)	55.2	7.5
Discharge	6 (40)	53.7	13.1	6 (40)	43.7	12.6	11 (73)	41.1	12.7	11 (73)	45.5	10.8
4 weeks	7 (47)	53.2	10.0	6 (40)	49.9	15.2	9 (60)	51.8	10.0	10 (66)	43.6	13.0
PCS[2]												
Baseline	11 (73)	39.1	8.9	11 (73)	46.0	8.5	9 (60)	41.3	8.7	8 (53)	45.6	8.8
Discharge	6 (40)	37.2	9.4	6 (40)	41.7	4.1	11 (73)	34.9	8.2	11 (73)	35.1	8.2
4 weeks	7 (47)	42.7	6.0	6 (40)	38.3	6.8	9 (60)	34.1	6.4	10 (67)	36.8	3.2
HADS-A[3]												
Baseline	11 (73)	4.9	4.1	11 (73)	4.9	3.1	12 (80)	5.2	3.3	10 (67)	4.3	2.5
Discharge	7 (47)	7.0	0.6	7 (47)	7.4	1.7	11 (73)	6.4	2.5	11 (73)	6.8	1.5
4 weeks	7 (47)	2.3	0.5	6 (40)	5.7	3.0	10 (67)	4.7	3.7	12 (80)	3.9	3.2
HADS-D[4]												
Baseline	11 (73)	6.2	2.9	11 (73)	6.2	2.7	12 (80)	6.9	3.0	10 (67)	5.9	2.7
Discharge	7 (11)	5.9	1.6	7 (47)	6.6	2.4	11 (73)	8.7	3.0	11 (73)	7.5	3.4
4 weeks	7 (11)	5.9	1.8	6 (40)	6.5	2.2	10 (67)	8.2	3.7	12 (80)	3.9	3.2
PSQI total[5]												
Baseline	10 (67)	6.7	4.2	8 (53)	8.0	3.4	9 (60)	4.8	2.4	10 (67)	6.7	3.6
4 weeks	5 (33)	7.2	3.8	4 (27)	11.2	4.9	7 (47)	9.3	5.4	10 (67)	7.1	4.3
MET total[6]												
Baseline	10 (67)	5448.5	13979.2	11 (73)	3096.8	3283.4	11 (73)	1729.6	1775.8	10 (67)	5160.7	7641.3
4 weeks	6 (40)	5145.0	2016.7	5 (33)	5608.8	6499.6	9 (60)	3799.0	3655.5	11 (73)	4786.4	3967.5
HeartQol[7] **physical**												
Baseline	13 (87)	1.4	1.0	11 (73)	1.8	0.7	12 (80)	1.4	0.8	11 (73)	1.5	0.7
4 weeks	7 (47)	2.0	0.7	6 (40)	1.5	0.8	10 (67)	1.5	0.8	13 (87)	1.3	0.7

HeartQol[8] emotional												
Baseline	13 (87)	1.8	1.1	11 (73)	2.0	0.8	12 (80)	2.2	0.8	13 (87)	1.9	0.9
4 weeks	7 (47)	2.7	0.5	6 (40)	1.6	1.2	10 (67)	2.0	1.0	13 (87)	1.9	1.0
HeartQol[9] global	13 (87)	1.3	0.9	11 (73)	1.9	0.7	80 (12)	1.6	0.8	13 (87)	1.	0.7
Baseline	7 (47)	1.9	0.6	6 (40)	1.5	1.0	10 (67)	1.6	0.5	13 (87)	1.4	0.7
4 weeks												
OMPQ[10]	10 (67)	54.0	28.9	7 (47)	46.3	25.5	11 (73)	49.5	27.6	5 (33)	41.2	23.5
Baseline	7 (47)	57.6	24.4	7 (47)	64.0	15.0	11 (73)	79.0	25.5	8 (53)	76.7	30.9
Discharge	5 (33)	56.6	12.9	5 (33)	62.0	34.9	8 (53)	67.9	23.2	6 (40)	56.7	37.9
4 weeks												
General[11] fatique	11 (73)	11.7	5.0	11 (73)	10.5	5.9	10 (73)	13.4	4.2	10 (67)	10.6	5.0
Baseline	7 (47)	10.3	5.47	5 (33)	12.2	4.3	10 (67)	11.3	4.1	12 (80)	12.2	4.0
4 weeks												
B-IPQtotal[12]	11 (73)	44.3	9.1	11 (47)	38.6	18.0	11 (73)	39.6	15.7	10 (67)	40.3	16.8
Baseline	7 (47)	28.3	12.4	7 (47)	36.4	17.5	11 (73)	42.7	12.6	11 (73)	41.0	18.0
Discharge	7 (47)	26.4	12.1	6 (40)	36.7	21.4	10 (67)	44.0	13.7	12 (80)	39.6	20.6
4 weeks												
Max watt[13]							3 (20)	53.3	37.5	3 (20)	83.3	14.4
Discharge	5 (33)	75.0	25.0	2 (13)	75.0	0.0	7 (47)	117.9	35.4	9 (60)	108.3	35.4
4 weeks	6 (40)	101.8	58.0	4 (27)	106.2	23.9						
Peak VO_2[14]	5(33)	16.4	3.2	2 (13)	19.4	2.2	3 (20)	15.0	5.8	3 (20)	16.8	0.7
Discharge	5(33)	22.3	4.5	4 (27)	22.3	1.6	7 (47)	23.4	4.1	9 (60)	22.0	5.2
4 weeks												
6MWT[15]	5 (33)	264.2	103.7	6 (40)	410.7	29.8	5 (33)	433.0	93.1	5 (33)	331.0	147.5
Discharge	7 (47)	459.7	94.5	6 (40)	504.0	39.0	9 (60)	548.1	104.7	9 (60)	450.9	74.5
4 weeks												
Sit to stand[16]												
Discharge	6 (40)	10.3	3.1	6 (40)	11.5	1.9	6 (40)	11.8	4.1	6 (40)	8.8	1.7
4 weeks	7 (47)	15.0	3.4	6 (40)	14.0	1.7	9 (60)	15.3	6.3	10 (67)	11.7	2.9

[1]Mental health evaluated The MOS 36 Item Short Form Health Survey ; [2]Physical health by The MOS 36 Item Short Form Health Survey; [3]Anxiety by The Hospital Anxiety and Depression Scale; [4]Depression by The Hospital Anxiety and Depression Scale – Depression; [5] Sleep by The Pittsburgh Sleep Quality Index;[6] Physical activity by The International Physical Activity Questionnaire; [7] Physical health-related quality of life by The HeartQoL questionnaire; [8] Emotional health-related quality of life by The HeartQoL questionnaire, [9] Health-related quality of life The HeartQoL questionnaire; [10] Pain by The Örebro Musculoskeletal Screening Questionnaire; [11] Fatigue by The Measurement of Fatigue Instrument, [12] Cognitive and emotional representations of illness by The Brief Illness Perception Questionnaire (total score);[13] Maximum wattage produced at cardiopulmonary test;[14] Maximum wattage produced at cardiopulmonary test; [15] Peak VO_2 estimated from maximal wattage achieved in cardiopulmonary (ml/kg/min), [16]Number of times the patient stood up and sat down from a chair by the Sit-To-Stand test.

EVALUATION OF THE PILOT TRIAL

Pilot testing of the comprehensive phase one rehabilitation programme identified the possibility of recruiting patient who had to undergo CABG surgery to participate in phase one rehabilitation. Secondly foci were on feasibility, acceptance, safety and compliance to intervention. Feasibility to the intervention was evaluated as adherence. Unfortunately, adherence was not complete for either the physical or the psycho-educational components.

Fourteen to 43% cardiac patients participate in rehabilitation programmes.[108-110] In the SheppHeartCABG pilot trial two thirds of eligible patients were included which seems acceptable, however representativeness is always a concern in rehabilitation trials. A general challenge in recruiting patients in cardiovascular clinical trials has been underrepresentation of women and distorted men/women ratios which might result in a non-representative trial population, [111] but that was not an issue in the pilot trial.

Based on the pilot trial certain modifications were considered required. The last of the four psycho-educational consultations took place four weeks after surgery, but would probably have been better if scheduled earlier. The first psycho-educational consultation on admission day was difficult to integrate into an already busy schedule. Also organizational issues arose at day of discharge when hospital discharge was abrupt or when no intervention or testing personnel was available.

The physical training intervention and test appeared to be safe and tolerable for the participants which are important due to lack of evidence regarding the safety of cardiopulmonary testing during the first week after CABG surgery. The pilot test provided basis for exploring the potential for improving the defined outcomes. Some outcomes of both the questionnaires and the physical test did not show sufficient sensitivity toward changes over time.

One third of the patients completed CPET at hospital discharge, but due to drop outs only half of the participants completed all tests four weeks after CABG surgery. A test protocol including safety procedures was developed prior to the test. No serious events were reported and patients' capability to face the CPET was tolerable. Also Eder et al. found early mobilisation tolerable after

CABG surgery.[67] However, the number of patients included is low and therefore further research in measuring VO_2 by CPET in phase one rehabilitation after heart surgery is needed.

For some of the PRO instruments there were missing response on several items, which could be explained by several reasons. One explanation might be that different instruments were encompassed in one comprehensive questionnaire. Some questions then might have been overlapping, resulting in lacking response on some of them. Also some items in the questionnaires might not have felt meaningful to the responders and resulted in missing responses.[112] The MOS 36 item (SF-36)[94] is an example of an outcome for which the responsiveness was low. Some questions in SF-36 were not meaningful during hospitalization. For example the question regarding the ability to hoover is not relevant for patients that have recently undergone CABG surgery because hoovering is contraindicated due to the sternum split. Also this could have resulted in incomplete responses.

Modelling the trial

Based on evaluation of the pilot trial, relevant changes regarding design, intervention and outcomes measures were implemented in the main trial.

Design and sample size calculation

Data from the pilot trial were used for sample size calculation and the trial design was changed to a randomized controlled trial with 1:1 allocation because the two-by-two factorial design necessitate a large number of participants that could be difficult and time consuming to recruit in a CABG population. The organizational set-up of the trial was adjusted so that it was possible to intervene and test seven days a week.

The argument for the sample size was an estimated 30 meters difference between the experimental and usual care groups in regards to the 6MWT. The minimum clinical relevant effect difference in 6MWT is 25 m.[113] Furthermore, we chose to use an imputation strategy that does not impose us to increase the sample size to compensate for drop-outs.

Intervention

During hospitalisation the physical component was supplemented with systematic daily walking to initiate early post-operative physical activity while the exercises after discharge was unchanged from that applied in the pilot study. Walking is a simple way to be active and practical to be performed anywhere and with an intensity that matches the patients' capacity.[1]

The last consultation was moved from four to three weeks after surgery so it was before the last assessment at week 4. The approach was changed from face-to-face to be by phone to avoid another hospital visit and thereby strengthen adherence.[114] Also the diaries were simplified to have positive influence on adherence.

Physical outcome

Even though the CPET was tolerated and safe, the primary physical outcome was changed from VO_2 peak measured by CPET to functional capacity expressed by 6MWT. This decision was based on no effect in VO_2 in the pilot study, which was probably due to the short period of intervention. Also as cardiac rehabilitation aim to improve functional capacity in daily activity the 6MWT was considered as primary outcome in order to reflect that aim.

Secondary outcome

An important consideration in determining outcomes is to utilise instruments that measure changes and interventional effects over time. Assessment points were not changed from the pilot to the main trial. A number of the secondary outcomes were sub-grouped to be explorative; Multidimensional Fatique Inventory (MFI);[99-101,115] The International Physical Activity Questionnaire (IPAQ);[103] perception of Illness measured by The Brief Perception Questionnaire (B-IPQ)[102] and the EuroQol five dimensions questionnaire (EQ-5D). The EQ-5D is a standardized instrument to measure the current health status. It provides a simple descriptive profile and a single index that can be used in clinical and economic evaluation of healthcare and in population health surveys.[116]

The other questionnaires were identical to those used in the pilot trial but The MOS 36 item Short Health Survey (SF-36)[94] was replaced by The MOS 12 Item Short Form Health Survey (SF-12)[117] with a recall time of one week which was found applicable for the short intervention period.

STUDY II: RANDOMIZED CONTROLLED TRIAL (PAPER II + III)

Design and population

For a full design, method and intervention description please see the design paper of the randomized controlled trial.[118] In the following the differences in regards to the pilot trial is presented.

The SheppHeartCABG was a randomized, controlled, two-site trial. The randomized, controlled design was used and reported according to CONSORT guidelines[119] for non-pharmacological trials. CONSORT is considered to be the standard guide to follow when reporting high quality clinical or non-pharmacological trials and, thus increase the likely validity and applicability of the results. The aim of Paper II was to present the protocol for a randomized controlled trial to assess the effect of phase one rehabilitation versus usual care after CABG surgery (Paper III).

The setting was two university hospitals in Denmark. Enrolment of patients began November 2014 at Rigshospitalet and by June 2015 at Odense University Hospital and inclusion was finalised by June 2016, four weeks follow-up ended July 2016.

Recruitment, randomization and blinding

Consecutive patients hospitalised to undergo CABG were screened for inclusion and if eligible invited to participate. Included patients were 18 years of age or older, Danish speaking and providing verbal and written informed consent. Exclusion criteria included diagnoses of a musculoskeletal or neurological disease precluding exercise testing and training.

Patients were randomized in a 1:1 ratio to the comprehensive phase one cardiac rehabilitation plus usual care (experimental group) or usual care (control group) using a computer-generated allocation sequence varying in block size to avoid investigator bias. The allocation concealment and generation was by central randomization performed by the Copenhagen Trial Unit. The allocation was stratified according to sex and site. Blinding participants and clinicians is challenging in rehabilitation trials, but an attempt was made to obtain blinding for tests at discharge and for four weeks following surgery by informing the patients that research staff was blinded.

Data management was carried out by blinded research assistants and analysis was by a blinded trial-independent stastistian. In the final analysis the experimental and usual care groups were coded as X and Y. The results of the analysis were presented to the SheppHeartCABG study group with the codes X and Y. After the presentation two conclusions were formulated, one assuming that X was the experimental group and Y was the usual care group and one conclusion where the opposite conclusion was considered. After the two conclusions were formulated, the code was opened and the results of the trial exposed to the research group.

Sample size and power calculations

The study represents a randomized trial with the outcome 6MWT including one control patient per experimental participant. In the pilot trial, the outcome was normally distributed with a standard deviation of 90 m. If the true difference in the experimental and control means is 30 m, the trial should include 163 experimental and 163 control participants (total participants 326) to be able to reject the null hypothesis that the populations of the experimental and usual care groups are equal with a probability (power) of 85%. The type I error probability associated with this test of this null hypothesis is 5%.

Based on SheppHeartCABG pilot trial, several of the secondary outcomes were overpowered. For all outcomes except HeartQol physical, the power to reject the null hypothesis was above 85% (type I error 5%).

Outcome and outcome evaluation

Outcome was assessed at three time points: baseline (after randomization), at discharge and four weeks after CABG surgery. The PRO measures are presented in the design paper (Paper II).[118] Figure 4 presents the comprehensive phase one rehabilitation programme and outcomes measures.

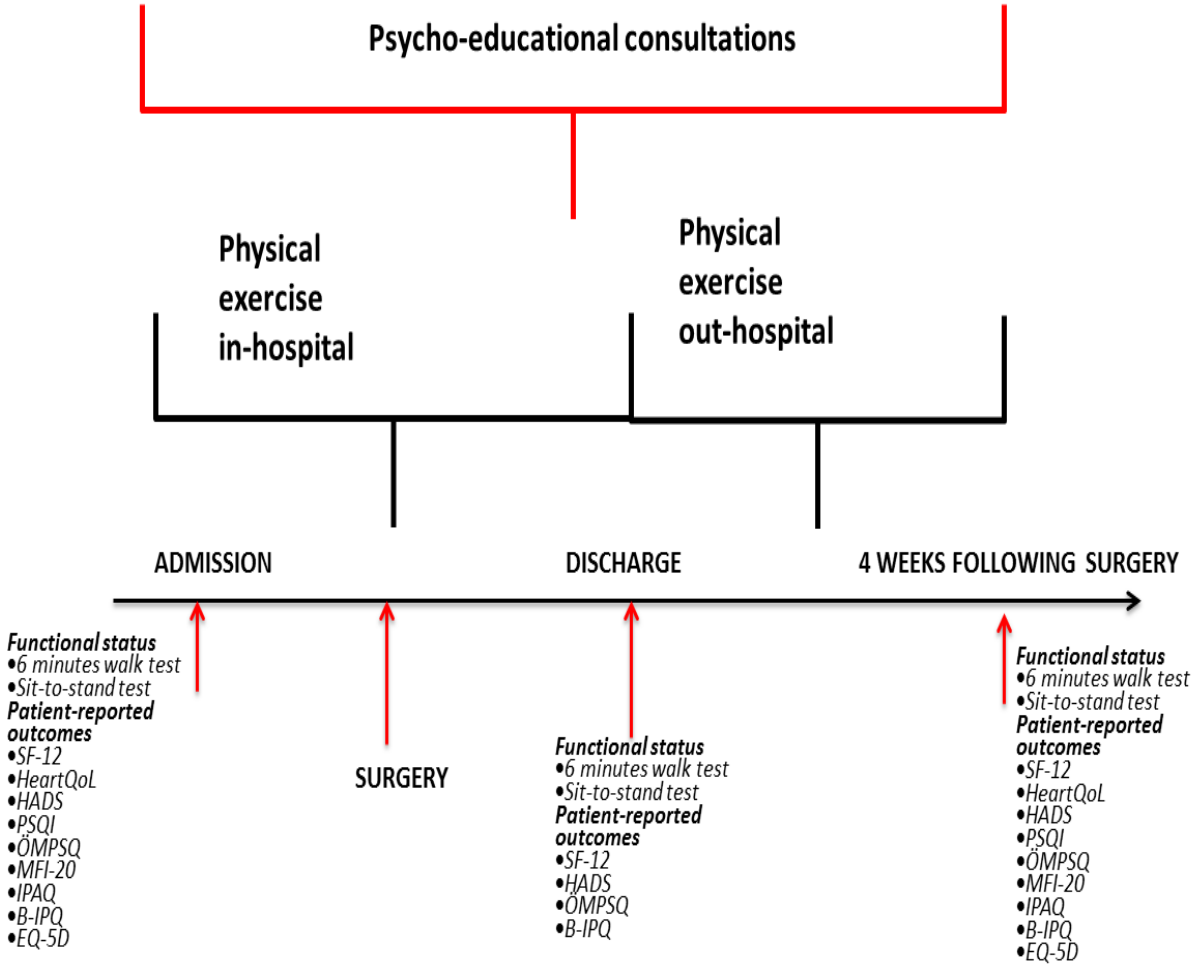


Figure 4. Timeline of the phase one cardiac programme with outcome assessments.

Primary outcome: physical function level

Physical function level 4 weeks following CABG was evaluated as 6MWT.[68] For the 6MWT, the participants walked up and down a 30 m hallway for 6 min according to guidelines.[90]

Secondary outcomes

Mental health and physical activity was evaluated by the MOS 12 Item Short Form Health Survey (SF-12)[117] which is a short version of SF-36, expressing self-perceived health including 12 items.

Reliability statistics have exceeded Cronbach´s alpha 0.87 for PCS and 0.84 for MCS and shown a high internal consistency.[117]

Exploratory outcomes

The HeartQol physical component was analyzed as an exploratory outcome.[97,98] Furthermore, a series of questionnaires regarding fatigue, physical activity and perception of illness were applied. The Fatigue Instrument[99-101,115] is a 20 item self-reported questionnaire. The International Physical Activity Questionnaire[103] is used to express health-related physical activity. Perception of illness is evaluated by The Brief Perception Questionnaire[102] that assesses cognitive and emotional representations of illness on the basis of eight items. EuroQol five dimensions questionnaire (EQ-5D) is a standardized instrument for current health that provides a simple descriptive profile and a single index that can be used in clinical and economic evaluation of health care as in population health surveys.[116]

Safety considerations

6MWT was undertaken by an experienced nurse or physiotherapist at baseline and by a physiotherapist at discharge and four weeks after surgery. Criteria for termination were defined.[120] Serious adverse events were registered and discussed with the physician responsible for the trial and the primary investigator.

Intervention

The comprehensive phase one cardiac rehabilitation programme had prior to this trial been modified in light of the organizational, interventional and administrative challenges in outcome assessment highlighted in the pilot trial. The physical exercise programme in the SheppHeartCABG trial meets the European[121] and Danish guidelines[122] for physical exercise in patients with heart disease and complies with The National Danish Board of Health recommendations for physical exercise in daily living for patients with heart disease.[65]

Physical exercise

The aim of the physical exercise programme was to maintain or to improve physical function initiated at the day of admission.[1] A physiotherapist experienced with patients who had gone through CABG and cardiac rehabilitation initiated the programme and provided the participants standardized instructions to each part of the programme. All elements of the exercise programme were documented in a training diary. Figure 5 presents each component in the physical exercise programme.

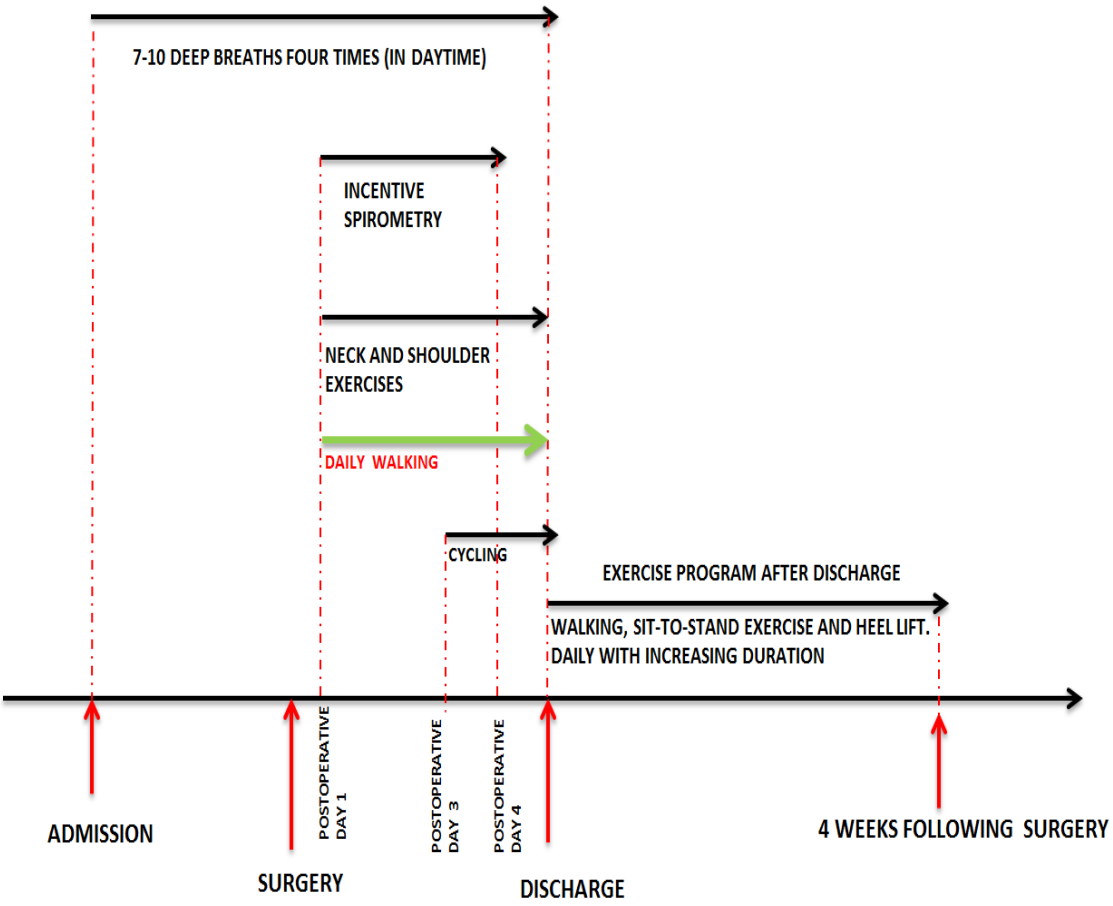


Figure 5. Exercise programme.

Physical xercise during hospitalization

Some of the exercise components were adjusted and new were added in consequence of the evaluation of the pilot trial. Physical intervention during hospitalization included the same components, but walking sessions were added as a result of the pilot evaluation. *Walking sessions* were performed twice daily from post-operative day 1 to discharge with increased intensity from low to moderate during admission; post-operative day 1 a 2×5 min walk, post-operative day 2 a 2×7 min walk, post-operative day 3 a 3×7 min walk and from post-operative day until discharge a 3×10 min walk.

Physical exercise from discharge to 4 weeks following surgery

After hospital discharge until four weeks after CABG, physical exercise included daily walking and muscle and endurance exercises; sit-to-stand and heel lifting exercises.

- *Daily walking* sessions increased from hospital discharge until four weeks after surgery 3 x 10, 2 x 15, 2 x 20, 2 x 25, 2 x 30 min at a moderate intensity: the first and last 2-3 min intensity corresponding to ≤ 10-13 on the Borg scale and the last period between 12- 14 on the Borg scale.
- *Sit and stand* exercise and *heel lift* with 10 repetitions twice daily from hospital discharge to 4 weeks after CABG.

Psycho-educational consultations

Four psycho-educational consultations were scheduled: on admission, on the second post-operative day, at discharge and three weeks after CABG. The first three consultations were in hospital and the fourth was by phone. A consultation guide outlining the topics for the psycho-educational consultation is described (Paper III).[118] The consultations were conducted by trained nurses and lasted about 45 min. Patients were introduced to mindfulness and an audio mindfulness programme at the first consultation. An overview of the consultation and mindfulness is presented in Figure 6.

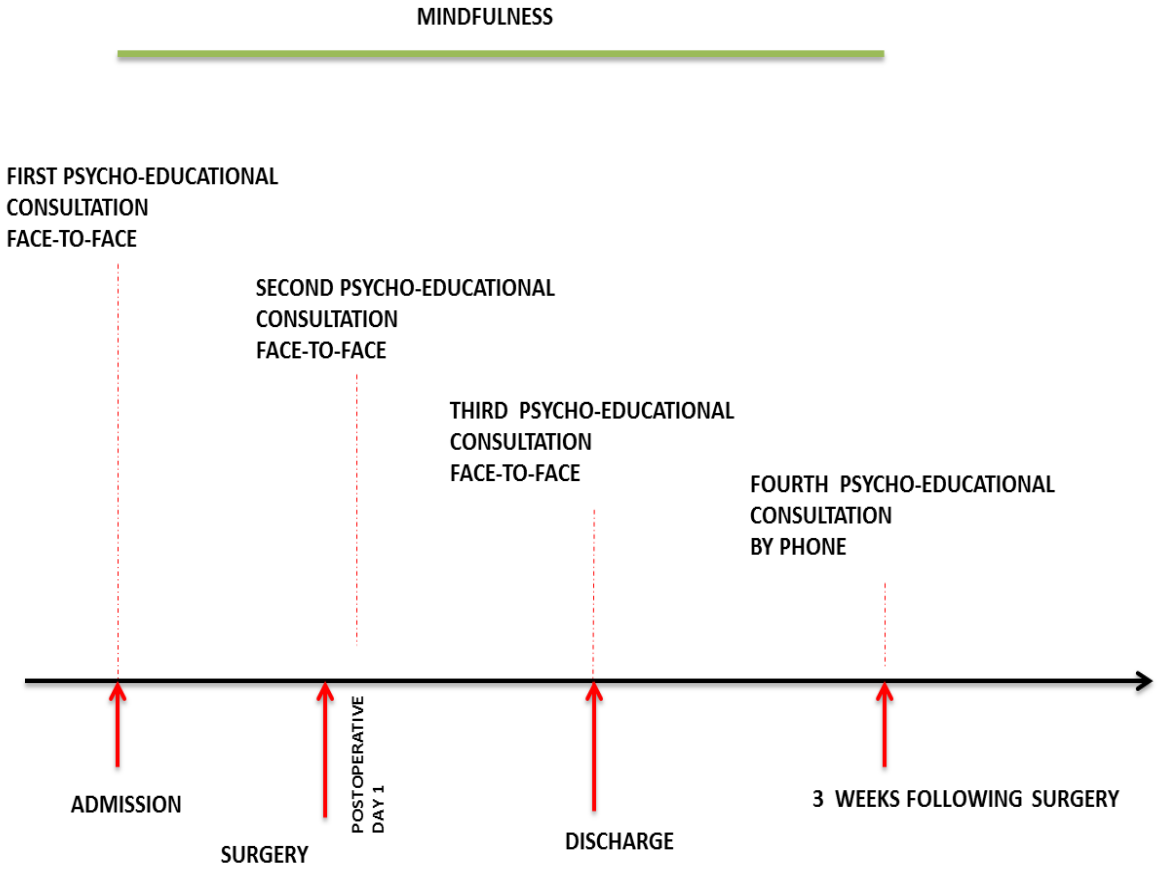


Figure 6. Psycho-educational consultations and mindfulness

Statistical analysis

All analyses for the primary and secondary outcomes were performed by an independent statistician blinded to the intervention group. All other analyses were by IEH.

The data analysis was carried out based on intention-to-treat. For the primary and secondary outcomes, multiple imputation of missing values using the Markov Chain Monte Carlo approach was used since the number of participants with missing values was above 5%. The variables included the group allocation, stratifying variables (hospital and sex), time (baseline, discharge and four weeks after discharge) and outcomes. The primary outcome (6MWT) was tested using a significance level of 0.05. Analyses of the secondary outcome measures, as planned in the protocol

were carried out with no adjustment of p-values due to multiplicity. Thus, the interpretation of each secondary outcome measure was assessed in the light of multiple testing. In order to evaluate the clinical effect Cohen's d was calculated for primary and secondary outcomes.[123]

The pre-specified per-protocol levels of intervention adherence were defined in the protocol[118] as completing at least 75% of the exercise and mindfulness sessions and consultations. However, only one participant fulfilled that criterion and therefore it was decided before the start of the analysis to change the per-protocol level to at least 50% of the exercise sessions and psycho-educational consultations. Adherence to the exercise intervention was evaluated by the patient-reported exercise diary and to the psycho-educational intervention recordings were made at each visit. Statistical analyses were performed using SPSS V.22 (SPSS Inc. IPM), R version 3.1.2 (R Foundation for Statistical Computing, Vienna Austria) and SAS V.9.3 (SAS Institute, Cary North Carolina, USA).

STUDY III: ADHERENCE TO PHASE ONE CARDIAC REHABILITATION (PAPER IV)

Design and population

This study was exploratory. The paper relates non-adherence to phase one rehabilitation after coronary artery bypass surgery to sociodemographic and clinical baseline data. The study included all participants randomized to the experimental group in the SheppHeartCABG trial.

Outcome

Baseline sociodemographic and clinical data differences between adherent and non-adherent patients were evaluated using t-tests for continuous variables and Pearson χ2 tests for categorical variables. In order, to test association between adherence to the exercise intervention and age, sex, marital status, occupational status, educational level, left ventricular ejection fraction (LVEF) and New York Heart Association classification (NYHA) multivariate regressions were used to estimate odds ratios (OR) for training during hospitalization and after discharge.

Statistical analysis

Baseline sociodemographic and clinical data differences between adherent and non-adherent patients were tested using Pearson χ^2 tests. In order to evaluate association between non-adherence to the exercise training and socio-economic and clinical data, multivariate logistic regression was used to estimate odds ratios (OR) for training during hospitalization and after discharge adjusted for age, sex and LVEF.

The sociodemographic data age, occupational status and educational level, NYHA class, LVEF were reduced into dichotomous data and that was also the case for the clinical data: NYHA, LVEF and BMI (body mass index). Data were analysed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Study II: Randomized clinical trial design and results (Papers II + III)

Participants

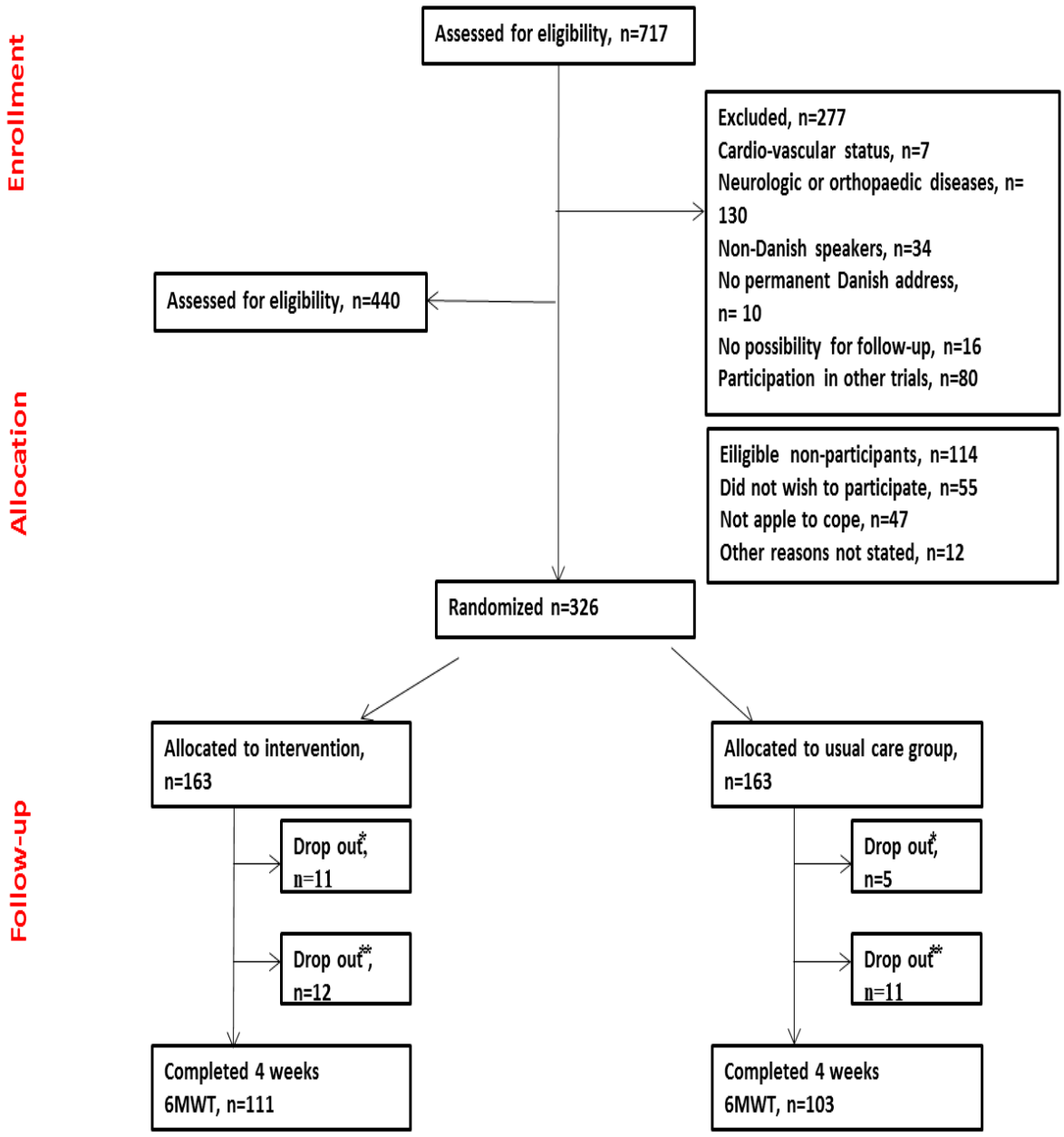
Between November 17, 2014 and June 23, 2016, 717 patients were identified and screened. 277 patients were excluded and 114/440 (26%) declined to participate. The sex ratio was equal among patients who declined to participate and those who were included in the study. A total of 326 patients provided informed written consent and were randomized. Of these 11 dropped out in the experimental group and 5 in the usual care group due to complications after surgery, or withdrawal of consent. Of 310 remaining patients, 87% were men and the mean age was 65 years (range 33 to 83). NYHA class ranged from I to IV. No baseline imbalances were found. Figure 8 shows the flow of the trial.

Outcomes

There was no statistically significant difference in 6MWT between the experimental and usual care groups four weeks after CABG (16.2 m (95% CI: -13.0 to 45.4, p= 0.27) and no significant interaction between intervention and time (p=0.55). Cohen's d was 0.14 (Table 4).

Secondary outcome

Also the secondary outcomes showed no statistical significant difference between groups, except for a difference in favour of the intervention detected on HADS-D≥8 (odds ratio=0.46 (95% CI: 0.22 to 0.97), p= 0.04). The tendency in all secondary outcomes was however that the intervention had a positive effect (Table 5).



*Dropout: dropped out and wanted to extract their data from the trial. **Dropout: dropped out from the trial with acceptance to use data.

Figure 8. Flowchart for the SheppHeartCABG randomized controlled trial.

Table 4. Mean difference in outcome and OR between 152 experimental participants and 158 usual care participants.

	n	Group	Admission	Discharge	Four weeks after surgery
HADS-A, (±SD)	310	Experimental	5.4 (4.3)	5.7 (4.0)	3.5 (3.4)
		Usual care	6.0 (4,5)	5.8.(4.3)	4.3 (3.7)
HADS-D, (±SD)	310	Experimental	4.0 (3.5)	5.8 (3.7)	3.7 (3.2)
		usual care	3.9 (3.5)	5.7 (4.1)	4.3 (3.7)

Table 5. HADS-A and HADS-D mean values and standard deviation.

Primary outcome	**n**	**Estimate (95% CI)**	**p-value**	**SD**	**Cohen's d**
6-MWT	310	16.2 (-13.0; 45.4)	0.27	119.8	0.14
Secondary outcomes	**n**	**Estimate (95% CI)**	**p-value**	**SD**	**Cohen's d**
SF-12 MCS	310	1.18 (-1.74; 4.09)	0.43	11.8	0.10
SF-12 PCS	310	-0.82 (-3.18; 1.54)	0.49	10.2	-0.08
Pittsburgh Sleep QI	310	-0.91 (-2.06; 0.23)	0.12	4.6	-0.20
Örebro MSQ	310	-1.92 (-4.34; 0.51)	0.12	10.9	-0.18
Sit-To-Stand test	310	1.09 (-0.34; 2.52)	0.13	5.0	0.22
HADS-A	310	-0.59 (-1.50; 0.32)	0.20	4.0	-0.15
HADS-D	310	-0.43 (-1.33; 0.46)	0.34	3.8	-0.11
Binary outcomes	**n**	**OR (95% CI)**	**p-value**		
HADS-A (8+)	310	0.62 (0.29; 1.29)	0.20		
HADS-D (8+)	310	0.46 (0.22; 0.97)	0.04		
HeartQol (>median)					
HeartQol global	310	0.78 (0.45; 1.35)	0.37		
HeartQol emotional	310	0.93 (0.42; 2.09)	0.86		

Adherence

Seventy two percent (110/152) in the intervention group participated in the exercise training programme. The number of sessions completed depended on the length of hospitalization. Sixteen (15%) participants conducted ≥ 75% of the sessions, 35 (32%) 50-74% and 59 patients

(54%) < 50%. Overall, the patients participated in 65% of the sessions during admission and in 54% after discharge as identified by the training diaries. A total of 152 of the experimental group participated in the psycho-educational intervention, of which 76% (115/152) attended all four consultations. Regarding the mindfulness component 60% (91/152) participated in the introductions provided as part of the psycho-educational consultation. Of these two (2%) later went on by using the "mindfulness toolbox" exercises on ≥75% of the following days at hospital, 10 (11%) on 50-74% of the days, and 79 (86%) used them more rarely or not at all.

Per-protocol analysis

There was a difference between the intervention and the usual care group in regard to 6MWT (41.1 m (95% CI: 8.0 to 74.3 m), p=0.02) and on STST (1.87 repetitions (95% CI: 0.04 to 3.70 repetitions), p=0.046) four weeks after surgery, resulting in a Cohen´s d of 0.40 and 0.36, respectively (Table 6).

Table 6. Per protocol analysis in a general univariate linear model with primary and secondary outcomes. The estimates are the mean difference in outcome and odds ratio between experimental and usual care groups.

Primary outcome	**n**	**Estimate (95%CI)**	**p-Value**	**Cohen´s d**
6MWT	209	41.1 (8.0; 74.3)	0.02	0.40
Secondary outcomes	**n**	**Estimate (95%CI)**	**p-Value**	**Cohen´s d**
SF-12 MCS	209	1.84 (-1.80; 5.49)	0.32	0.17
SF-12 PCS	209	-1.50 (-4.69; 1.70)	0.36	-0.16
Pittsburgh Sleep QI	209	-1.49 (-3.02; 0.04)	0.06	-0.31
Örebro MSQ	209	-3.54 (-6.92; -0.17)	0.04	-0.34
Sit-To-Stand test	209	1.87 (0.04; 3.70)	0.046	0.36
Binary outcomes	**n**	**OR (95%CI)**	**p-Value**	
HADS-A (8+)	209	0.56 (0.20; 1.52)	0.25	
HADS-D (8+)	209	0.46 (0.17; 1.27)	0.13	
HeartQol (>median)				
HeartQol global	209	0.76 (0.36; 1.61)	0.48	
HeartQol physical	209	0.70 (0.34; 1.41)	0.32	
HeartQol emotional	209	0.87 (0.42; 1.82)	0.72	

Safety

One serious event was reported at baseline after the 6MWT in the intervention group versus none in the usual care group. The participant had after 6MWT two events of ventricular tachycardia, but the event was evaluated not to be related to the 6MWT test.

Study III: Adherence to phase one cardiac rehabilitation (Paper IV)

A total of 326 patients undergoing CABG were randomized to comprehensive phase one rehabilitation or usual care. Sixteen patients dropped out during the intervention period or did not grant permission for the use of their data. Of 310 remaining patients, 152 were in the experimental group (132 men) at a mean age of 65 years (SD±9.1). Sociodemographic and clinical baseline data are presented in Table 7.

The experimental group included 152 patients of whom 48 (31%) were non-adherent to the in-hospital physical exercise programme during hospitalization. Number of patients not participating in the out-patient exercise programme was 81 (53%). Of the females 20% (4/20) were non-adherent to the in-hospital training increasing to 70% (14/20) during the out-patient training. Non-adherence to mindfulness included 87% (132/152) in-hospital and 70% (106/132) after discharge. Male patients not using mindfulness were 112 (85%) in-hospital and 92 (70%) after discharge. Non-adherent to psycho-educational consultations came to 5 (3%) of whom 4 (80%) were men.

Baseline sociodemographic data and clinical characteristics of the experimental group in relation to adherence/non-adherence are presented in Table 8. Non-adherence in hospital was associated with educational level and out of hospital with diabetes. Also differences in occupational status were found in training during hospitalization and in psycho-educational consultations. No differences in age, sex, NYHA class or LVEF manifested. Patients with education at university level were more adherent to training during hospitalization than other patients (odds ratio=3.14, (95% confidence interval (CI); 1.16-8.51), p=0.02)) as adjusted for age, sex and LVEF. In contrast patients with diabetes were les adherent to training after discharge than other patient (odds ratio=3.74 (CI); 1.54-9.08), p=0.004) adjusted for age, sex and LVEF. Also patients with normal weight were more adherent than overweight patients (odds ratio=0.37, (CI); 0.17—0.80), p=0.01) adjusted for age, sex and LVEF (Table 9).

Table 7. Sociodemographic and clinical baseline characteristics of the experimental group for those adherent and non-adherent to the programme.

	Total experimental group (n= 152)	Experimental adherent (n= 51)	Experimental non-adherent (n= 101)
Age in years, mean (±SD)	65 (9.1)	65 (7.7)	65 (9,7)
Male, n (%)	132 (87)	46 (90)	86 (85)
Female, n (%)	20 (13)	5(10)	15 (15)
Cohabitation status			
Single/divorced/widowed, n (%)	32 (21)	8 (16)	24 (23)
Married/domestic partner, n (%)	120 (79)	43 (84)	82 (77)
Occupational status			
Active employment, n (%)	61 (41)	25(49)	36 (37)
Pensioner, n (%)	86 (57)	25 (49)	61 (60)
Early retirement, n (%)	4 (3)	1 (2)	3 (3)
Person on job release scheme, n (%)	1 (1)	0 (0)	1 (1)
Educational level			
Vocational level, n (%)	69 (45)	22 (43)	47 (47)
College, n (%)	36 (23)	11 (22)	25 (25)
University, n (%)	34 (22)	15 (30)	19 (19)
None, n (%)	2 (1)	1 (2)	1 (1)
Undisclosed, n (%)	11 (7)	2 (4)	9 (9)
Body mass index[1]			
< 18.5 (kg/m2), n (%)	1 (1)	0 (0)	1 (1)
≥ 18.5 < 25 (kg/m2), n (%)	39 (26)	22 (43)	17 (17)
≥25 < 30 (kg/m2), n (%)	64 (42)	19 (37)	45 (45)
>30 (kg/m2), n (%)	47 (31)	10 (20)	37 (37)
Undisclosed, n (%)	1 (1)	0 (0)	1(1)
Type of heart disease			
Ischemic heart disease n (%)	40 (30)	10(20)	30 (30)
Morbus cordis artiosclerosis, n (%)	63 (41)	21 (41)	42 (42)
Others, n (%)	3 (2)	1 (2)	2 (2)

Undisclosed, n (%)	45 (30)	19(37)	26 (26)
NYHA class[2]			
NYHA class I, n (%)	44 (39)	24 (47)	20 (20)
NYHA class II, n (%)	53 (35)	14 (27)	39 (39)
NYHA class III, n (%)	31 (29)	7 (14)	24 (24)
NYHA class IV, n (%)	2(1)	0 (0)	2 (2)
Undisclosed, n (%)	22 (14)	6(14)	16 (16)
LVEF[3]			
Normal (50-70), n (%)	112 (74)	40 (78)	77 (73)
Under normal (36-49), n (%)	30 (20)	9(18)	21 (20)
Low (<35), n (%)	9 (6)	2 (4)	7 (7)
Undisclosed, n (%)	1 (1)	0(0)	1 (1)
Smoker			
Current smoker, n (%)	20 (13)	5 (10)	15 (15)
Previous smoker, n (%)	79 (52)	27 (53)	52 (5)
Non-smoker, n (%)	53(35)	19(36)	35 (33)
Diabetes Mellitus			
Type I, n (%)	6 (4)	1(2)	5 (5)
Type II, n (%)	29 (19)	4 (8)	25 (25)
Undisclosed, n (%)	1 (1)	0(0)	1 (1)
Prescribed medication			
Blood pressure-lowering drugs, n (%)	89 (59)	30 (59)	59 (58)
ACE inhibitor, n (%)	27 (18)	8 (16)	19 (19)
Beta-blocker, n (%)	43 (28)	16 (31)	27 (27)
Calcium antagonist, n (%)	33 (22)	11 (22)	22 (22)
Anti-arrhythmia, n (%)	3 (2)	2 (4)	1 (1)
Antiplatelet drugs, n (%)	127 (84)	44 (83)	83 (82)
Diuretic, n (%)	27 (18)	5 (10)	22 (22)
Anti-diabetic, n (%)	24 (16)	2(4)	22 (22)
Statin, n (%)	126 (83)	45 (88)	81 (80)
Antidepressant, n (%)	9 (6)	2 (4)	7 (7)
Pain reliever, n (%)	21 (14)	2(4)	14 (14)
Sleeping medicine, n (%)	5 (3)	1(2)	3 (3)

[1]BMI; Body Mass Index; [2]LVEF Left Ventricular Ejection Fraction [3]NYHA; New York Heart Association Functional Classification

Table 8. Sociodemographic and clinical baseline data related to differences in adherence and non-adherence to the separate intervention components.

Experimental group	**< 50% training during hospita-lization** *n=48(31%)*	**P-value**	**< 50% training after discharge** *n= 81(53%)*	**P-value**	**< 50% Mindfulness during hospita-lization** *n=132(87%)*	**P-value**	**< 50% Mindfulness after discharge** *n=106(70%)*	**p-value**	**< 50% Psycho-educational consultations** *n=5(3%)*	**P-value**
Age in years										
> 65 years	19 (31)	0.95	30 (48)	0.31	51 (82)	0.16	43 (69)	0.93	1 (2)	0.34
<65 years	28 (31)		51 (57)		81 (90)		63 (70)		4(4)	
Sex										
Male, n (%)	43 (33)	0.26	67 (51)	0.11	112 (85)	0.06	92 (70)	0.98	4 (3)	0.64
Female, n (%)	4 (20)		14(70)		20 (100)		14 (70)		1(5)	
Cohabitation status										
Single/divorced/widowed, n (%)	11 (34)	0.70	21 (66)	0.15	28 (87)	0.90	20 (62)	0.32	2 (6)	0.29
Married/domestic partner, n (%)	37 (31)		60 (50)		104 (87)		86 (72)		3 (3)	
Occupational status										
Active employment, n (%)	20 (34)	0.04	27 (43)	0.05	55 (89)	0.57	44 (71)	0.78	0 (0)	0.06
Retried, n (%)	25 (30)		54 (60)		77 (86)		62 (69)		5 (6)	
Educational level										
Vocational level/college n (%)	41 (35)	0.04	64 (55)	0.52	100 (86)	0.36	83 (71)	0.56	4 (3)	0.87
University, n (%)	6 (17)		17 (49)		32 (91)		23 (66)		1(3)	
NYHA class[1]										
Unknown, n (%)	9 (19)	0.15	12 (57)	0.64	16 (76)	0.27	17 (81)	0.23	2 (10)	0.21
NYHA class I +II n (%)	26 (26)		50 (50)		87 (88)		70 (71)		2 (2)	
NYHA class II+III, n (%)	13 (27)		19 (59)		29 (91)		19 (60)		1 (3)	
LVEF[2]										
Normal, n (%)	38 (28)	0.73	69 (51)	0.22	116 (87)	0.78	93 (69)	0.81	4 (3)	0.57
Low, n (%)	9 (50)		12 (66)		16 (89)		13 (72)		1(6)	
BMI[3]										
Normal, n (%)	12 (25)	0.71	15 (37)	0.01	36 (88)	0.83	28 (68)	0.81	28 (68)	0.84
Overweight, n (%)	36 (32)		66 (60)		96 (87)		78 (70)		78 (70)	
Diabetes Mellitus										
Yes, n (%)	10 (29)	0.83	26 (77)	0.02	29 (85)	0.76	56 (67)	0.76	1 (3)	0.90

No, n (%)	37 (31)		55 (46)		103 (87)		83 (70)		4 (3)	
Smoker										
Smoker, n (%)	7 (24)	0.38	17 (59)	0.52	26 (90)	0.62	21 (72)	0.72	0 (0)	0.27
Non-smoker, n (%)	40 (31)		64 (52)		106 (86)		85 (69)		5 (4)	
Medication[4]										
Blood pressure-lowering drugs, n (%)	27(57)	0.85	45 (51)	0.42	79 (89)	0.40	66 (74)	0.16	4 (4)	0.32
ACE inhibitor, n (%)	8 (30)	0.87	17 (63)	0.27	24 (89)	0.73	16 (59)	0.19	0 (0)	0.29
Beta-blocker, n (%)	8 (19)	0.04	24 (56)	0.70	36 (84)	0.47	29 (67)	0.70	0 (0)	0.15
Calcium antagonist, n (%)	7 (21)	0.18	18 (54)	0.81	27 (82)	0.35	14 (30)	0.10	0 (0)	0.23
Anti-arrhythmia, n (%)	1 (33)	0.83	1 (33)	0.48	3 (100)	0.51	1 (33)	0.19	0 (0)	0.72
Antiplatelet drugs, n (%)	39 (31)	0.90	62 (52)	0.46	109 (86)	0.40	89 (70)	0.84	5 (4)	0.31
Diuretic, n (%)	12 (44)	0.09	19 (70)	0.05	24 (88)	0.73	20 (74)	0.59	5 (7)	0.19
Anti-diabetic, n (%)	11 (46)	0.08	20 (83)	0.00	21 (88)	0.92	19 (79)	0.27	0 (0)	0.33
Statin, n (%)	36 (29)	0.17	67 (53)	0.95	109 (86)	0.79	88 (70)	0.95	2 (2)	0.10
Antidepressant, n (%)	2 (22)	0.60	6 (67)	0.41	9 (100)	0.23	6 (66)	0.84	0 (0)	0.57
Pain reliever, n (%)	8 (38)	0.44	10 (48)	0.58	17 (81)	0.39	14 (67)	0,74	3 (14)	0.00
Sleeping medicine, n (%)	2 (40)	0.65	2 (40)	0.54	5 (100)	0.38	4 (80)	0.61	0 (0)	0.68

[1]NYHA: New York Heart Association Functional Classification; [2]LVEF: Left ventricular ejection fraction; [3]BMI: Body Mass Index; [4]Tested for differences in non-adherence/adherence medication in the separate intervention components.

Table 9. Demographic and clinical baseline characteristics associated with training during hospitalization and training after discharge in CABG-patients participating in a four week comprehensive rehabilitation programme. Univariate and multivariate factors associated with training during hospitalization and training after discharge.

	Training during hopsitalization				Training after discharge			
	Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age								
< 65 years	0.98 (0.49-1.97)	0.95	0.91 (0.44-1.86)	0.08	0.72 (0.37-1.37)	0.31	0.72 (0.37-1.40)	0.34
>65 years(1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Sex								
Male	1.93 (0.61-6.13)	0.26	1.82 (0.56-5.80)	0.31	0.44 (0.16-1.22)	0.11	0.43 (0.15-1.20)	0.11
Female (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Cohabitation status								
Single/divorced/widowed	1.18 (0.51-2-68)	0.70	1.58 (0.65-3.84)	0.31	1.91 (0.85-4.30)	0.12	1.83 (0.78-4.31)	0.16
Married/domestic partner(1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Occupational status								
Active employment	1.22 (0.53-2.80)	0.63	1.13 (0.48-2.68)	0.78	0.51 (0.27-0.99)	0.05	0.54(0.24-1.20)	0.13
Retried(1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Educational level								
Vocational level/college	2.60 (1.01-6.79)	0.05	3.14 (1.16-8.51)	0.02	1.28 (0.60-2.724)	2.71	1.23 (0.57-2.68)	0.60
University(1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Diabetes								
Yes	1.10 (0.48-2.52)	0.83	0.96 (0.41-2.26)	0.93	0.27 (0.12-0.64)	0.003	3.74 (1.54-9.08)	0.004
No (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
NYHA class[2]								
NYHA class I +II	1.10 (0.35-3.34)	0.87	1.24(0.38-4.00)	0.72	0.91 (0.30-2.78)	0.87	1.27 (0.39-4.07)	0.69
NYHA class II+III (1)	0.49 (0.21-1.14)	0.10	0.50 (0.21-1.21)	0.13	0.70 (0.31-1.57)	0.83	0.81 (0.35-1.88)	0.62
Unknown	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
LVEF[3]								
Normal	0.39 (0.15-1.07)	0.07	0.41 (0.15-1.12)	0.08	0.53 (0.19-1.50)	0.23	0.48 (0.167-1.36)	0.17
Low (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	

BMI[4]								
Normal	0.90 (0.41-1.97)	0.78	1.04 (0.46-2.32)	0.92	0.39 (0.19-0.82)	0.01	0.37 (0.17-0.80)	0.01
Overweight (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Smoker								
Smoker	0.66 (0.26-1.67)	0.80	1.36 (0.52- 3.56)	0.53	0.77 (0.34-1.74)	0.77	1.39 (0.59-3.28)	0.45
Non-smoker (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Medication								
Blood pressure-lowering drugs	0.94 (0.46-1.88)	0.85	0.87 (0.43-1.78)	0.83	0.76 (0.40-1.47)	0.42	0.76 (0.39-1.48)	0.43
ACE inhibitor,	0.92 (0.37-2.30)	0.87	0.81 (0.31-1.10)	0.65	1.62 (0.69-3.81)	0.27	1.81 (0.75-4.36)	0.19
Beta-blocker,	0.41 (0.17-0.97)	0.043	0.40 (0.17-0.97)	0.04	1.15 (0.58-2.34)	0.69	1.27 (0.61-2.62)	0.53
Calcium antagonist,	0.39 (0.17-0.93)	0.39	0.42 (0.22-1.41)	0.22	1.10 (0.51-2.39)	0.81	1.13 (0.51-2.49)	0.76
Antirytmia,	0.79 (0.70-9.0)	0.85	0.56 (0.08-10.87)	0.94	0.43 (0.38-4.87)	0.50	0.27 (0.20-3.76)	0.33
Antiplatelet drugs,	0.94 (0.37-2.37)	0.89	0.90 (0.34-2.32)	0.82	0.72 (0.30-1.73)	0.46	0.76 (0.31-1.85)	0.54
Diuretic	0.49 (0.20-1.14)	0.10	1.76 (0.68-4.54)	0.25	2.41 (0.98-5.92)	0.054	1.96 (0.74-5.19)	0.17
Anti-diabetic,	2.16 (0.89-5.27)	0.10	2.10 (0.84-.5.16)	0.11	5.49 (1.77-16.97)	0.003	5.49 (1.78-16.97)	0.003
Statin, n (%)	0.54 (0.23-1.30)	0.17	0.49 (0.20-1.19)	0.13	1.03 (0.44-2.40)	0.95	0.97 (0.42-2.27)	0.95
Antidepressant, n (%)	1.60 (0.32-8.04)	0.57	0.64 (0.12-3.47)	0.61	0.55 (0.13-2.29)	0.41	1.81 (0.44-7.53)	0.41
Pain reliever, n (%)	1.45 (0.56-3.78)	0.44	1.81 (0.66-5.00)	0.25	1.30 (0.51-3.27)	0.57	0.76 (0.30-1.93)	0.58
Sleeping medicine, n (%)	0.66 (0.11-4.10)	0.66	1.80 (0.28-11.33)	0.53	1.74 (0.28-10.74)	0.55	0.58 (0.09-3.72)	0.56

[1] Adjusted for age, sex and Left Ventricular Ejection Fraction (LVEF) ¸[2]NYHA; New York Heart Association Functional Classification [3]LVEF Left Ventricular Enjection Fraction [4]BMI; Body Mass Index

DISCUSSION

The MRC framework was used to guide the development and evaluation of the complex early rehabilitation intervention that CABG patients were exposed to. Based on current evidence exercise-based rehabilitation and psychological intervention for coronary heart diseases were developed into a comprehensive phase one rehabilitation programme.

The intervention was tested in a pilot trial with an acceptable inclusion rate and was found to be safe. The comprehensive phase one rehabilitation programme showed no effect on the primary or the secondary outcomes, except a beneficial effect on depression. Adherence to the programme was low however to some of the components and from a "comparative effectiveness research" point of view the intervention had positive effect for adherent participants, who were better educated than those who did not follow the programme.

The result inspired to further elaboration. Even though no significant difference between groups was found, the group of patients who followed the phase one exercise programme had a beneficial effect. The programme was developed to be "comprehensive" and included both physical and psycho-educational components to minimalize symptoms. However, the programme may have been too ambitious. There was acceptable adherence to parts of the exercise programme and the consultations which indicates that parts of the programme can be applied, but also need for modification as some patients did not follow the programme and focus should be on addressing patients with a high BMI, diabetic patients and those with limited education.

Methodology issues

Design

Problems associated with CABG surgery include both physical and psychological dimensions, but when evaluating an intervention that addresses separate components it becomes difficult to identify the specific effect of each element. The pilot trial was a feasibility study and the 2-by-2 factorial design was chosen even though that design requires a larger sample size. Evaluation of the pilot trial showed an effect in the trial arm including both physical and psycho-educational

intervention. Therefore the design of the main trial was changed to a randomized controlled trial with two groups; an experimental and a usual care group (control). The randomization ensured no systematic differences at baseline, and therefore estimated treatment effect was not considered to be biased by confounding factors.[124] Potential difference between the two groups was considered to be due to the interventions.

Missing data is a problem in clinical trials with low adherence to the intervention influencing results relevant to rehabilitation.[125] The analysis plan in the main trial was an intention-to-treat analysis with multiple imputations.[126] In an intention-to-treat analysis patients are analysed according to their original group assessment to avoid the possibility of any bias associated with loss, miss-allocation and non-adherence of participants.[127] Per-protocol analysis based on the actual intervention received with criteria for minimum adherence to the intervention could provide complementary information. A concern is though that the randomization is lost resulting in non-comparability between intervention and usual care groups, i.e. confounding. Therefore, the per-protocol analysis should be interpreted with caution.[128]

Initially, adherence to the intervention was decided to be larger than 75% in all sessions as is a standard for rehabilitation trials.[129-131] However, only one participant reached that level. Due to the low adherence to the comprehensive intervention in the trial the adherence level was scaled down to 50%. The rationale for changing the level of adherence was pragmatic and used to generate knowledge about the impact of the intervention. However, reducing the adherence level can have affected findings in the per-protocol analyses of 6MWT.

The CABG-population has an acceptable volume but research has been based on small samples which can compromise certainty of results.[61,67,132] There is a risk of producing wide confidence intervals and limiting analysis options, e.g. in comparative analysis when subgroups are small and there are several confounders in model testing for a regression analysis. In the pilot trial the sampling was arbitral, but with an acceptable number of participants in each trial arm.

A sample size calculation was conducted in the randomized controlled trial based on the pilot trial and the few previous trials to ensure sufficient power and avoid inconclusive results. We did not increase sample in order to compensate for low adherence because the intention-to-treat analysis

was incorporated in the analysis plan. Patients were recruited consecutively to avoid selection bias and recruitment was at two sites in the randomized controlled trial.

Choosing the primary outcome of interest in the trial among many possible options is difficult especially when testing a complex intervention. The choice is affected by what the intervention is assumed to be able to modify and by what is believed can be measured. Choosing a physical primary outcome seemed obvious as the intervention had a physical perspective while the psychological aspect was covered by the patient-reported outcome. Some of the outcome assessment parameters chosen for the SheppHeartCABG pilot trial appeared not to be sensitive and were replaced in the randomized controlled SheppHeartCABG trial. The outcome assessment that was used had been used in rehabilitation trials and found to be sensitive and responsive to a complex intervention.[133,134]

Findings

Development of the comprehensive phase one rehabilitation

Based on the MRC framework evidence must be taken into account when developing a complex intervention and when the evidence is found insufficient, primary research needs to be undertaken.[48]

Evidence based on positions papers and systematic reviews to guide the design of a comprehensive phase one rehabilitation programme addressing both physical and psychological issues after CABG[34] are sparse and based on old studies with small selected samples[32]. However a position paper recommends the physical part of rehabilitation to begin early after surgery, but without further detailed description.[34,135,136]

In developing a comprehensive phase one rehabilitation programme, understanding of CABG patients' health, recovery and rehabilitation is needed. It was necessary for developing the physical components to understand the physical mechanism that patients undergoing CABG surgery and recovery are exposed to.[32,137-139] Major surgery involves haemodynamic stress and increased oxygen consumption peri- and postoperatively. A combination of major surgery and inactivity induces a catabolic state and muscle restitution after major surgery has a time frame of

approximately 30 days. [140] Saltin et al. identified that 10 to 20 days are needed to achieve baseline maximum VO_2 after 21 days of bedrest.[141] Postoperative catabolism and muscle inactivity are important factors for postoperative fatique.[142,143] The exercise programme intended to attenuate the catabolic state by early mobilization and respiratory physiotherapy. The exercise programme was planned to be performed before meals (lunch and dinner) to avoid interrupting daily meals since food intake is most effective for building up muscles if provided shortly after exercise.[144] The psychological issues were addressed based on psycho-education to support and educate the patients to cope with their situation short and long term.

The comprehensive phase one rehabilitation

Testing the complex intervention in a pilot trial was valuable. To test important issues as feasibility, acceptability and compliance to the intervention was evaluated. The pilot trial sample was sized so that it was plausible to test the intervention. Pilot testing provides a basis for exploring the potential for an intervention with different perspectives.[48] A high level of recruitment was shown, but there was unfortunately suboptimal adherence to the intervention and adherence is a challenge for cardiac rehabilitation and may explain that only a few studies address exercise training in phase one after CABG surgery and that the samples are small.[61,132] Also in regard to psychological intervention adherence is low.[15,145,146]

Some outcomes did not show sufficient sensitivity to changes in the pilot trial including both questionnaires and physical tests. Furthermore, the cardiopulmonary test did not seem to be applicable for evaluating a short moderate intensity exercise intervention.

The effect of the comprehensive phase one rehabilitation

The effect of the comprehensive phase one rehabilitation programme was evaluated in a randomized controlled trial and through exploratory measures produced information in regards to health before surgery, at discharge and four weeks after surgery (Paper III). Difference between the experimental and the usual care group in 6MWT was statistically insignificant and only a small clinical effect was indicated by Cohen´s d. However, the per-protocol analysis showed a difference

between the two groups in physical outcome in regard to the 6MWT and STST albeit with only a small clinical effect as indicated by Cohen's d, suggesting that non-adherence might have affected the results. The findings from the experimental adherent group are identical to those of studies on physical training in phase one rehabilitation.[61,132] The per-protocol analysis is a supplementary analysis and should be interpreted as an explorative analysis where randomization of the groups is lost. Nevertheless, the intervention had from a comparative effectiveness point of view positive effect for adherent participants.

An exploratory and hypothesis-generating analysis indicates that the intervention did have an effect on those patients who were exposed to a certain "dose", but the effective level of intervention has to be clarified. The knowledge generated by this project is important for phase one rehabilitation after open heart surgery. The intervention should be both beneficial and designed to increase adherence.

Major surgery as open heart surgery is associated with a postoperative catabolic state[143]. Early mobilisation is important for reducing that state. Nutritional supplement in combination with a physical exercise programme has a positive effect.[147] Adding a nutritional supplement might improve outcome.

The severity of heart disease can influence the patients' possibility of fulfilling a comprehensive programme. Unfortunately for 30% of the patients the type of heart disease was undisclosed with no difference between groups. In the experimental group with undisclosed heart disease 26% of patients were in NYHA III versus only 19% in the usual care group and that difference might influence the adherence to the intervention.

The secondary outcomes showed no difference between groups, except for a potential difference in favour of the experimental intervention on HADS-D. Depression is more prevalent than anxiety in CABG patients.[148] The intervention showed no effect in self-reported physical and mental health, anxiety, pain, sleep or heart related quality of life, but there was a positive tendency in all outcomes except for SF-12 PCS. However, it is a secondary outcome and the result should be interpreted with caution. Furthermore, the HADS data were dichotomised which produces a risk of reducing the complexity.

Responsiveness is crucial for evaluating rehabilitation interventions relying on the instrument ability to detect a clinically important change over time.[149] Several methodological factors as size of population, time between measurements and characteristic of the population influence responsiveness.[150] In the pilot trial poor responsiveness on the SF-36 might have been an issue, as a four week recall might not be able to pick up differences between measurements.

In the pilot we used VO_2 as outcome measure, but it did not show responsiveness to the intervention. Therefore 6MWT was the primary outcome in the main trial because it responded to the interventions. [69] PROs have to demonstrate sensitivity to actual change[151] and even though there were no significant differences between groups, responsiveness to most of the PROs in the main trial was demonstrated.

It is necessary to consider whether the choice of primary and secondary outcomes has been adequate for the purpose of the trial. It is not clear why changes did not manifest. The most obvious explanation is lack of power and adherence to intervention.

The comprehensive test battery included separate instruments used in other rehabilitation trials.[129,130] However, the order of the instruments could influence the responders approach to the answer. Even though instruments are different, questions sometimes look a-like, which could have been irritating for some responders. Non-response to the questionnaires could reduce the effective sample size and introduce bias.

Adherence in the pilot and the randomized controlled trial was low to moderate, and is a challenge in cardiac rehabilitation. In the SheppHeartCABG trial an association was found between overweight and non-adherence to training after discharge as found by others[152,153] (Paper IV). Being overweight could be a reason for being physically in-active and combined with recent surgery explain the high level of non-adherence to the physical program. This study also identified an association between diabetes and non-adherence to training after discharge.

Strength and limitation

Bias in Patient reported outcomes

Self-reported data are, by their nature, subjective and non-respond bias might carry important information.[82] However, all questionnaires both in the pilot and main trial (RCT) were answered independently of the researchers and data management was handled centrally.

Bias in rehabilitation

Significant limitations should be considered when conducting a rehabilitation trial with a physical exercise intervention. Sequence generation and allocation concealment were conducted with low risk of bias. Insufficient blinding of personnel, patients and outcome assessors in rehabilitation trials with complex intervention might induce systematic bias. Even more challenging in rehabilitation trials is the process of blinding the outcome assessment. Effort can be made to obtain sufficient blinding such as information to the patients about the necessity of not to disclose their group allocation. In the pilot trial as in the SheppHeartCABG trial, patients were asked not to disclose their group allocation at the time of outcome assessment (physical testing and VO_2 measurement). However in some cases it was not possible to avoid identification of training regime and that might have introduced bias. The number of drop-outs was clearly assessed which minimized the risk of attrition bias. The risk of reporting bias was considered to be low as all intended outcomes have been reported, groups were balanced at baseline and intention-to-treat analysis was used.

There is a risk of performance bias for the usual care group. Participants in rehabilitation trials are highly selected with regards to comorbidity and personal competences. Further, being more physically active in the usual care group is well-known in exercise-based trials.[154]

VO_2 peak

Exercise testing used CPET with an ergo spirometer cycle and there might be variation from day-to-day and for time-of-day, but that applies to both the experimental and the usual care group. A protocol for minimising detection bias was developed to guide the personnel when encouraging patients in the cardiac rehabilitation group.[155] However, CPET showed not to be useful in the pilot

trial. The use of CPET entailed to encourage patients independent of the person who directed the test and for some patients the CPET can be too overwhelming early after surgery.

Missing data and multiple imputation

Missing data is part of data management in clinical research. Data can be missing for some (but not all) variables (item non-response) and for some (but not all) cases (unit response).[127] If data are missing on a variable for all cases, then the variable is latent or unobserved. Low adherence to intervention and uncompleted questionnaires entailed missing data as seen in numerous rehabilitation trials.

Missing data is a problem because conventional statistical methods and programmes presume that all variables are measured for all cases. Multiple imputation is a general strategy for handling missing data problems but is based on some assumption that missing values are missing at random, i.e. are predictable on the observed variables. This assumption seems reasonably in this trial since most baseline values are available for included patients. Multiple imputation is a general strategy for attacking missing data problems and does eliminate that missing data can threaten the validity of the trial.[126]

CONCLUSIONS

Based on the findings, the main conclusions are:

- Recruitment to phase one rehabilitation is possible (study I + III).
- Even early after surgery it is possible for CABG patients to participate safely in a comprehensive phase one rehabilitation programme.
- Comprehensive phase one rehabilitation seems to have a beneficial effect on depression (study II).
- Following phase one rehabilitation only one third of patients were adherent to the intervention (study II).
- The intervention had a positive effect for adherent participants (study III).
- Non-adherence is a challenge for phase one rehabilitation (study III + III).

Clinical implications

The evidence produced in this thesis emphasizes that relevant interventions can be introduced to prevent deconditioning and psychological problems that seem to affect patients following CABG. However, low adherence to rehabilitation is a concern. Attention should be directed to the transition between in and out of hospital rehabilitation. The time between discharge and the start of rehabilitation is often without contact to health professionals and that can have a negative influence on participation in rehabilitation programmes. Although the current evidence is inadequate, the results of the two studies undertaken to form this thesis suggest that comprehensive programs of phase one rehabilitation can in a modified form be adopted to be part of treatment care to improve physical and mental health for patients following CABG surgery. Furthermore, the results suggest that phase one rehabilitation should be arranged so that it associates with increased adherence before it can be adopted after CABG surgery.

Research implications

This adds evidence for phase one rehabilitation in patients undergoing CABG surgery. However, there are several questions that should be considered as research addressing the patient´s

perspective and return to everyday life since this is unclear. Focus on early rehabilitation post-CABG, research areas includes:

- Qualitative focus on how patients experience participation in rehabilitation post-CABG.
- Randomized clinical trials with a modified comprehensive phase one rehabilitation programme to assess a suitable “dose” of intervention and to consider barriers for adherence to the intervention components.

DANSK RESUMÉ

Åben hjertekirurgi er både en fysisk og psykisk belastning. Årligt gennemgår 1.700 patienter i Danmark og 500.000 i Europa koronar bypass kirurgi. Patienter med iskæmisk hjertesygdom, som gennemgår koronar bypass operation, har behov for støtte til at vende tilbage til hverdagen. Patienter oplever træthed, søvnbesvær og nedsat fysisk aktivitet. For nogle patienter udløser forløbet angst og depressive symptomer.

Rehabilitering i den tidlige fase efter operationen og i den første periode efter udskrivelse er sparsomt beskrevet, idet der kun er publiceret få studier. Den viden, der er nødvendig for at tilrettelægge efterbehandling og reducere risikoen for et negativt outcome hos patienter efter åben hjertekirurgi er således utilstrækkelig.

Formålet med dette projekt var: 1) at udvikle et fase 1 rehabiliteringsprogram (rehabilitering under indlæggelse) og frem til fase 2 (4-6 uger efter operation) (artikel I), 2) at opnå viden om muligheden for at gennemføre et fase 1 rehabiliteringsprogram, accept og kompliance for rehabiliteringsprogrammet (artikel I) og 3) at designe og undersøge effekten af et rehabiliteringsprogram rettet mod både fysiske og psykiske symptomer og problemer i forbindelse med CABG (artikel II+ III + IV). De vigtigste konklusioner er, at det er muligt at rekruttere patienter, der skal gennemgå koronar bypass operation, til at deltage i et tidligt rehabiliteringsprogram. Et pilotforsøg viste sig at være værdifuld i forhold til accept og tolerance overfor intervention. Nogle af de valgte effektmål viste sig ikke at være tilstrækkelig sensitive i forhold til interventionen. Der var moderat accept og kompliance til nogle af komponenterne i interventionerne.

Evaluering af pilot undersøgelsen betød en modificering af intervention og effektmål i det kliniske forsøg. I forsøget blev effekten af det tidlige rehabiliteringsprogram undersøgt. Der blev ikke vist noget effekt på fysik funktionsniveau af interventionen, men der var en gavnlig effekt på depressive symptomer. Der var en høj grad af non-adherence til interventionen, hvilket kan være årsag til den manglende viste effekt. Analyse af de patienter, som fulgte programmet, viste dog forbedret fysisk funktionsniveau efter 4 uger rehabilitering. Resultatet peger på, at patienter, der gennemfører tidlig rehabilitering, har en positiv effekt af tidlig rehabilitering og viser, at der er brug fokus på at øge graden af patienterne, der ikke gennemfører interventionen.

ENGLISH SUMMARY

Open heart surgery is both a physical and mental challenge. Annually 1,700 people in Denmark and 500,000 in Europe undergo coronary bypass surgery. Patients with ischemic heart disease undergoing coronary bypass surgery need support to return to everyday life as they experience fatigue, insomnia and reduced physical capacity and some suffer from anxiety or depression.

Rehabilitation during hospitalization and in the first period after discharge is only sparsely described. Thus the evidence necessary for planning recovery and reducing the risk of adverse outcomes in this patient population is inadequate.

The objective of this project was: 1) to develop a phase 1 rehabilitation program (rehabilitation during hospitalization) until phase 2 (4-6 weeks after surgery) (Paper I), 2) to evaluate feasibility, acceptance and compliance facing such a rehabilitation programme (Paper I), and 3) examine the effect of a rehabilitation programme aimed at both physical and psychological symptoms associated with CABG (Paper II + III + IV).

The main findings were that it was possible to recruit patients undergoing coronary bypass surgery to participate in an early rehabilitation programme. Implementation of the pilot test proved valuable in relation to acceptance and tolerance for the intervention, but some of the selected outcomes were not sufficiently sensitive to the intervention. There was moderate acceptance and compliance for the intervention and suboptimal adherence for some components of the intervention.

Evaluation of the pilot test involved modification of the intervention and outcomes in a randomized clinical trial that, however, did not show any effect on physical function, but there was a demonstrated beneficial effect on depressive symptoms. There was a low degree of adherence to the intervention, which could be the reason for the lack of efficacy since patients who followed the program showed improved physical function after four weeks.

This study shows that patients undergoing CABG who participate in phase one rehabilitation receive positive benefits. Further research is needed with focus on increasing the degree of adherence to early rehabilitation.

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APPENDIX

Paper I

Højskov IE, Moons P, Hansen NV, Greve H, Olsen DB, La Cour S, Gluud C, Winkel P, Lindschou L, Egerod I, Christensen AV, Berg SK. Early physical training and psycho-educational intervention for patients undergoing coronary artery bypass grafting. The SheppHeart randomized 2 x 2 factorial clinical pilot trial. *Eur J Cardiovasc Nurs. 2016 Oct; 15(6):425-37. doi: 10.1177/1474515115594524. Epub 2015 Jul 17.*

Paper II

Højskov IE, Moons P, Hansen NV, La Cour S, Olsen PS, Gluud C, Winkel P, Lindschou J, Thygesen LC, Egerod I, Berg SK. SheppHeartCABG trial-comprehensive early rehabilitation after coronary artery bypass grafting: a protocol for a randomised clinical trial. *BMJ Open; 2017: 7:e013038,2016-013038.*

Paper III

Højskov IE, Moons P., Egerod I, Olsen, PS, Thygesen LT, Hansen NV, La Cour S, Bech KH, Borregaard B, Gluud C, Winkel P, Lindschou J, Berg SK. Comprehensive phase one rehabilitation versus usual care in patients following coronary artery bypass grafting: Results from the SheppHeartCABG trial. *Submission prepared.*

Paper IV

Højskov IE, Thygesen LC, Moons P, Egerod I, Olsen PS, Berg SK. Non-adherence: a challenge in phase one rehabilitation after coronary artery bypass surgery: Secondary results from the SheppHeartCABG trial. *Submission prepared.*

Paper I

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Early physical training and psycho-educational intervention for patients undergoing coronary artery bypass grafting. The SheppHeart randomized 2 × 2 factorial clinical pilot trial

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Abstract

Background: Patients undergoing coronary artery bypass graft surgery often experience a range of problems and symptoms such as immobility, pain and insufficient sleep. Results from trials investigating testing in-hospital physical exercise or psychological intervention have been promising. However, no randomized clinical trials have tested a comprehensive rehabilitation programme consisting of both physical exercise and psycho-education in the early rehabilitation phase.

Aims: The aims of the present SheppHeart pilot randomized clinical trial were to evaluate the feasibility of patient recruitment, patient acceptance of the intervention, safety and tolerability of the intervention.

Methods and design: Sixty patients admitted for coronary artery bypass graft were randomized 1:1:1:1 to: 1) physical exercise plus usual care, or 2) psycho-educational intervention plus usual care, or 3) physical exercise and psycho-educational plus usual care, or 4) usual care alone during a four week period after surgery.

Results: The acceptability of trial participation was 67% during the three month recruitment period. In the physical exercise groups, patients complied with 59% of the total expected training sessions during hospitalization. Nine patients (30%) complied with >75% and nine patients (30%) complied with 50% of the planned exercise sessions. Eleven patients (42%) participated in ⩾75% of the four consultations and six patients (23%) participated in 50% of the psycho-educational programme.

Conclusion: Comprehensive phase one rehabilitation combining physical exercise and psycho-education in coronary artery bypass graft patients shows reasonably high inclusion, feasibility and safety.

Keywords

Phase one rehabilitation, coronary artery bypass grafting, physical exercise, psycho-education.

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Introduction

Coronary artery bypass grafting (CABG) is one of the most frequent types of open heart surgery in the western world. The average yearly CABG rate in Europe is 490 per million inhabitants. In Denmark, this figure is 740 per million.[1] Surgery outcomes are generally good, but recovery can be complicated. Patients undergoing CABG often experience a range of physical and psychological problems and symptoms[2] which are related to the procedure and the underlying heart disease. These problems include anxiety and depressive symptoms, immobility issues, complications such as neck and shoulder pains, respiratory complications, insufficient sleep and postoperative fatigue.[2]

Cardiac rehabilitation is an important aspect of recovery after heart surgery. Cardiac rehabilitation programmes are generally divided into three main phases: phase 1, which is inpatient cardiac rehabilitation; phase 2, which is early outpatient cardiac rehabilitation; and phase 3, which is long-term outpatient cardiac rehabilitation. It has been established that exercise training in cardiac rehabilitation after hospital discharge in phase 2 has a positive effect in patients after CABG[3] and for this reason phase 1 rehabilitation starting in hospital seems reasonable,[4] but evidence regarding phase 1 rehabilitation is sparse in CABG populations.

Exercise interventions such as respiratory physiotherapy or aerobic training in phase 1 rehabilitation after CABG have demonstrated improvements in patient outcomes measured by pulmonary complications and physical functional capacity.[5,6] Also psycho-educative interventions have a positive influence on anxiety and depression in the post-hospital recovery period.[7] A combined rehabilitation approach consisting of physical exercise and psycho-education has been found to improve various patient outcomes such as physical and psychological functioning.[8] Trials targeting psychological interventions in the early postoperative period after CABG have shown improvements in depression and anxiety symptoms; however, no randomized clinical trials with sufficient power have been published.[9] Mindfulness-based interventions have been found effective in reducing anxiety and other types of psychological distress in a wide range of contexts, including a few promising results in patients with cardiovascular disease. But more scientific knowledge about the implementation, acceptability and effects of mindfulness during a cardiovascular hospitalization is needed.

Accordingly, there is a need for trials to investigate the effectiveness of physical rehabilitation and psycho-education in the early postoperative phase after CABG. Before a large trial is mounted, uncertainties regarding patient recruitment and feasibility of the interventions should be addressed in a pilot trial. Therefore, the aims of the present pilot trial are: (i) to evaluate the feasibility of patient recruitment and interventions; (ii) to test the safety and tolerability of the interventions; and (iii) to provide outcome data that can be used for sample size calculations in a comprehensive randomized clinical trial.

Materials and methods

Trial design, population

The SheppHeartCABG (SheppHeart is the acronym for 'SHaping outcomes by Exercise training and Psycho-education in Phase 1 for Heart patients') pilot was designed as an investigator-initiated 2 × 2 factorial randomized clinical pilot trial with blinded outcome assessment. The setting was a thoracic clinic at a large university hospital in Denmark. Included were patients who were going to receive first time elective CABG, who gave informed consent. Excluded were patients younger than 18 years of age, diagnosed with a musculoskeletal or neurological disease precluding exercise testing and training, who were non-Danish speaking and who did not consent. The four intervention groups were: 1) physical exercise plus usual care; 2) psycho-educative intervention plus usual care; 3) physical exercise plus psycho-educative intervention plus usual care; and 4) usual care alone. Recruitment was undertaken at one site, with a 1:1:1:1 central randomization. The allocation sequence was computer-generated in varying block sizes of 8 and 12 and kept unknown to the investigators.

Interventions

Figure 1 details the intervention components and their timing for the four intervention groups.

Usual care. All patients followed the usual care procedure. The patients were admitted the day before surgery and discharged on postoperative day 6–8. The usual care programme included medical follow-up as well as standard treatment according to disease specific guidelines. The physiotherapist instructed patients at admission how to cough, protect their sternum, sit down and get up from a chair, get out of bed and take daily walks after surgery and answered patients' questions. There was no respiratory physiotherapy in usual care but, if needed, it could be prescribed by the physician. Group training for patients who had undergone heart surgery and were ready to discharge was offered in the gym three days a week. Furthermore, at hospital discharge the physiotherapist gave directions on how to manage daily activities with sternotomy, advice on being physically active daily and shoulder and neck exercises after hospital discharge.

The main features of preoperative care were: admission interview, preoperative screening (falls, nutrition),

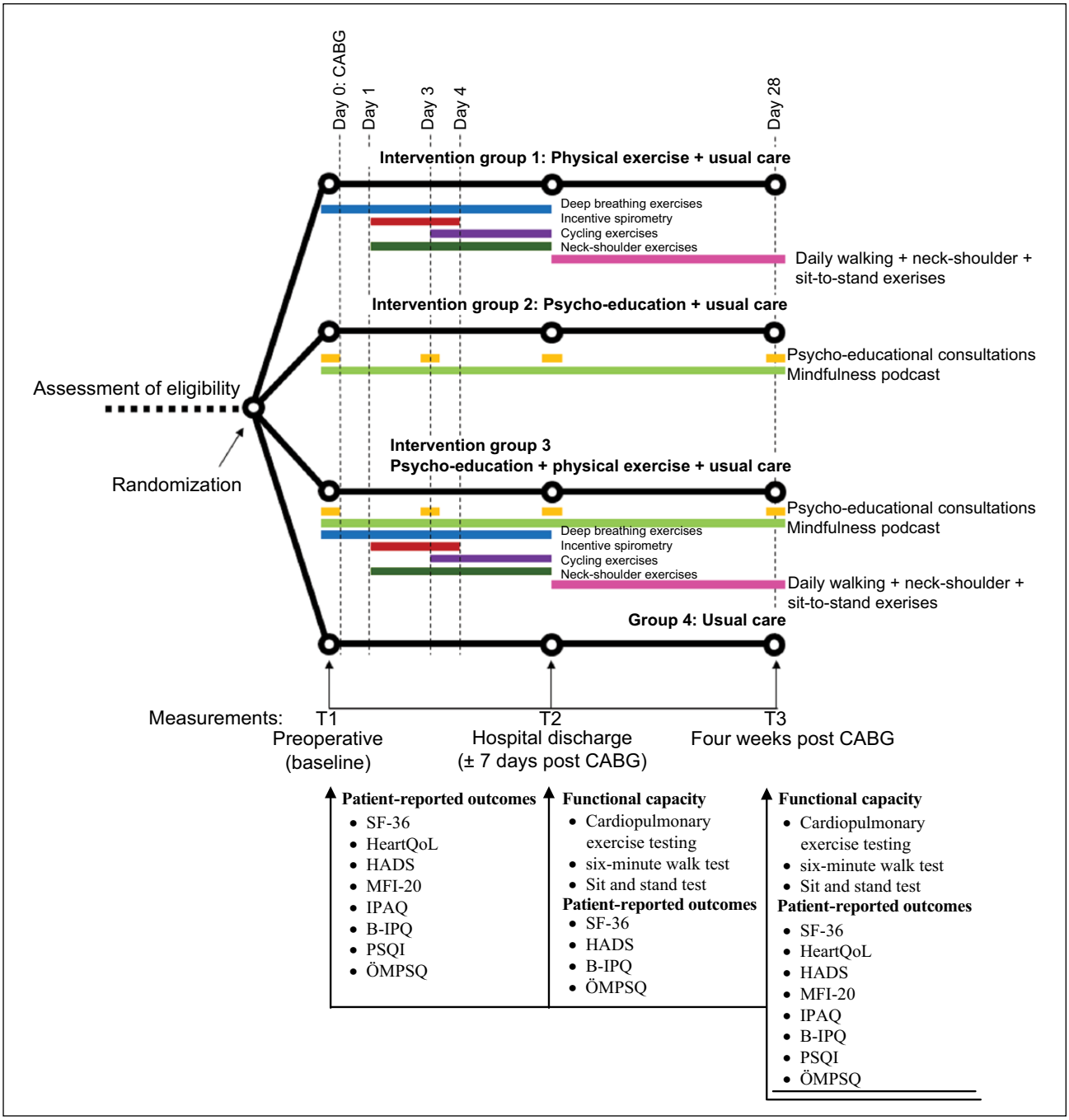

Figure 1. Trial design.
SF-36: Medical Outcome Study Short Form 36; HeartQoL: HeartQoL questionnaire; HADS: Hospital Anxiety and Depression Scale; MFI-20: Multidimensional Fatigue Inventory-20; IPAQ: International Physical Activity Questionnaire; B-IPQ: Brief Illness Perception Questionnaire; PSQI: Pittsburgh Sleep Quality Index; OMPSQ: Örebro Musculoskeletal Screening Questionnaire

introduction to postoperative pain and nausea medication, pain assessment and postoperative activities. Furthermore, patients were prepared for surgery by an introduction to fasting procedures, epilation and a disinfecting bath. The early postoperative care was focused on observation of vital signs. The remaining hospitalization included recovery and preparation for hospital discharge. Psychological issues were discussed with a nurse as needed. At hospital discharge, the patient was informed of long-term care issues, for example, care of scar tissue; identification, prevention and care of infection; pain management; and driving, swimming, and lifting restrictions. Usual care did not include systematic psycho-educational follow-up, mindfulness or systematic physical exercise.

Physical exercise component. The physical interventions were administered by physiotherapists and consisted of exercise programmes that started at admission and continued to four weeks after CABG. The physical intervention was divided into two parts: respiratory physiotherapy and aerobic training. Respiratory physiotherapy consisted of deep breathing exercises and incentive spirometry with positive expiratory pressure airway. Deep breathing exercises extended from admission to hospital discharge. Between 08:00 and 22:00, participants performed 7–10 deep breaths four times. Incentive spirometry was performed from postoperative day 1 to day 4 by deep breathing with positive expiratory pressure for 3–5 min twice daily. Related to the respiratory physiotherapy, patients performed neck and shoulder exercises consisting of rolling and lifting the shoulders, looking over one shoulder and then moving the head in a semicircle in front of the body to the opposite shoulder. Each exercise was repeated 10 times and done twice daily from postoperative day 1 until hospital discharge.

The aerobic training was on a stationary bicycle with moderate intensity. Patients were familiarized with the RPE (Ratings of Perceived Exertion) Borg scale®[10] prior to the first three sessions and were instructed to exercise at an RPE of 13–15 ('moderate' to 'somewhat strong') on a scale from 6 to 20. At the three first cycling sessions, heart rate and saturation were measured and patients used pulse watches during cycle training. Cycling interventions were 10-min sessions preceded by 5-min warm-ups and followed by 5 min of cool-down to achieve cardiovascular adjustment and reduce the risk of ischaemia and arrhythmia. The intensity at warm-up and cool-down was $\leqslant$10 RPE Borg and the cycling sessions were performed from postoperative day 3 until discharge twice daily, morning and afternoon.

After hospital discharge, until four weeks after CABG, physical exercise consisted of daily walking with increasing duration, and muscle and endurance exercises consisted of sit-to-stand and heel lifting exercises with increasing number of repetitions. The physiotherapist introduced the exercises, enabling patients to perform the exercise sessions independently at home (Figure 1).

Psycho-educational component. The psycho-educative intervention consisted of four individual consultations with a nurse: at admission, postoperative day 3, day of hospital discharge, and four weeks after surgery. The intervention had a theoretical basis of the patient-centred approach where the emphasis was on support and education. The method was based on a holistic patient view and focus on the handling of life and managing time post CABG. The topics dealt with initially covered life before admission and CABG surgery, present life, and visions of future short- and long-term life. Subsequently, events and opportunities were explored and discussed and imagined possibilities were pursued, inspired by three dimensions of RR Parse's *The Human Becoming School of Thought: A Perspective for Nurses and Other Health Professionals*.[11] According to this theory, three ways of changing health are possible: (i) creative imaging; that is, to see, hear and feel what a situation might be like if lived in a different way; (ii) affirming personal patterns and value priorities; and (iii) shedding light on paradoxes, that is, looking at the incongruence in a situation and changing existing views. The emphasis was on openness in the interviews and on the nurse's ability to be silently present while the patient talked, asking questions that encouraged reflection, letting the patient find answers and solutions, and to contribute with knowledge and provide advice and guidance when it was requested and relevant. An inspirational guide formed the basis for the consultations. The guide (Table 1) consisted of several elements and issues (medical, psychosocial and educational) as inspiration.

Finally, elements of mindfulness were integrated into the psycho-educational component, as support for stress reduction, capacity for intimacy, and self-care through meditation-based exercises. The delivery of the elements of mindfulness was adapted to fit into the clinical situation where standardized group-based courses of mindfulness exercises would not have been feasible. Instead, nurses were trained in introducing mindfulness exercises, and in mindfulness supported communication skills. During the first session with a patient, the nurse would give a brief introduction to mindfulness followed by an exercise. Depending on the patient's needs, this was briefly repeated at the following sessions. In addition, the mindfulness intervention included three guided meditation sessions on an mp3 player (recorded with the voice of the patient's own consulting nurse). Participants were encouraged to incorporate the mindfulness exercises into their daily lives during hospitalization and after hospital discharge.

Outcomes

All participants were assessed three times: at admission (T1), at hospital discharge (T2) and four weeks post CABG (T3) (Figure 1). The following explorative outcomes were used. Physical capacity was measured by VO_2 using a standardized protocol in accordance with guidelines[12] at hospital discharge and four weeks post CABG. The cardiopulmonary testing protocol consisted of a 4-min rest period followed by an increase every minute until exhaustion. Blood pressure and electrocardiogram were continuously monitored. VO_2 was estimated from maximal wattage achieved. The tests follow current standards for cardiopulmonary exercise testing.[13]

Functional capacity was also measured by a six-minute walk test, leg strength and endurance measured by a sit-to-stand test performed at hospital discharge and four weeks post surgery. For the six-minute walk test, the participants walked up and down a 30 m hallway for 6 min according to the guidelines for the test.[14] For the sit-to-stand test, the participants repeatedly sat in a chair and got up to a full

Table 1. Inspiration guide for nursing consultation.

	C_1	C_2	C_3	C_4
Discuss the events leading up to the CABG surgery and experiences before admission	✓			
Address present thoughts and questions	✓	✓	✓	✓
How have the heart disease and the CABG pending affected daily living? Are specific activities avoided?	✓			
How has the CABG affected daily life? Are specific activities avoided?				✓
Status of mobilization and activities				✓
Discuss pain, sleep, fatigue and mobility		✓	✓	✓
Discuss family; how do they tackle changing patterns in the family?	✓		✓	✓
Impact of CABG surgery on working conditions				✓
Education about preparation and precaution following CABG surgery	✓	✓	✓	✓

C_1: consultation at admission; C2: consultation postoperative day 3; C_3: consultation at hospital discharge; C_4: consultation four weeks post coronary artery bypass grafting (CABG)

standing position as many times as possible in 30 s to test leg strength and endurance. The test was performed in accordance with guidelines.[15] Physical tests were not done at baseline due to the risk of complications pre-CABG.

Psychological and physical health was measured by the Medical Outcome Study Short Form 36 (SF-36) at admission, at discharge and four weeks post surgery.[16] Furthermore, a set of patient self-reported outcomes were assessed: anxiety and depression using the Hospital Anxiety and Depression Scale,[17] health related quality of life using The HeartQoL questionnaire,[18] fatigue was measured using the Multidimensional Fatigue Inventory[19] and illness-related knowledge was measured using the Brief Illness Perception Questionnaire.[20] Physical activity was measured using the International Physical Activity Questionnaire[21] and, finally, sleep and pain were measured using The Pittsburgh Sleep Quality Index and The Örebro Musculoskeletal Screening Questionnaire.[22,23] Detailed information about the instruments used to assess the clinical impact of the rehabilitation programme and timing of assessments is shown in Table 2.

Sample size

As this was a pilot trial, we arbitrarily decided to include 60 participants, corresponding to 15 participants in each of the four intervention groups.

Blinding

Because of the conditions for rehabilitation, it was not possible to blind the staff and patients. The statistical analysis of outcomes and conclusions was blinded.

Ethical considerations

Patients gave their written informed consent after receiving verbal and written information about the trial. Data were handled confidentially and patients were assured anonymity. The pilot trial followed the recommendations of the updated Declaration of Helsinki[24] and was approved by the Regional Ethics Committee in the Capital Region of Denmark (H-3-2013-112) and the Danish Data Protection Agency (2007-58-0015). The pilot trial was registered at ClinicalTrials.gov (NCT01941355).

Data analysis

Outcomes. The estimates of the mean and the standard deviations of patient-reported outcomes were calculated (Table 3).

Feasibility. The feasibility of the SheppHeartCABG pilot was evaluated in terms of acceptability, adherence and attrition.[25] Acceptability was measured by the percentage of eligible patients who agreed to participate in the trial. For each individual component in the programme, adherence to the intervention was measured by calculating the percentage of recommended exercise sessions performed by the patient versus the number of sessions/number of sessions prescribed. Adherence calculations include only the prescribed sessions. Attrition was calculated by the percentage of patients who did not complete the trial.

Safety and tolerability. Patients were taken off the intervention programme in cases of high or low blood pressure (diastolic <50 or >120 mmHg and systolic <90 or >200 mmHg), fast or slow heart rate <50 or >100 beats/min; temperature >38°C, or finger saturation <90%. In terms of safety and tolerability, we assessed the number of days the patient was off the programme.

Results

Demographic data

The demographic data and preoperative clinical characteristics of the four groups are presented in Table 4.

Table 2. Overview of variables and measurements in the quantitative study.

Variable	Measurement	Time	Items	Validity	Reliability	Responsiveness	Interpretation
Psychological and physical health	The Medical Outcome Study Short Form 36 (SF-36)	T1 T2 T3	36	Construct and content validity confirmed[16]	The minimum standard of α= 0.70 recommended for measures used in group comparisons in more than 25 studies and most have exceeded α=0.80 (41) Reliability estimates for physical and mental summary scores usually exceed α=0.90 (42)	NR	Scores range 0–10 Higher scores indicate better perceived health
Anxiety and depression	The Hospital Anxiety and Depression Scale (HADS)	T1 T2 T3	14	Content validity confirmed[17]	Internal consistency confirmed Adolescents' self-report scores: HADS-A α=0.83; HADS-D α=0.82	Responsiveness confirmed	Scores of 7 for either subscale are regarded as normal 8–10 suggests the presence of a mood disorder 11 and above suggests probable presence of a mood disorder
Health-related quality of life in cardiac patients	The HeartQoL questionnaire (HeartQoL)	T1 T3	14	Content validity confirmed[18]	Proven as a reliable instrument with α= 0.80-0.91 for the global score (40)	Responsiveness confirmed (36)	NR
Fatigue	The Measurement of Fatigue Instrument (MFI)	T1 T3	20	Construct validity confirmed[19]	Internal consistency confirmed: general fatigue α=0.82 physical fatigue α=0.81	Responsiveness confirmed (37)	Scores range 4–20 Higher scores indicate a higher degree of fatigue
Cognitive and emotional representations of illness	The Brief Illness Perception Questionnaire (B-IPQ)	T1 T2 T3	8	Content validity confirmed[20]	Good test–retest reliability (38)	Responsiveness confirmed (38)	Scores range 0–10 A higher score reflects a more threatening view of the illness
Health-related physical activity	The International Physical Activity Questionnaire (IPAQ)	T1 T3	4	Content validity confirmed[21]	NR	NR	Three levels of physical activity proposed to classify populations: low, moderate and high
Sleep	The Pittsburgh Sleep Quality Index (PSQI)	T1 T3	19	Content validity confirmed[22]	α= 0.83 obtained indicates a high degree of internal homogeneity (40)	NR	PSQII total: minimum score = 0 (better); maximum score = 21 (worse) Interpretation: total < 5 associated with good sleep quality; total > 5 associated with poor sleep quality
Musculoskeletal pain	The Örebro Musculoskeletal Screening Questionnaire (OMPSQ)	T1 T2 T3	25	Construct validity confirmed[23]	High reliability (41)	NR	Scores from 1 to 200. Higher scores are associated with increased risk of long-term disability

T1: baseline; T2: hospital discharge; T3: four weeks post surgery; NR: not reported

Table 3. Patient-reported outcomes.

Quantity	Physical exercise			Psycho-education			Psycho-education/physical exercise			Usual care		
	N (%)	Mean	SD	*N* (%)	Mean	SD	*N* (%)	Mean	SD	*N* (%)	Mean	SD
MCS[a]												
Baseline	11 (73)	48.01	14.86	11 (73)	51.40	10.58	9 (60)	50.95	11.26	8 (53)	55.17	7.53
Discharge	6 (40)	53.74	13.08	6 (40)	43.74	12.61	11 (73)	41.15	12.74	11 (73)	45.48	10.80
Four weeks	7 (47)	53.24	10.04	6 (40)	49.94	15.22	9 (60)	51.82	10.04	10 (66)	43.61	12.99
PCS[b]												
Baseline	11 (73)	39.09	8.87	11 (73)	46.00	8.47	9 (60)	41.28	8.73	8 (53)	45.62	8.78
Discharge	6 (40)	37.22	9.36	6 (40)	41.73	4.10	11 (73)	34.90	8.23	11 (73)	35.07	8.20
Four weeks	7 (47)	42.72	5.96	6 (40)	38.31	6.80	9 (60)	34.15	6.43	10 (67)	36.85	3.25
HADS-A[c]												
Baseline	11 (73)	4.91	4.11	11 (73)	4.91	3.14	12 (80)	5.25	3.31	10 (67)	4.30	2.54
Discharge	7 (47)	7.00	0.58	7 (47)	7.43	1.72	11 (73)	6.45	2.55	11 (73)	6.82	1.48
Four weeks	7 (47)	2.29	0.49	6 (40)	5.67	3.01	10 (67)	4.70	3.71	12 (80)	3.92	3.23
HADS-D[d]												
Baseline	11 (73)	6.18	2.93	11 (73)	6.18	2.75	12 (80)	6.92	2.97	10 (67)	5.90	2.69
Discharge	7 (11)	5.86	1.57	7 (47)	6.57	2.44	11 (73)	8.72	3.04	11 (73)	7.54	3.42
Four weeks	7 (11)	5.86	1.77	6 (40)	6.50	2.17	10 (67)	8.20	3.71	12 (80)	3.92	3.23
PSQI total[e]												
Baseline	10 (67)	6.70	4.23	8 (53)	8.00	3.42	9 (60)	4.78	2.39	10 (67)	6.70	3.56
Four weeks	5 (33)	7.20	3.84	4 (27)	11.25	4.92	7 (47)	9.29	5.41	10 (67)	7.10	4.31
MET total[f]												
Baseline	10 (67)	5448.5	13979.25	11 (73)	3096.81	3283.37	11 (73)	1729.63	1775.76	10 (67)	5160.70	7641.28
Four weeks	6 (40)	5145.0	2016.66	5 (33)	5608.80	6499.59	9 (60)	3799.00	3655.47	11 (73)	4786.36	3967.53
HeartQoL physical[g]												
Baseline	13 (87)	1.43	1.00	11 (73)	1.81	0.74	12 (80)	1.42	0.80	11 (73)	1.55	0.73
Four weeks	7 (47)	2.03	0.73	6 (40)	1.46	0.77	10 (67)	1.46	0.77	13 (87)	1.27	0.68
HeartQoL emotional[h]												
Baseline	13 (87)	1.81	1.13	11 (73)	2.00	0.81	12 (80)	2.23	0.85	13 (87)	1.89	0.90
Four weeks	7 (47)	2.71	0.47	6 (40)	1.58	1.23	10 (67)	2.00	0.96	13 (87)	1.92	1.00
HeartQoL global[i]												
Baseline	13 (87)	1.34	0.91	11 (73)	1.86	0.67	80 (12)	1.60	0.81	13 (87)	1.64	0.71
Four weeks	7 (47)	1.95	0.60	6 (40)	1.50	0.97	10 (67)	1.62	0.52	13 (87)	1.41	0.74
OMPSQ[j]												
Baseline	10 (67)	54.00	28.95	7 (47)	46.29	25.51	11 (73)	49.55	27.62	5 (33)	41.20	23.48
Discharge	7 (47)	57.57	24.40	7 (47)	64.00	15.04	11 (73)	79.00	25.48	8 (53)	76.75	30.87

(Continued)

Table 3. (Continued)

Quantity	Physical exercise			Psycho-education			Psycho-education/physical exercise			Usual care		
	N (%)	Mean	SD	*N* (%)	Mean	SD	*N* (%)	Mean	SD	*N* (%)	Mean	SD
Four weeks	5 (33)	56.60	12.87	5 (33)	62.00	34.91	8 (53)	66.88	23.24	6 (40)	56.67	37.95
General fatigue[k]												
Baseline	11 (73)	11.73	4.98	11 (73)	10.55	5.92	10 (73)	13.36	4.23	10 (67)	10.60	4.97
Four weeks	7 (47)	10.29	5.47	5 (33)	12.20	4.32	10 (67)	11.30	4.11	12 (80)	12.25	4.00
Max watt[l]												
Discharge	5 (33)	75.00	25.00	2 (13)	75.00	0.00	3 (20)	53.33	37.53	3 (20)	83.33	14.43
Four weeks	6 (40)	101.67	58.02	4 (27)	106.25	23.94	7 (47)	117.86	35.36	9 (60)	108.33	35.36
Peak VO_2[m]												
Discharge	5 (33)	16.36	3.19	2 (13)	19.45	2.19	3 (20)	14.97	5.82	3 (20)	16.83	0.74
Four weeks	5(33)	22.32	4.53	4 (27)	22.35	1.65	7 (47)	23.40	4.14	9 (60)	21.99	5.24
6MWT[n]												
Discharge	5 (33)	264.20	103.70	6 (40)	410.67	29.81	5 (33)	433.00	93.15	5 (33)	331.00	147.49
Four weeks	7 (47)	459.71	94.49	6 (40)	504.00	39.01	9 (60)	548.11	104.66	9 (60)	450.89	74.53
Sit-to-stand[o]												
Discharge	6 (40)	10.33	3.14	6 (40)	11.50	1.95	6 (40)	11.83	4.07	6 (40)	8.83	1.72
Four weeks	7 (47)	15.00	3.41	6 (40)	14.00	1.67	9 (60)	15.33	6.30	10 (67)	11.70	2.86

[a]Mental health measured by the Medical Outcome Study 36-item Short Form health survey.
[b]Physical health measured by the Medical Outcome Study 36-item Short Form health survey.
[c]Anxiety measured by the Hospital Anxiety and Depression Scale.
[d]Depression measured by the Hospital Anxiety and Depression Scale – Depression.
[e]Sleep measured by the Pittsburgh Sleep Quality Index.
[f]Physical activity measured by the International Physical Activity Questionnaire.
[g]Physical health-related quality of life measured by the HeartQoL questionnaire.
[h]Emotional health-related quality of life measured by the HeartQoL questionnaire.
[i]Health-related quality of life the HeartQoL questionnaire.
[j]Pain measured by the Örebro Musculoskeletal Screening Questionnaire.
[k]Fatigue measured by the Measurement of Fatigue Instrument.
[l]Maximal watt performed at cardiopulmonary test.
[m]Peak VO_2 estimated from maximal wattage achieved in cardiopulmonary test.
[n]Distance in metres achieved in six minute walking test (6MWT).
[o]Number of times the participant stood up and sat down in a chair measured by the sit-to-stand test.

Table 4. Demographic and clinical characteristics of the sample by group.

	Physical exercise group (*n*=15)	Psycho-educational group (*n*=15)	Combined psycho-educational/ physical exercise group (*n*=15)	Usual care group (*n*=15)
Age, years, mean (±SD)	61.3 (12.3)	68.3 (11.9)	62.3 (10.2)	67.2 (8.0)
Sex, *n* (%)				
Male	11 (73)	12 (80)	13 (87)	11 (73)
Female	4 (27)	3 (20)	2 (13)	4 (27)
Marital status, *n* (%)				
Single/divorced/widowed	4 (27)	6 (33)	3 (20)	8 (53)
Married/domestic partner	11 (73)	9 (60)	12 (80)	7 (47)
Occupational status, *n* (%)				
Active employment, *n* (%)	8 (53)	3 (20)	6 (40)	6 (40)
Pensioner, *n* (%)	4 (27)	11 (73)	5 (33)	5 (33)
Early retirement, *n* (%)	2 (13)	1 (7)	2 (13)	2 (13)
Person on job release scheme, *n* (%)	1 (7)			1 (7)
Undisclosed, *n* (%)				1 (7)
Educational level, *n* (%)				
Vocational education, *n* (%)	6 (33)	8 (53)	7 (47)	7 (47)
College, *n* (%)	1 (7)	2 (13)	2 (13)	
University, *n* (%)	3 (20)	1(7)	3 (20)	5 (33)
None, *n* (%)	3 (20)			
Other, *n* (%)				
Undisclosed, *n* (%)	2 (13)	4 (27)	3 (20)	6 (40)
Body mass index, *n* (%)				
< 18.5 (kg/m^2)	0	0	0	0
> 25 < 30 (kg/m^2), *n* (%)	6 (40)	5 (33)	3 (20)	7 (47)
> 30 (kg/m^2), *n* (%)	3 (20)	5 (33)	5 (33)	4 (27)
Type of heart disease, *n*				
Ischaemic heart disease	15	15	15	15
Heart failure	0	0	0	0
NYHA class I, *n (%)*				
NYHA class II, *n (%)*	5 (33)	7 (47)	4 (27)	5 (33)
NYHA class III, *n (%)*	5 (33)	7 (47)	11 (73)	9 (60)
NYHA class IV, *n (%)*	5 (33)	1 (7)		1 (7)
LVEF mean (±SD)	48.0 (12.8)	50.0 (9.4)	53.2 (11.6)	52.1 (12.4)
Current smoker, *n* (%)	3 (20)	2(13)	1 (7)	1 (1)
Previous smoker, *n* (%)	6 (40)	8 (53)	9 (60)	7 (47)
Prescribed medication, *n* (%)				
Blood pressure-lowering drugs	3 (20)	5 (33)	4 (27)	3 (20)
ACE inhibitor	3 (20)	1 (7)	2 (13)	2 (13)
Beta-blocker	13 (87)	9 (60)	12 (80)	10 (67)
Calcium antagonist	3 (20)	3 (20)	4 (27)	1 (1)
Antiplatelet drugs	15 (100)	13 (87)	14 (93)	14 (93)
Diuretic	2 (13)	4 (27)	4 (27)	4 (27)
Anti-diabetic	3 (20)	2 (13)	5 (33)	3 (20)
Statin	14 (93)	12 (80)	13 (87)	14 (93)
Antidepressant	1 (7)	2 (13)	1 (7)	1 (7)
Pain reliever			1 (7)	3 (20)
Sleeping medicine	None	None	None	None

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme

Feasibility

Acceptance. During the inclusion period September–December 2013, 104 patients were admitted for elective CABG surgery and 90 were found eligible to participate (87%). Sixty patients provided informed consent to participate in the trial, corresponding to 58% of all patients admitted and 67% of all eligible patients (Figure 2). Reasons for

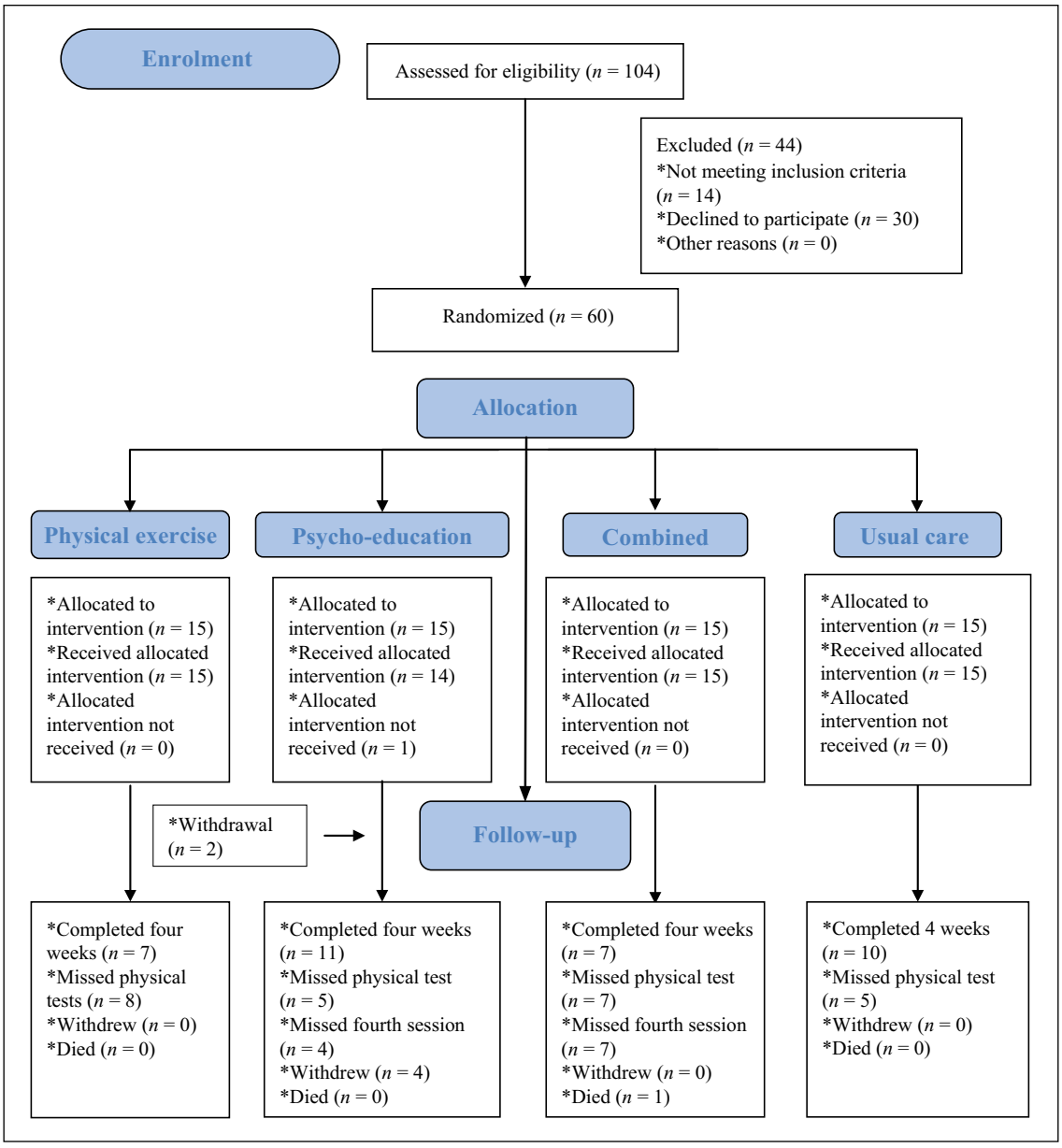

Figure 2. CONSORT flow chart – SheppHeartCABG pilot.

refusal to participate included a lack of interest in participation (40%; 12/30), fatigue (47%; 14/30) and apprehension regarding surgery (7%; 2/30).

A flowchart indicating the progress of patients through the pilot trial is shown in Figure 2 as a CONSORT flow chart (CONsolidated Standards Of Reporting Trials).[26] Four patients, all of whom were assigned to the psycho-educational group, dropped out of the pilot trial: one during the first session; one before and two after hospital discharge. The reasons were a refusal to participate further due to the distance to the hospital; two participants did not want to give an explanation, and one patient died.

Adherence. In the two intervention groups that included physical exercise, the patients carried out 59% (924/1565) of the total expected training sessions during hospitalization. One patient (3%) performed all training sessions (52/52). Nine patients (30%) carried out >75% (348/447) and 18 patients (63%) carried out ⩾ 50% of the planned sessions (363/642).

Regarding the psycho-educational intervention, 11 patients (42%) participated in ⩾75% of the four consultations and 17 patients (65%) in >50% of the four consultations. Twelve patients (46%) indicated that they had used mindfulness during the psycho-educational programme.

Attrition. Eight patients in the physical exercise group, four patients in the psycho-educational group, seven patients in the combined group, and five patients in the usual care group

failed to complete the physical tests at discharge because of sudden discharge or transfer to the cardiology department at their regional hospital. In the psycho-educational groups, four patients in the single group and seven in the combined group failed to complete the fourth session.

Safety and tolerability

One patient randomized to the combined group died three weeks post CABG. No other adverse reactions or events were observed as a result of the testing, consultations or exercise programme.

Outcomes

Table 3 shows the mean values and standard deviations over time of each of the patient-reported outcomes.

Discussion

This pilot trial provides data concerning the feasibility of patient recruitment and intervention and the safety and tolerability of a phase 1 rehabilitation intervention in patients undergoing CABG. The intervention was a comprehensive rehabilitation programme from admission to four weeks post surgery that involved physical exercise with moderate to high intensity and a psycho-educational programme, including mindfulness. A comprehensive rehabilitation programme consisting of both a physical and a psycho-educative component is not routine after cardiac surgery.

We were uncertain as to whether it would be possible to recruit a sufficient number of participants for a phase 1 rehabilitation trial following CABG. The present pilot trial showed that 67% of all eligible patients admitted for CABG within the time frame could be included. However, inclusion of participants is not enough, adherence to the intervention components is also critical in order to achieve results. We found that only six per 10 of the expected exercise sessions were performed and only half of the patients used mindfulness. Obviously, this is suboptimal adherence to the intervention. In a future SheppHeart trial, we need to put more emphasis on 'why and how to do exercises' and motivate patients to perform the interventional components as prescribed. The most challenging task is to improve adherence to both programmes. Up until now no trials have investigated improvement to adherence in cardiac rehabilitation in the in-hospital phase. However, trials to increase adherence to cardiac rehabilitation phase 2 have shown significant improvements in adherence to cardiac rehabilitation, for example, the use of a simple diary had a positive influence on adherence to physical exercise.[27] Therefore in a future confirmatory SheppHeart trial, nurses and physiotherapist in daily contact with the participant have to be motivating and supporting regarding exercise and consultations.

Based on the experiences from this pilot trial, we suggest modifying certain aspects of the intervention. The first three sessions in the psycho-educational programme took place during hospitalization and the last one was held four weeks after surgery. We found that the last consultation should be scheduled before the last assessment four weeks after CABG and might be performed as a telephone call, which is common in cardiac rehabilitation.[8] During the pilot trial, we encountered some organizational challenges. First, it was difficult to integrate the consultations (T1) in the already busy schedule for patients on the day of admission. However, the greatest number of organizational issues arose at T2, the day of hospital discharge. Indeed, quite often hospital discharge was abrupt (to give way to new patients), and occurred when no intervention or testing personnel were available. Since hasty hospital discharge is common, we need a plan to accommodate this situation. Furthermore, we will give more attention to questionnaire response rates by closely monitoring patients' follow-up.

One of the aims of this pilot trial was to evaluate the tolerability of interventions for patients. Normally, physical tests are not performed in the days immediately following cardiac surgery. Hence, evidence is lacking regarding the safety of cardiopulmonary testing during the first week after CABG surgery. This pilot trial showed that the physical interventions and tests appear to be safe and tolerable for the participants. However, it would be useful to include the patient perspective of safety and tolerability by conducting in-depth interviews with patients. This type of information would have been applicable in the evaluation of this pilot trial. There was no data monitoring and safety committee established for the pilot trial, but such a committee should be established for a larger trial.

These pilot data provide a good basis for exploring the potential for improvement for the different outcomes. In addition, it may allow us to estimate the required sample size for a larger trial, relying on mean values and standard deviations of the primary outcome obtained from the present pilot trial. Furthermore, similar data from other outcomes may be used for calculating the power for these outcomes in a future trial and deciding which are going to become secondary outcomes (e.g. outcomes with $\geqslant$80% power) and which should become exploratory outcomes (e.g. outcomes with <80% power).

Some outcomes did not show sufficient sensitivity towards changes over time in this pilot trial. This was the case for some of the questionnaires as well as physical tests and might be due to a poor interventional effect or random variation or, alternatively, due to poor sensitivity of the outcome measures; for example, SF-36 with a four week recall obviously did not pick up differences between T1 and T2, as could have been anticipated. Furthermore, the cardiopulmonary test did not seem to be useful in testing a short to moderate intensity exercise intervention. A

main reason for CABG patients to participate in cardiac rehabilitation was to improve their functional capacity in daily life. Therefore, outcomes have to be related to the improvement of daily life and thus measures such as walking capacity, six minute walk test and muscle strength in legs (measured by the sit-to-stand test) reduced pain in neck and shoulder, and provided better sleep.

Conclusions

The SheppHeartCABG pilot trial suggests potentials for further investigation. The SheppHeartCABG pilot trial demonstrates feasibility, with a sufficient inclusion rate but with low adherence. The pilot trial highlighted some organizational, interventional, and administrative challenges as well as challenges with regard to which outcomes to use in future trials. These are the challenges which will have to be dealt with in a large scale trial, which is required to determine the effects of comprehensive phase 1 rehabilitation after CABG surgery.

Implications for practice

- The SheppHeartCABG pilot trial demonstrates feasibility, with a sufficient inclusion rate but with low adherence.
- The pilot trial highlighted some organizational, interventional and administrative challenges as well as challenges with regard to which outcomes to use in future trials.
- These are the challenges which will have to be dealt with in a large scale trial, which is required to determine the effects of comprehensive phase 1 rehabilitation after coronary artery bypass grafting surgery.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Paper II

BMJ Open

SheppHeartCABG trial—comprehensive early rehabilitation after coronary artery bypass grafting: a protocol for a randomised clinical trial

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ABSTRACT

Introduction: Patients undergoing coronary artery bypass graft surgery often experience a range of symptoms. Studies indicate that non-pharmacological interventions such as exercise training and psychoeducation have a positive physiological and psychological effect in early outpatient rehabilitation. The SheppHeartCABG trial will investigate the effect of early comprehensive rehabilitation in early phase rehabilitation versus usual care. The aim of this paper is to present the protocol for the SheppHeartCABG trial.

Methods/analysis: SheppHeartCABG is an investigator-initiated randomised clinical superiority trial with blinded outcome assessment, employing 1:1 central randomisation to rehabilitation plus usual care versus usual care alone. On the basis of a sample size calculation, 326 patients undergoing coronary artery bypass grafting will be included from two clinical sites. All patients receive usual care and patients allocated to the experimental intervention follow 4 weeks rehabilitation consisting of an exercise programme, psycho-educative consultations and a compact mindfulness programme. The primary outcome is physical function measured by the 6-min walk test. The secondary outcomes are mental health and physical activity measured by the Medical Outcome Study Short Form (SF-12), anxiety and depression measured by the Hospital Anxiety and Depression Scale questionnaire, physical, emotional and global scores by the HeartQoL questionnaire, sleep measured by the Pittsburgh Sleep Quality Index, pain measured by the Örebro Musculoskeletal Screening Questionnaire and muscle endurance measured by the sit-to-stand test. A number of explorative analyses will also be conducted.

Ethics and dissemination: SheppHeartCABG is approved by the regional ethics committee (no. H-4-2014-109) and the Danish Data Protection Agency (no. 30-1309) and is performed in accordance with good clinical practice and the Declaration of Helsinki in its latest form. Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. Furthermore, results will be presented at national and international conferences relevant to the subject fields.

Trial registration number: NCT02290262; pre-results.

Strengths and limitations of this study

- This study has been designed to meet the criteria for high quality in a non-pharmacological randomised clinical trial with computer-generated randomisation, multicentre participation and blinded outcome assessment and analysis.
- We are aware of the subjective nature of the self-reported secondary outcomes. Accordingly, we will interpret data conservatively.
- This trial is the first larger trial testing the effects of a phase I comprehensive cardiac rehabilitation programme after coronary artery bypass graft surgery.

BACKGROUND

Following coronary artery bypass grafting (CABG), patients often experience a range of symptoms caused by the surgical procedure and the ischaemic heart disease and the subsequently return to everyday life is often prolonged.[1] Symptoms of anxiety and depression peak before heart surgery and again 2 weeks after and may persist up to 4 months after discharge.[2] Pain, fatigue and sleep disorders are common symptoms after CABG and may be partly due to the lack of postoperative physical activity.[1 3 4] To tackle these issues, cardiac rehabilitation is recommended.[5]

Cardiac rehabilitation programmes are generally described according to three main phases: inpatient (phase I), early outpatient (phase II) and long-term outpatient cardiac rehabilitation (phase III).[6] Rehabilitation phase I normally ends 4 weeks following CABG and ought to be followed by rehabilitation phase II.[6] Enrolment in cardiac rehabilitation after coronary revascularisation positively impacts the psychological status of

patients and reduces cardiovascular mortality.[7] More specifically, physical exercise in rehabilitation phase II has positive effects on quality of life, exercise capacity, coronary blood vessels, the myocardium, the endothelial function and coagulation.[8–13] There are no randomised clinical trials assessing cardiac rehabilitation programmes in phase I.

Non-pharmacological treatment potential

Open heart surgery is a severe physical and mental strain. Indeed, cardiopulmonary bypass has a temporary negative effect on physical functions.[8 9] However, studies show that psychosocial factors are also vital for patients' prognosis in the short and longer term.[10] The interventions in phase I rehabilitation after CABG have either investigated the physical or the psychological perspective. The effect of respiratory exercise preoperatively and in the early postoperative period after CABG surgery has been examined using different techniques.[11–14] Trials generally indicate a clinically significant effect of respiratory physiotherapy, but these trials are small and include selected trial populations. Cardiopulmonary bypass has a temporary negative effect on the physical function level.[8 9] Examination of anxiety and depression in the postoperative period is needed due to the limited power and the use of non-validated instruments in the studies.[2] Furthermore, it has been shown that a combination of a psycho-educative intervention plus physical exercise has a positive effect on physical and mental self-related health.[15 16] Mindfulness is a form of psychosocial intervention that offers stress reduction, calm accepting awareness and support of self-care through meditation-based exercises. Until now, trials of mindfulness have not been conducted in the context of CABG patients but several trials with cardiovascular patients in other contexts have shown reduction of perceived stress, pain, depression, sleeping problems and anxiety.[17–20]

International guidelines recommend early mobilisation during hospitalisation, outpatient exercise training and patient education after CABG.[21] Since the symptoms related to CABG include a physical and a psychological component, it is plausible that patients with CABG benefit from a comprehensive rehabilitation intervention.[22] The SheppHeartCABG pilot trial was initiated in 2013 to test the safety and tolerability of a comprehensive intervention and to provide outcome data for designing a larger trial.[23] The pilot trial included 60 patients and indicated the feasibility of physical and psycho-educational cardiac rehabilitation in addition to sufficient inclusion rate and high compliance with most elements.[23] The results were used to modify the rehabilitation programme and optimise the protocol and targeted outcomes.

In summary, there is evidence that physical exercise benefits heart patients' rehabilitation associated with open heart surgery. This part normally begins 2–4 weeks after discharge, and the effects of early action are not known. In addition, the positive effect of rehabilitation may be stronger when physical exercise is combined with a psychological intervention component.

TRIAL OBJECTIVES

The objective of the SheppHeartCABG trial is to investigate the benefits and harms of a phase I comprehensive cardiac rehabilitation programme consisting of an exercise training component and a psycho-educative component, in addition to usual treatment in patients with CABG. The primary hypothesis is that a comprehensive rehabilitation programme improves the functional level measured by a 6-min walk test (6MWT) by 30 m in the experimental group compared with the control group. The estimated increase in the primary outcome is a conservatively expected estimate based on the SheppHeartCABG pilot trial, where we found a mean of 548 m in the intervention group receiving physical training and psycho-education versus a mean of 451 m in the control group measured by 6MWT.[23] The secondary hypotheses are that a comprehensive rehabilitation programme will improve: quality of life, sleep disorder, pain, anxiety, depression and leg strength and endurance. Exploratory analyses will evaluate whether the intervention will have a positive impact on: fatigue, physical activity, cognitive and emotional representation of illness and self-rated health.

METHODS

SheppHeartCABG is an investigator-initiated randomised clinical superiority trial with a blinded outcome assessment, employing 1:1 randomisation to a comprehensive cardiac rehabilitation programme plus usual care versus usual care alone. Patients will be recruited from two university hospitals in Denmark. Figure 1 shows the trial design.

Trial population and eligibility criteria

Patients aged 18 years and older admitted for elective CABG who speak and understand Danish, and provide written informed content, are considered eligible for participation. Exclusion criteria are patients at intermediate or high risk in relation to their cardiovascular status[24] and patients with orthopaedic conditions that would prohibit walking and cycling exercise.

Experimental intervention

The experimental intervention is a comprehensive rehabilitation programme with an exercise training component and a psycho-educational component from admission until 4 weeks after CABG surgery.

The physical components

The exercise programme during hospitalisation consists of respiratory physiotherapy, neck and shoulder exercises, walking and cycling. The purpose is preventing respiratory complications such as atelectasis and pneumonia, neck and shoulder pain and increasing the

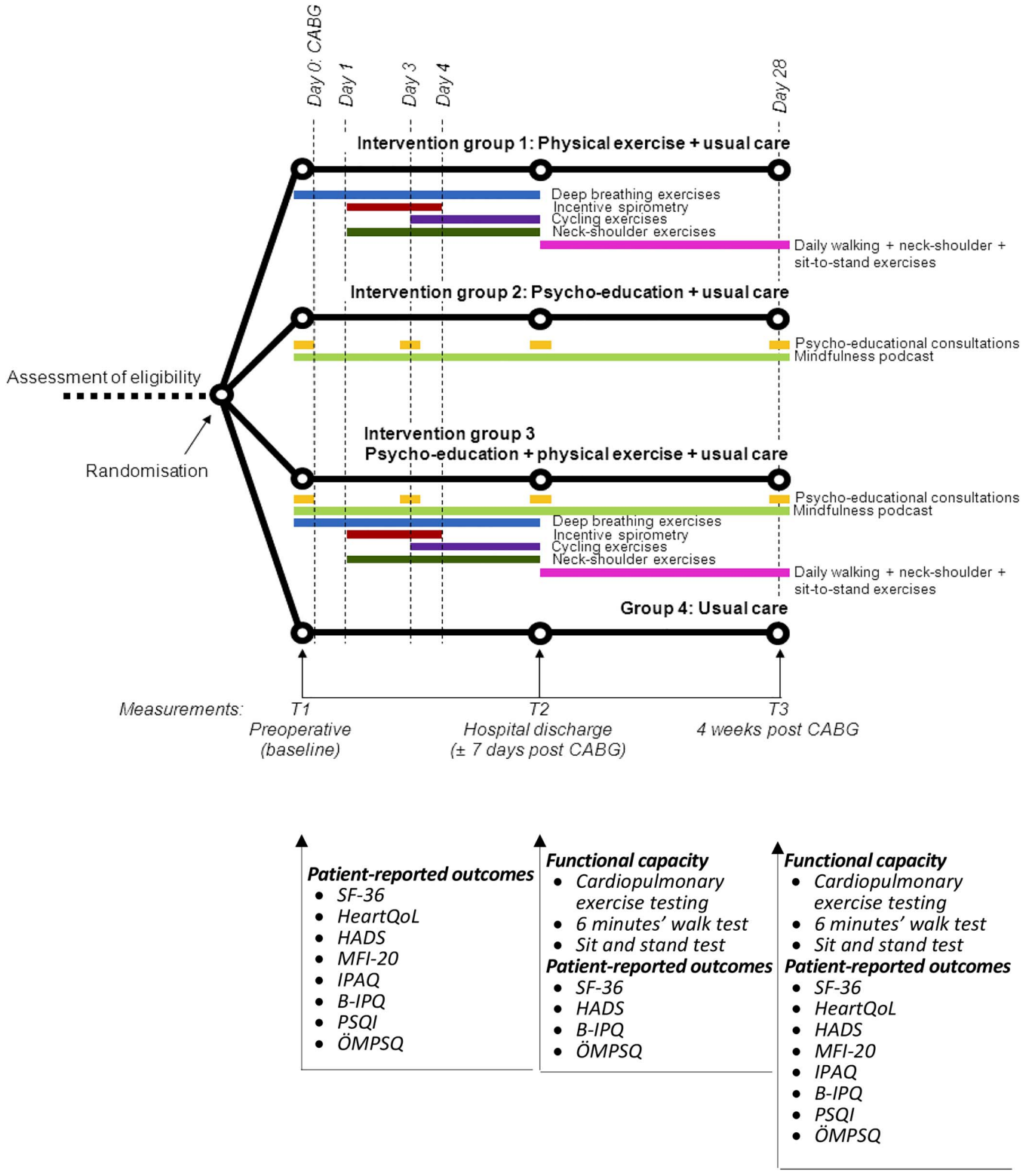

Figure 1 Trial design. CABG, coronary artery bypass grafting; HADS, Hospital Anxiety and Depression Scale; NYHA, New York Heart Association; PSQI, Pittsburgh Sleep Quality Index.

physical functional level. Each exercise in the training programme is based on guidelines,[25] public health recommendations for physical activity for adults[26] and supported by European recommendations for physical training in patients with cardiac disease.[21 27] Physical exercise starts immediately after surgery and follows the ACSM's Guidelines for Exercise Testing and Prescription.[25] A physiotherapist with specific knowledge of open heart surgery and cardiac rehabilitation initiates the programme and gives the participants standardised

instructions in each part of the programme. All the completions of exercises are documented in the training diary.

Physical exercises during hospitalisation

Breathing exercise

This consists of 7–10 deep breaths four times each day when awake in daytime. Begin at admission and continue until hospital discharge.

Peak flow spirometry

Participants are encouraged to perform breathing exercises consisting of 3–5 min of breathing in the PEP-flute four times daily during postoperative days 1 through 4.

Walking

Walking exercises are performed in the hallway at the hospital ward on postoperative day 1 continuing to 4 weeks postsurgery. Walking exercise begins on the first postoperative day with a 2×5 min walk; second postoperative day a 2×7 min walk; third postoperative day a 3×7 min walk and from the fourth postoperative day until discharge a 3×10 min walk. The participant has to increase the intensity of walking from low to moderate during hospital admission.

Neck and shoulder

This consists of shoulder lifts, shoulder rolls and head rolls with 10 sessions of each exercise two times per day from postoperative day 1 until hospital discharge.

Cycling

Cycling exercise training is conducted on stationary bicycles or alternatively using bed bikes.[28] Heart rate and saturation are monitored at three scheduled times during the two first exercise sessions. The participants are encouraged to train using moderate intensity, so that they are not exhausted and the training is safe and has effect.[29] Time for cycling will be 10 min. The rating of perceived exertion scales (RPE) is used to measure the exercise intensity. The cycling exercise intensity is at RPE Borg between 13 and 15 on a scale of 6–20,[30] and the power on the cycle is programmed so that it matches this intensity. There will be a 5 min warm-up and a 5 min cool-down to achieve cardiovascular adjustment with exercise intensity ≤10 RPE Borg.[31 32] The cycling exercise consists of two daily sessions from the third postoperative day until discharge.

Physical exercise from discharge to 4 weeks after surgery

Exercise training will take place at the participants' home and outdoors including resistance training and walking to obtain muscle strength and physical capacity.[33] At hospital, the physiotherapist introduces the exercises and the training diary.

Walking

The length of daily walk will be increased from hospital discharge until 4 weeks as follows: 3×10 min, 2×15 min, 2×20 min, 2×25 min and 2×30 min. The walking intensity is moderate: the first 2–3 min ≤10–13 on the Borg Scale and the last 2–3 min at the same intensity level and the time between 12 and 14 on the Borg Scale.

Leg endurance and strength

The participants perform a sit and stand exercise and 'up on toes' with 10 repetitions two times per day from hospital discharge until 4 weeks after CABG.

The psycho-educational components

The interventions consist of four consultations: admission day, second postoperative day, discharge and 3 weeks after CABG. The first three consultations are in-hospital, and the fourth is by phone. The psycho-educative intervention has two parts: one inspired by the three dimensions in Rosemarie R Parse's 'Human Becoming Practice Methodologies'[34] and the second is a compact mindfulness programme combing dialogue and recorded instructions for individual practice.[35] The overall goal of the psycho-educative intervention is that the patients learn to construe and react to relevant physical and psychological symptoms and thus learn to cope with anxiety and fear after CABG.

Consultations

Four consultations are scheduled: admission day, second postoperative day, discharge and 3 weeks after CABG. The first three consultations are in-hospital, and the fourth is by phone. The consultations are conducted by specially trained nurses and last for about 45 min. Rosemarie R Parse's 'Human Becoming Practice Methodologies'[34] forms the conceptual foundation for the dialogues with the patients.

The Human becoming Practice Method describes three dimensions for dialogue: (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 method, there are three ways to make health changes: (1) using creative images to explore, (2) recognising personal patterns and (3) value priorities and shed light on the paradoxes by looking at the incongruence in a situation and change the view of reality. The nurse is 'truly present' in the process through discussion, silent immersion and reflection.

Mindfulness

The other part of the psycho-educational intervention is a set of mindfulness exercises that patients can use *ad libitum* for stress reduction, calm awareness and self-care through meditation-based exercises.[17 36] For this trial, a brief mindfulness intervention with several components has been developed in cooperation with the Center for Research in Existence and Society, University of

Copenhagen. It particularly focuses on the patients with CABG in need of calming down in physically and emotionally stressful situations. At the first consultation, participants are introduced to mindfulness through a short mindfulness exercise lead by the nurse, followed by a dialogue. The participants receive an mp-3 player with an audio mindfulness programme. The audio mindfulness programme consists of three guided meditations of 5 min, 15 min and 20 min, and the participants are encouraged to listen to all three meditations from admission to 4 weeks after CABG.

Usual care

Patient in both arms of the trial receive usual care according to the guidelines.[6 37] The standard admission time after CABG is 5–8 days. Usual treatment involves preoperative and postoperative information provided by physicians, nurses and physiotherapists. Instructions regarding precautions after sternotomy are provided by physiotherapists covering the immediate postoperative period during hospitalisation and after discharge. Primary perioperative nursing consists of admission interview with preoperative screening (falls, nutrition); introduction to postoperative pain and nausea medications; pain assessment and postoperative activities. Early postoperative care focuses on the observation of vital signs, while the remainder of the hospital admission focuses on recovery and preparation for discharge.

Outcomes and data collection

Data will be collected at admission, discharge and 4 weeks following surgery (see table 1).

Primary outcome

The primary outcome in this trial is physical functional level as measured by the 6MWT. 6MWT is a simple tool and will be administered at admission, discharge and 4 weeks following CABG.[38] For the 6MWT, the participants walked up and down a 30 m hallway for 6 min according to the guidelines.[39] To ensure standard testing, a standardised instruction for patients has been developed.

Secondary outcomes

Furthermore, we will assess nine preplanned secondary hypotheses based on estimates using the SDs from the SheppHeartCABG pilot trial.[23] The variables, instruments, subscales, Cronbach's α and hypothesised differences are detailed in table 2.

The Medical Outcome Study Short Form 12 (SF-12)

Mental health and physical health are measured by the Medical Outcome Study Short Form 12 (SF-12) 4 weeks after surgery. The SF-12 is a 12-item validated version of the SF-36 and is a brief, reliable measure of overall health status that generates a physical component score and a mental component score (PCS and MCS).[40]

The Hospital Anxiety and Depression Scale

This 14-item instrument measures symptoms of anxiety and depression[41 42] The scale offers two scores HADS-A and HADS-D, each of which can range from 0 to 21. Scores of 0–7 for either subscale are regarded as normal; 8–10 suggest the presence of a mood disorder and 11 and above suggest the probable presence of a mood disorder.

The HeartQol Questionnaire

Health-related quality of life is measured with the use of the HeartQol questionnaire.[43] The emotional subscale and the global scale will be included which are scored from 0 to 3. The questionnaire consists of 14 items.

Table 1 SheppHeartCABG: demographic and baseline characteristics, tests and questionnaires

Quantity	Time of measure	Type of quantity
Demographic		
Age, height, weight, martial, educational	Baseline	Continuous
Occupational status	Baseline	Categorical
Smoking	Baseline	Binary (Y/N)
Clinical		
Nutritional status (BMI)	Baseline	Continuous
NYHA calcification	Baseline	Continuous
Type of heart disease	Baseline	Categorical
Diabetes mellitus	Baseline	Binary (Y/N)
Medical status	Baseline	Categorical
Level of physical activity	Baseline, discharge, W4	Continuous
Functional level		
6MWT and Sit and stand test	Baseline, discharge, W4	Continuous
Questionnaire		
SF 12, HADS, ÖMPSQ, B-IPQ, EQ-5D	Baseline, discharge, W4	Continuous
HeartQol, PSQI, MFI-20, IPAQ	Baseline, W4	Continuous

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; 6MWT, 6-min walk test.

Table 2 Overview of secondary outcomes

Variables	Instrument	Subscales	Cronbach's alpha	Hypothesised difference (anticipated power)
Health status	Medical Outcome Study Short Form 12 (SF-12)	Physical Component Summary (PCS) [0–100] Mental Component Summary (MCS) [0–100]	0.87 0.84	2.4 (97%) 8.21(100%)
Anxiety—depression	Hospital Anxiety and Depression Scale (HADS)[41 42]	HADS-A scale [0–21] HADS-D scale [0–21]	0.83 0.82	1.26 (86%) 4.3 (100%)
Quality of life	HeartQol questionnaire[43 57]	The emotional subscales [0–3] The global subscales [0–3]	0.80–0.91 0.80–0.91	0.3 (85%) 0.2 (95%)
Sleep	Pittsburgh Sleep Quality Index (PSQI)[58]	*Component 1*: Subjective sleep quality score [0–3] *Component 2*: Sleep latency score [0–3] Component 3: Sleep duration score [0–3] Component 4: Habitual sleep efficiency score [0–3] Component 5: Step disturbances score[0–3] Component 6: Use of sleeping medication score [0–3] Component 7: Daytime dysfunction score [0–3] Global PQSI score [0–21]	0.83	2.2 (96%)
Pain	Örebro Musculoskeletal Pain Questionnaire (OMPQ)[44]	OMPQ total score [0–210]	0.86	10.2 (98%)
Strength and endurance in legs	Sit-to-stand test[39]	Total number of repetitions	NR	3.6 (100%)

HADS, Hospital Anxiety and Depression Scale; NR, not reported.

The Pittsburgh Sleep Quality Index

This is a self-rated questionnaire which assesses quality and disturbances of sleep over a 1-month time interval. Nineteen items generate seven component scores. The sum of scores for these seven components yields one global score.

The Örebro Musculoskeletal Screening Questionnaire

Pain is measured by the Örebro Musculoskeletal Screening Questionnaire. This 25-item self-administered questionnaire is formulated such that all musculoskeletal pains are addressed and assessed in five categories.[44]

Sit-to-stand test

Strength and endurance in legs is measured by a sit-to-stand test 4 weeks following surgery.[45] The test is carried out using a chair. The participants are then seated on the chair and have to get up to full standing position and then return to the initial seated position as many times as possible in 30 s. The test will be performed in accordance with guidelines.[46]

Exploratory outcomes

Clinical and demographic data will be evaluated. The HeartQol physical component will be analysed as an exploratory outcome.[43] Furthermore, a series of questionnaires regarding fatigue, physical activity and perception of illness are administered. The Measurement of Fatigue Instrument[47–50] is a 20 item self-report instrument designed to measure fatigue. The International Physical Activity Questionnaire[51] is used to measure health-related physical activity. Perception of illness is measured by The Brief perception Questionnaire,[52] which is a short questionnaire that assesses cognitive and emotional representations of illness on the basis of eight items. The EQ-5D is a standardised instrument for use as a measure of current health status that provides a simple descriptive profile and a single index value that can be used in clinical and economic evaluation of healthcare and in population health surveys.[53]

Sample size and power calculations

The study is a randomised superiority trial with the continuous outcome 6MWT with 1 control per experimental participant. In the pilot trial, the outcome was normally distributed with an SD of 90 m. If the true difference in the experimental and control means is 30 m, the trial shall include 163 experimental participants and 163 control participants (total participants 326) to be

able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 85%. The type I error probability associated with this test of this null hypothesis is 5%.

Based on SheppHeartCABG the pilot trial, several of the secondary outcomes are overpowered as shown previously. For all outcomes except HeartQol physical, the power to reject the null hypothesis was above 85% (type I error 5%) (see table 2).

Study procedure and randomisation

To achieve our estimated sample size of 326 participants, patients will be identified and screened consecutively from the current elective CABG waiting list. Patients similar to the New York Heart Association (NYHA) groups I–III and without physical illness which prevents physical exercise are suitable participants in the trial. Verbal information will be given to the patient on admission day and is planned so it is possible for relatives to participate by staff personal. If a patient accepts to participate after verbal and written informed consent, the patient is randomised to the rehabilitation plus usual care or usual care alone. The allocation sequence is computer generated with a varying block size concealed by the investigators. The allocation will be conducted centrally using the web-based 'Copenhagen Trial Unit Online Randomisation System', and selected relevant participant information will be registered (civil registration number (CPR), participant number and stratum). Stratification variables are Rigshospitalet, University of Copenhagen and Odense Universitetshospital, University of Southern Denmark and sex. After allocation, the investigator immediately informs the patient of the result and the further plan. For both groups, follow-up assessments including physical tests and questionnaires will take place at admission, discharge and 4 weeks following surgery. Questionnaires will be completed on paper or electronically in the questionnaire system Enalyzer. 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 spreadsheet, which is only accessible by the SheppHeart staff. The recruitment process will continue until 326 patients have been included.

Blinding

It is not possible to blind the interventions to the staff and patients. However, all physical tests, data collection and data management will be conducted by staff blinded to the interventions. Statistical analyses and drawing of conclusions from these will also be conducted blinded to the intervention group.

Statistical analysis

Analysis of primary and secondary outcomes

The primary and all secondary outcomes are continuous. For all primary and secondary outcomes except HeartQol and HADS, it is expected that the scores will be normally distributed.

Analyses will be intention-to-treat analyses using two-sided tests with a significance level of 5%. There are two types of comparison between the intervention groups: (1) comparison of values measured at week 4 and (2) comparison of values measured at discharge and at 4 weeks. In the first type, a general univariate linear model is used (except for HeartQol and HADS (see below)), adjusted for baseline values. In the second type (except for HeartQol and HADS (see below)), a mixed linear model including an unstructured covariance matrix is used. In this model, the interaction between intervention and time is of main interest. If assumptions of the models are not fulfilled with reasonable approximation, non-parametric sensitivity tests will be performed.

HeartQol quantities are converted to binary quantities based on the median score, and logistic regression is used to compare the two groups at 4 weeks adjusted for value at baseline. HADS is reported as mean (SD) and is converted to binary quantities expressed as probable anxiety and depression (scores≥8). Logistic regression is used to compare the intervention and control groups at 4 weeks adjusted for value at baseline.

Since almost all secondary outcomes are overpowered, Cohen's d will be calculated for each outcome to test the clinical effect. SAS V.9.3 will be used.

Missing values and multiplicity

For the primary and secondary outcomes, multiple imputation (MI) of missing values using the Markov Chain Monte Carlo (MCMC) approach will be performed if the number of incomplete participants is above 5%. The variables included are the group membership, stratifying variables (site and sex), time (baseline, discharge and 4 weeks after discharge) and outcomes. If MI is used, the primary result will be that based on the multiply imputed data sets. Significant (adjusted $p<0.05$) results of the primary and secondary outcomes will be supplemented by the following worst case sensitivity analysis. Let A be the group where a beneficial significant effect is observed and B be the other group. Missing values in group A will be imputed by the minimum value found in the material, and missing values in group B will be imputed by the maximum value found. When the treatment code is broken, the results may be interpreted.

The primary outcome (6MWT) will first be tested using a significance level of 0.05. Analyses of the secondary outcome measures as preplanned in the protocol will be analysed with no adjustment of p values due to multiplicity. Instead, the interpretation of each secondary outcome measure will be assessed in the light of multiple testing, that is, statistically significant effects will be interpreted in the context of increased risk of type-I error. No significance testing will be performed for the explorative outcomes.

In addition to the primary intention-to-treat analysis, we will also perform a per-protocol analysis to include information on adherence to the intervention in the intervention group.[54] The per-protocol definition reflects the two components of the intervention, in that patients in the intervention group must have completed 75% per cent of the programme in the per-protocol analysis.

Ethics, safety and dissemination

The trial will be conducted according to the latest Declaration of Helsinki. It has been registered at ClinicalTrials.gov no NCT02290262 before inclusion of the first participant. Information about the trial is given verbally and in writing. Eligible patients will be enrolled as trial participants. Trial participants are free to withdraw their informed consent at any time and will be treated according to the department's standard procedures. Patients who leave the trial will be asked for permission to continue to collect data and to use already collected data. If the patient gives permission, data will be included in the final analysis. If a patient refuses the use of already collected data, all related data will be destroyed. The trial will be conducted according to 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 or serious adverse reactions. An independent Data Monitoring and Safety Committee (DMSC) has been established.

Safety

Throughout the trial, annual reports including all expected or unexpected adverse events or reactions will be submitted to the ethical committee. Reports will be accompanied by an assessment of the participants' safety. The investigator notifies the committee within 90 days of completion of the trial.

Dissemination plan

Positive, neutral and negative results of the trial will be submitted to international peer-reviewed journals. Furthermore, results will be presented at national and international conferences relevant to the subject fields. Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors and depends on personal involvement. Ethic Committees and component authorities will be able to obtain direct access to data and documentation.

DISCUSSION

This SheppHeartCABG trial, assessing the effect of a comprehensive cardiac rehabilitation in phase I rehabilitation on a population undergoing CABG, is the first randomised clinical trial in a representative population. This trial is expected to contribute results that can improve patient outcomes related to ischaemic heart disease treated by CABG and early rehabilitation. This is the first trial to test the effect of a comprehensive rehabilitation programme in rehabilitation phase I after CABG. SheppHeartCABG has been designed to meet the criteria for high quality in a non-pharmacological clinical trial with central stratified randomisation and two centre participation which secures against selection bias.[55 56]

The primary outcome and all statistical analysis are blinded to intervention, which should reduce detection and interpretation bias.[55 56]

Trajectory

Inclusion was initiated on November 2014 and is expected to continue until July 2016.

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Contributors IEH, LCT and SKB drafted the manuscript. LCT has specifically designed the statistical analysis plan. All authors designed the trial, developed the protocol, revised the manuscript critically and have given their final approval of the version to be published.

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Paper III

Comprehensive phase one rehabilitation versus usual care in patients following coronary artery bypass grafting: Results from the SheppHeartCABG trial

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Abstract

Objectives: Phase two rehabilitation enhances physical and mental health after coronary artery bypass grafting (CABG) surgery. Evidence for the effect of early rehabilitation (phase one) is sparse.

Methods: This is an investigator-initiated randomised controlled superiority trial including 326 CABG patients randomized to four weeks of comprehensive early rehabilitation including physical exercise and four psycho-educational consultations (intervention) versus usual care (control). The primary outcome was the Six Minute Walk Test (6MWT). Secondary outcomes were mental health and physical activity (Medical Outcome Study Short Form (SF-12)); anxiety and depression (Hospital Anxiety and Depression Scale); physical and emotional scores (HeartQoL); sleep (Pittsburgh Sleep Quality Index); pain (Örebro Musculoskeletal Screening Questionnaire) and muscle endurance (Sit-To-Stand test).

Results: Eleven in the experimental group and five in the control group dropped out. 310 participants had a mean age of 65 years (range 33-83) and 87% were male**.** No significant differences between groups were found after four weeks for 6MWT (p= 0.27). For secondary outcomes the experimental group had a more advantageous development than the usual care group, but the differences were not significant and with small clinical effects. However, odds ratio of HADS-D≥8 decreased in favour of the experimental intervention (p= 0.04). There was non-adherence to parts of the intervention. Per-protocol analysis showed differences between groups for 6MWT (41.1 m (95%CI: (8.0 to 74.3 m), p=0.02) and Sit-To-Stand-test (1.87 repetitions (95%CI: 0.04 to 3.70 repetitions), p=0.046).

Conclusions: SheppHeartCABG showed no effect on 6MWT primary, or secondary outcomes except the intervention might have had a beneficial effect on depressive symptoms. The intervention was associated with high non-adherence and the intervention had a positive effect for adherent participants.

Keywords: Rehabilitation post-CABG, phase one rehabilitation, coronary artery bypass grafting, physical exercise, psycho-education.

Trial registration: http://www.clinicaltrials.gov/ identifier; NCT02290262.

INTRODUCTION

Cardiac rehabilitation is an important part of secondary prevention in promoting cardiovascular health and differentiated into three main phases: in-hospital; early outpatient and long-term outpatient cardiac rehabilitation.[1] The clinical recommendations for phase one rehabilitation for patients undergoing coronary artery bypass graft surgery (CABG) are based on sparse evidence[2] based on trials with small sample size and unrepresentative trial populations.[2,3] It is now possible to provide surgical treatment to patients with chronic conditions,[2] but the postoperative period can be challenging with physical and psychological problems and symptoms such as anxiety and depression, immobility issues, respiratory complications, insufficient sleep, and fatigue.[4-7] It is therefore important to evaluate early postoperative structured management strategies, including cardiac rehabilitation programmes.

There are few recommendations regarding phase one rehabilitation after CABG.[1] Exercise training in cardiac rehabilitation after hospital discharge has a positive effect for post-CABG patients,[8] and it seems reasonable to start exercise training immediately after surgery.[9] Trials have demonstrated improvements in patient outcomes measured as pulmonary complications and physical functional capacity after CABG.[10-14] In addition, trials targeting psychological and psycho-educational interventions in rehabilitation patients have shown improvements in symptoms of depression and anxiety [15]; however, no published randomised clinical trial using phase one rehabilitation for CABG patients has had an adequate sample size.[16,17] A pilot trial was conducted to evaluate acceptability of inclusion, feasibility and intervention compliance.[18] The trial showed high inclusion, feasibility, and safety but moderate compliance with both the physical and the psycho-educational interventions.[18] We hypothesised that comprehensive cardiac rehabilitation would increase physical function and improve mental health.

The aim of this trial was to assess phase one rehabilitation compared to usual care in CABG patients on the primary outcome of physical function and on secondary outcomes of physical and mental health, anxiety, depression, sleep, pain and health related quality of life.

MATERIALS AND METHODS

The SheppHeartCABG trial is an investigator-initiated randomised clinical superiority trial investigating cardiac rehabilitation compared to usual care.[19] The trial followed recommendations of the updated Declarations of Helsinki[20] and was approved by the Regional Ethics Committee (H-4-2014-109) and the Danish Data Protection Agency (30-1309). The trial was registered at ClinicalTrials.gov (NCT02290262) and reported according to the Consolidated Standards of Reporting Trials (CONSORT).

Participants, setting and recruitment

The settings were thoracic clinics at two university hospitals; Odense and Copenhagen. Patients were screened consecutively for inclusion. First-time elective CABG patients who provided informed consent were included. Patients younger than 18 years of age, patients diagnosed with a musculoskeletal or neurological disease precluding exercise testing and training, and patients who did not speak Danish were excluded. Potential participants received verbal and written trial information at admission and were recruited over 19 month.

Randomization and blinding

Randomization was 1:1 by central randomization with the allocation sequence computer-generated using blocks varying between 4, 6, 8, 10, 12, and 14 and stratified according to site and sex and concealed from the investigators as allocation was done through a web-based system. Full blinding of clinicians and participants is impossible in a rehabilitation trial but data collection, outcome assessment, data management, statistical analyses, and conclusions were blinded to the allocation group.

Intervention group

An outline of the trial interventions[19] is presented in *Figure 1* including the intervention components, the timeline for the two groups and the outcome measures.

Physical exercise component

The aim of the physical intervention was to improve physical function four weeks after CABG and initiated on the day before surgery. To monitor adherence, patient-reported diaries and a heart rate monitor were used. The physical interventions were administrated by physiotherapists and included an exercise programme that started at admission and continued for four weeks after CABG. The physical intervention was divided into respiratory physiotherapy and aerobic training. After hospital discharge, until four weeks after CABG, exercise included continuous daily walking and muscle and endurance exercises, Figure 1.

Psycho-educational component

The goal of the psycho-educative intervention was to improve disease coping by applying a patient-centered approach. The conceptual foundation for the dialogue with the patients was based on the Human Becoming Practice Methodologies[21] of Rosemarie Rizzo Parse. The consultations were performed by six trained nurses and most participants met the same nurse at all consultations. A consultation guide was followed to ensure standardisation of the intervention[18] including recovery from major surgery, changed self-image, dependency on relatives and medical issues. The psycho-educative intervention consisted of four face-to-face consultations with the nurse. Mindfulness was integrated as an element in the psycho-educational consultation and provided as a toolbox of recorded meditation instruction for personal use e.g. as an alternative to medication for sleep disorders and physical and emotional stressful situations.[19,22]

Usual care group

All patients followed usual care procedure[23] including medical follow-up and standard treatment according to disease specific guidelines.[3]

Outcomes

Outcome assessment was carried out at three time points: baseline (after randomization), at discharge, and four weeks post CABG.

Primary outcome: physical function

Physical function at four weeks following CABG was measured by 6MWT.[24] The participants walked up and down a 30 meter (m) hallway for six minutes according to guidelines.[25]

Secondary outcomes

The secondary outcomes were mental health and physical activity measured by the Medical Outcome Study Short Form (SF-12)[26], anxiety and depression measured by the Hospital Anxiety and Depression Scale questionnaire[27], physical, emotional and global scores by the HeartQoL questionnaire[28], sleep expressed by the Pittsburgh Sleep Quality Index[29], pain evaluated by the Örebro Musculoskeletal Screening Questionnaire[30], and muscle endurance measured by a Sit-To-Stand test.[31]

Safety considerations

The 6MWT was administered by a nurse or a physiotherapist at baseline and by physiotherapists at discharge and four weeks after surgery with criteria for termination defined.[32] Serious adverse events were registered and discussed with the physician and primary investigator responsible for the trial.

Sample size

The sample size was 326 participants[19] based on a comprehensive rehabilitation programme that aimed to improve 6MWT by 30 m in the experimental group compared to the control group. A standard deviation of 90 m, an alpha of 5% and a power of 85% were used. In the SheppHeartCABG pilot, we found a mean of 548 m in the intervention group and 451 m in the control group measured by 6MWT.

Statistical analysis

Intention-to-treat analyses was used. There were two types of comparison between the intervention groups: 1) comparison of values at week four after surgery, this analysis used a general univariate linear model (except for HeartQol and HADS (see below) adjusted for baseline values and stratifying variables (sex and site) and 2) comparison of values at discharge and at four weeks. This analysis used a mixed linear model including an unstructured covariance matrix. In this model, the interaction between intervention and time was of principal interest. Also, this analysis was adjusted for baseline values and stratifying variables (sex and site). If the assumptions of the models were not fulfilled with reasonable approximation, removal of outliers and transformation of outcome were performed. HeartQol quantities were converted to binary quantities based on the median score among available cases. HADS was reported as mean and standard deviation and converted to binary quantities (score ≥8) as probable anxiety or depression. For both outcomes, logistic regression models were used to compare the experimental and usual care groups at four weeks, adjusted for value at baseline. Since almost all secondary outcomes were overpowered[19], Cohen's d was calculated for primary and secondary outcomes.[33]

For the primary and secondary outcomes, multiple imputation of missing values using the Markov chain Monte Carlo approach was carried out since the number of participants with missing values was above 5%. The variables included group, stratifying variables (site and sex), time (baseline, discharge and four weeks after discharge) and all outcomes. The primary outcome (6MWT) was tested using a significance level of 0.05. Analyses of the secondary outcome measures as pre-planned in the protocol were analyzed with no adjustment of p-values due to multiplicity. Instead, the interpretation of each secondary outcome measure was assessed in the light of multiple testing.

The pre-specified per-protocol levels of intervention adherence was defined [19] as completing at least 75% of the exercise sessions and consultations and using one of the mindfulness tools on 75% of the days. However, only one participant reached that level. Therefore, it was decided before the start of the analysis to change the per-protocol level to participation in at least 50% of the exercise sessions and psycho-educational consultations. Adherence to the exercise

intervention was assessed using the patient-reported exercise diary, and the recordings made for the psycho-educational intervention at each visit.

Statistical analyses were conducted in SPSS V.22 (SPSS Inc. IPM), R version 3.1.2 (R Foundation for Statistical Computing, Vienna Austria) and SAS V.9.3 (SAS Institute, Cary North Carolina, USA).

RESULTS

Between November 17, 2014 and June 23, 2016, 717 patients were identified and screened. 277 patients were excluded and 114 of the remaining 440 participants (26%) declined to participate, Figure 2.

Baseline characteristics

The sex ratio was equal among patients who declined to participate and included. Informed written consent was perceived by 326 patiens who were randomized. Of these, 11 patients drop out in the experimental group and 5 in the usual care group and their data were extracted from the trial. Of the 310 remaining patients, 87% were men and the mean age was 65 years (range 33 to 83). NYHA class ranged from I to IV.

Outcomes

Primary outcome: physical function

There was no statistically significant difference between experimental and control groups four weeks after CABG on 6MWT (16.2 m (95% confidence interval (CI): -13.0 to 45.4 m), p=0.27) and no significant interaction between intervention and time (p=0.55). Cohen's d was 0.14 (Table 2).

Secondary outcome

Also the secondary outcome showed no statistical significant difference between groups, except for a difference in favour of the experimental intervention detected on HADS-D≥8 (odds ratio=0.46 (95% CI: 0.22 to 0.97), p= 0.04),Tables 2 and 3. The secondary outcome showed a tendency of better scores in the experimental group on all outcomes except SF-12 PCS.

Adherence

In the intervention group 110/152 (72%) participated in the exercise training programme with the number of sessions completed depending on the length of hospitalization. Sixteen (15%) participants conducted ≥ 75% of the training programme, 35 patients (32%) 50% - 74% and 59 (54%) patients carried out < 50% of the sessions. Overall, the patients participated in 65% (median 68) of the training programme during admission and 54% (median 63) after discharge.

All of the participants in the experimental group participated in the psycho-educational intervention, of which (115/152) (76%) attended all four consultations. Regarding the mindfulness component 91/152 (60%) participated in the introduction given as part of the psycho-educational consultation. Of these 2 patients (2%) used the mindfulness toolbox exercises on ≥75% of the following days in hospital, 10 (11%) on 50-74% of the days and 79 (86%) used them rarely or not at all.

Per-protocol analysis

Per-protocol analysis was performed on patients who completed more than 50% of the exercise training programme in and out of hospital and the psycho-educational consultations. There was a difference between the intervention and the control group on primary outcome 6MWT (41.1 m (95% CI: 8.0 to 74.3 m), p=0.02) and on one of the secondary outcomes, the Sit-To-Stand test (1.87 repetitions (95% CI: 0.04 to 3.70 repetitions), p=0.046) four weeks after surgery, resulting in a Cohen's d of 0.40 and 0.36, respectively, Table 4. For the remaining secondary outcomes, there were no significant differences.

Safety

One serious adverse event was reported at baseline in the intervention group after the 6MWT. The participant had two episodes of ventricular tachycardia after ending the 6MWT. The event was evaluated to be independent of the 6MWT. There were no serious adverse events in the control group.

DISCUSSION

This is, to our knowledge, the largest randomized clinical trial to examine the effect of a comprehensive phase one rehabilitation programme including both a physical and a psychological component in patients who underwent CABG surgery. Intervention appeared safe with only one serious event not related to the trial.

The difference between the experimental group and the usual care group for 6MWT was statistically insignificant and only a small clinical effect was indicated by Cohens's d. After surgery, a spontaneous recovery is expected and the progress in 6MWT from admission to four weeks after surgery was parallel in the two groups.

The secondary outcomes showed no difference between groups, except for a potential difference in favour of intervention in regard to HADS-D and the intervention might have had a beneficial effect on depressive symptoms. However, it is a secondary outcome and the result should be interpreted with caution. Furthermore, the HADS data were dichotomised which produces a risk of reducing the complexity. When looking at the mean scores, there is a 0.6 points difference between groups in favour of the intervention group. Depression compared to anxiety is more prevalent in CABG patients,[34] but CABG patients have reported greater depression reduction after surgery compared with other patient populations undergoing open heart surgery.[35] No trial has investigated the effect of psycho-education combined with physical training after CABG. A systematic review with studies including CABG patients found psycho-education intervention to have a moderate effect in decreasing anxiety and depression[36] in keeping with our findings.

The intervention showed no effect on self-reported physical and mental health, anxiety, pain, sleep or health related quality of life but, there was a positive tendency in all outcomes. It is possible that the choice of primary and secondary outcomes has been inadequate, but all used instruments have been valid. It is not obvious to point out why changes were not found. The most obvious explanation is lack of power and poor adherence to intervention.

Patient adherence /participation was high for the psycho-educational consultations, including the mindfulness components of communication and stress reduction during the consultation. Subsequent use of the toolbox varied greatly. In most cases the taped mindfulness instructions

were used in a few instances for a specific problem, reflecting that mainly male participants expressed skepticism towards mindfulness. The sporadic use of mindfulness tools was expected given the brief (four weeks) rehabilitation programme. In other contexts effect of mindfulness components requires regular practice (e.g. weekly meetings extending for four-eight weeks after the hospitalization).[37]

The per-protocol analysis showed differences between the two groups in the 6MWT and Sit-To-Stand test albeit with small clinical effect expressed by Cohen's d, suggesting that non-adherence has affected the results. The findings from the experimental adherent group are identical with the few studies of physical training in phase one rehabilitation[11,38] and the pilot test prior to this trial.[18] A hypothesis from the findings is that low adherence has biased the results towards null.

Adherence is a known challenge in rehabilitation[39] and highlighted in the pilot trial.[18] The physiotherapists placed more emphasis on "why and how to do exercise" in this trial and the self-reported diary was simplified to enherence adherence. Further research in adherence and in the profile of non-adherent individuals is needed. The exploratory and hypothesis-generating analysis could indicate from a comparative effectiveness research point of view that the intervention had an effect in those patients who had a certain "dose" (level of participation) albeit it is unkown. In addition, the per-protocol analysis showed that for the majority of the secondary outcomes the experimental group had a more advantageous development than the usual care group, resulting in a Cohen's d indicating only a small clinical effect. Participating in a phase one rehabilitation programme requires involvement from the patients. Further randomised clinical trials are needed to optimize components and to identify barriers to increased adherence in early rehabilitation after CABG.

Strengths and limitations

Patients were included consecutively in an unselected CABG population with a reasonable number of exclusion and inclusion criteria securing external validity. The trial applied central stratified randomization securing against selection bias and a blinded assessment statistical analysis, reducing detection and interpretation bias. Of the 440 eligible patients 326 were randomized, which is a high inclusion rate in rehabilitation.

Participating in a clinical trial might exert an effect on the physical and mental health of patients through contact with health professionals. A concern is that the usual care group might have received unintended intervention during admission or at testing by the trial personal.[40] In other words, the trials results can have been affected by the participants awareness that they were being studied or that they received additional attention.

Self-reported outcomes as used in the diaries and the questionnaires are by nature subjective and therefore likely biased with a risk of recall bias.[41] Nonetheless, the patients filled in the questionnaires independently of researchers.

CONCLUSION

The SheppHeartCABG showed no effect on the primary outcome, 6MWT or on secondary outcomes except that the intervention might have had beneficial effect on depressive symptoms. Part of the intervention were associated with high level of non-adherence. However, from a comparative effectiveness research point of view the intervention had a positive effect for adherent participants shown by the per-protocol analysis where differences between the two groups on the physical outcomes 6MWT and Sit-To-Stand test were found. Furthermore, the majority of the secondary outcomes in the experimental group showed a more advantageous development than the usual care group; however this was non-significant with a small clinical effect.

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Contributors

IEH, SKB, CG, PW, JL, NVH, PM, SLC, IE and PSO designed the trial and developed the protocol. IEH drafted the manuscript in collaboration with SKB and LCT. LCT, IEH and SKB have designed the analysis plan, and LCT performed the statistical analyses for the primary and secondary outcomes. IEH designed the physical exercise and psycho-educational programme in collaboration with SKB. The mindfulness programme was created in collaboration with NVH and SLC. BB and KHB contributed significantly during data collection. IEH, PM, NVH, SLC, KHB, BB, CG, PW, JL, LCT, IE and SKB all revised the manuscript critically.

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Figure 1. Trial design. The figure is reproduced after the SheppHeartCABG pilot trial[18]

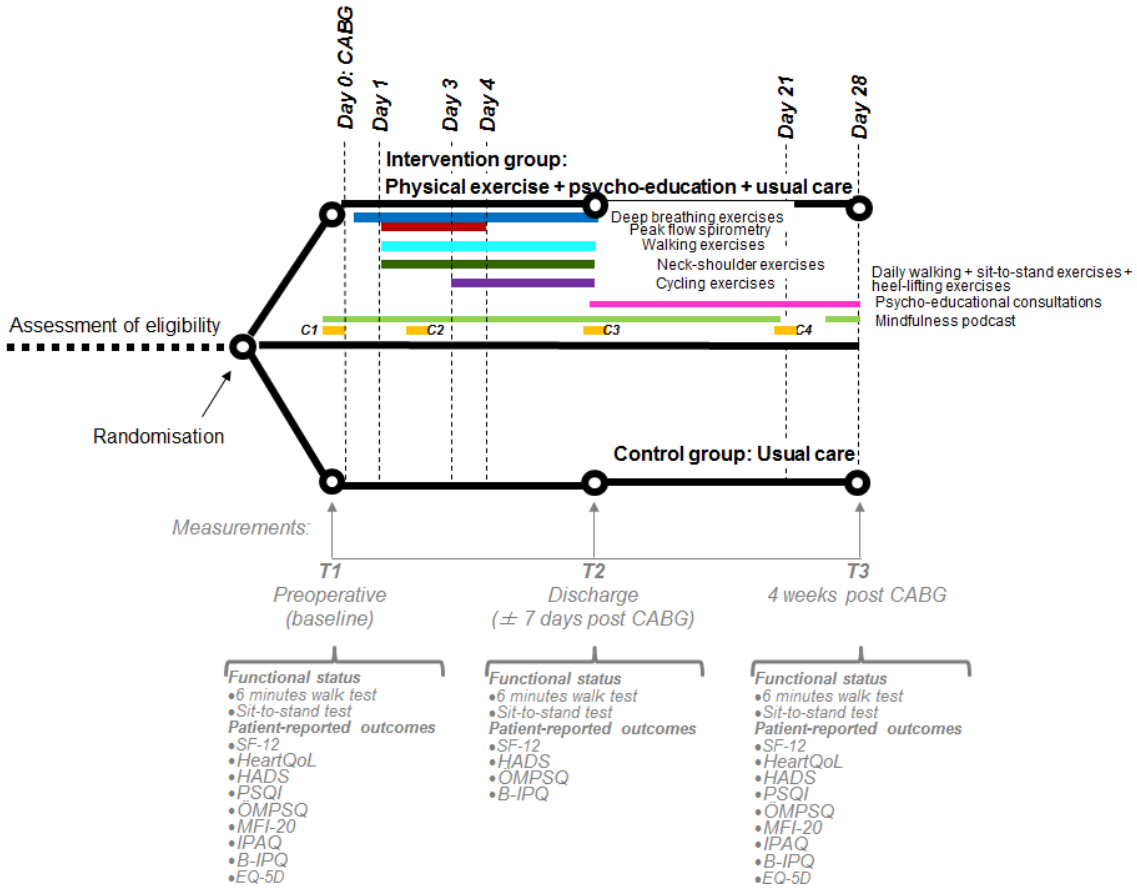
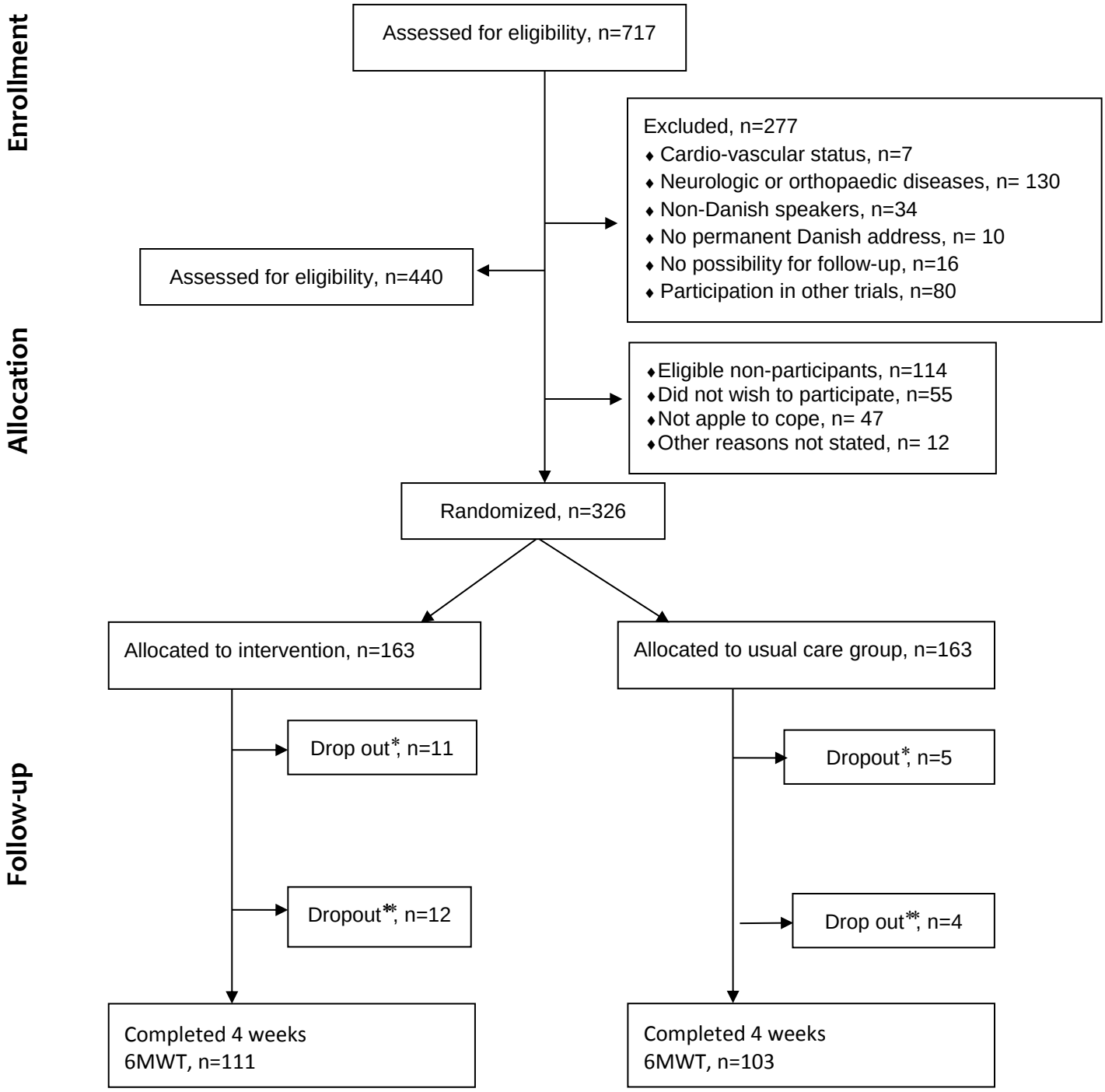


Figure 2. Consolidated Standard of Reporting Trials (CONSORT) flow diagram. Flow of patients in the SheppHeartCABG trial



*Dropout: dropped out and wanted to extract their data from the trial
**Dropout: dropped out from the trial with acceptance to use data.

Figure 3. Mean, median, Q1 and Q3 of six minute walk test in groups usual care (🔴) and experimental group (🔵) at time point 1(baseline), 2 (discharge) and 3 (4 weeks after surgery).

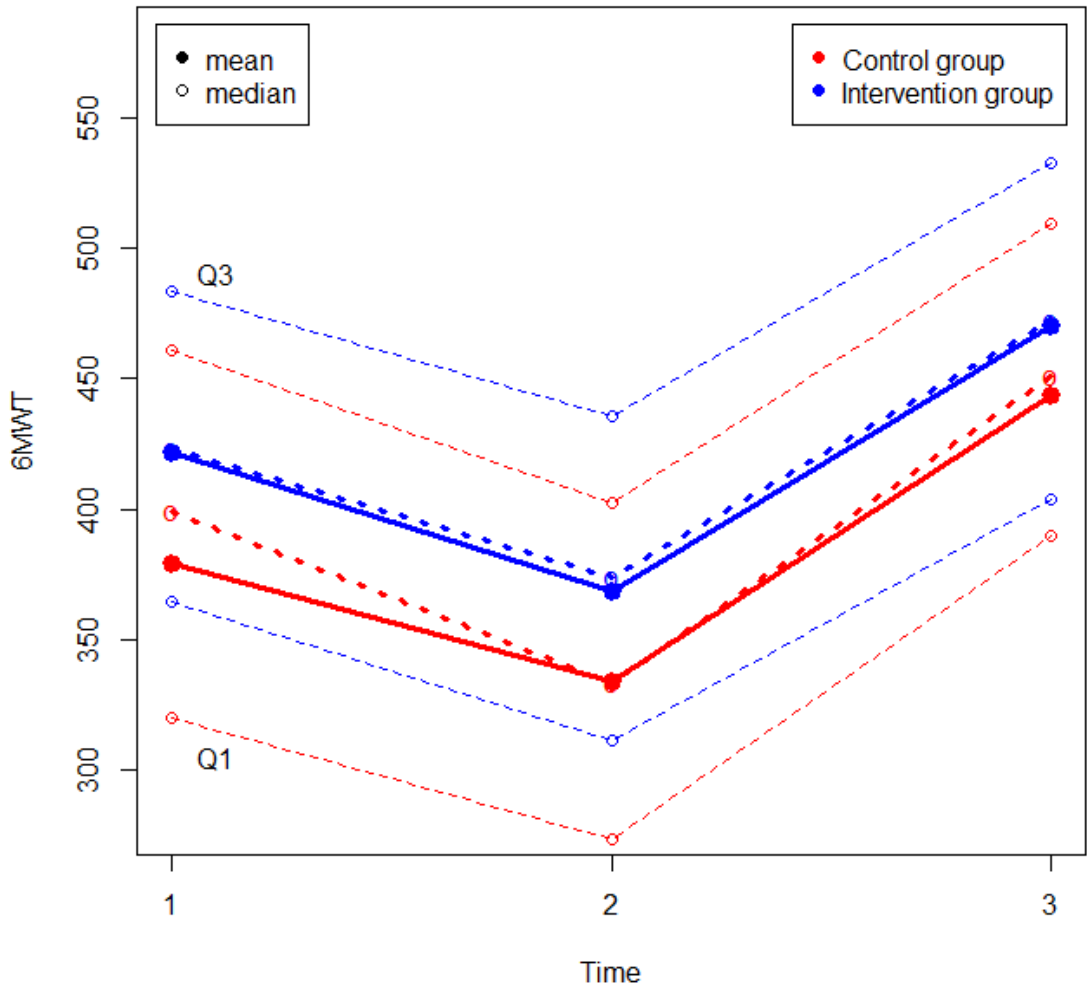


Table 1. Baseline characteristics experimental group and usual care group

	Experimental group (n= 152)	Usual care group (n= 158)
Age, years, mean (±SD)	65.0 (9.1)	65.1 (8.4)
Male	132 (87)	136 (86)
Female	20 (13)	22 (14)
Marital status, n (%)		
Single/divorced/widowed	32 (21)	37 (23)
Married/domestic partner	120 (79)	121 (77)
Occupational status, n (%)		
Active employment	61 (40)	80 (51)
Retired	86 (56)	76 (48)
Early retirement	4 (3)	1 (1)
Person on job release scheme	1 (1)	1 (1)
Educational level, n (%)		
Vocational level	68 (45)	90 (57)
College	37 (24)	31 (20)
University	34 (22)	22 (14)
None	2 (1)	2 (1)
Undisclosed	11 (7)	13 (8)
Body mass index[1], n (%)		
< 18.5 (kg/m2)	1 (1)	1 (0.6)
≥ 18.5 < 25 (kg/m2)	39 (26)	35 (22)
≥25 < 30 (kg/m2)	65 (42)	77 (49)
>30 (kg/m2)	46 (30)	40 (25)
Undisclosed	1 (1)	5 (3)
Type of heart disease, n (%)		
Ischemic heart disease	40 (26)	37 (23)
Morbus cordis artiosclerosis	62 (41)	69 (44)
Others	3 (2)	5 (3)
Undisclosed	46 (37)	47 (30)
NYHA class[2], n (%)		
NYHA class I	44 (29)	41 (26)
NYHA class II	51 (34)	60 (38)
NYHA class III	30 (20)	31 (20)
NYHA class IV	2 (1)	5 (3)
Undisclosed,	22 (14)	21 (13)
LVEF[3], n (%)		
Normal (50-70)	112 (74)	106 (67)
Under normal (36-49)	29 (19)	28 (17)
Low (<35)	9 (6)	20 (13)
Undisclosed	2 (1)	4 (3)
Smoker, n (%)		
Current smoker	20 (13)	26 (16)
Previous smoker	79 (52)	86 (54)
Undisclosed	2 (1)	2 (1)
DM[4], n (%)		
Type I	6 (4)	7 (4)
Type II	29 (19)	40 (25)
Undisclosed	1(0.7)	0
Prescribed medication, n (%)		
Blood pressure-lowering drugs	90 (59)	87 (57)
ACE inhibitor	26 (17)	32 (20)

Beta-blocker	42 (28)	42 (27)
Calcium antagonist	33 (22)	37 (23)
Antirytmia	3 (2)	2 (1)
Antiplatelet drugs	126 (83)	134 (84)
Diuretic	27 (18)	43 (27)
Anti-diabetic	24 (16)	0 (0)
Statin	126 (83)	131 ((83)
Antidepressant	9 (6)	10 (6)
Pain reliever	21 (14)	29 (18)
Sleeping medicine	12 (8)	5 (3)

[1]BMI; Body Mass Index; [2]LVEF Left Ventricular Ejection Fraction [3]NYHA; New York Heart Association Functional Classification;[4] DM; diabetes mellitus.

Table 2. **Mean difference in outcome and odds ratio between 152 experimental participants and 158 usual care participants**

Primary outcome	**n**	**Estimate (95% CI)**	**p-value**	**SD**	**Cohen's d**
6-MWT	310	16.2 (-13.0; 45.4)	0.27	119.8	0.14
Secondary outcomes	**n**	**Estimate (95% CI)**	**p-value**	**SD**	**Cohen's d**
SF-12 mental	310	1.18 (-1.74; 4.09)	0.43	11.8	0.10
SF-12 physical	310	-0.82 (-3.18; 1.54)	0.49	10.2	-0.08
Pittsburgh Sleep QI	310	-0.91 (-2.06; 0.23)	0.12	4.6	-0.20
Örebro MSQ	310	-1.92 (-4.34; 0.51)	0.12	10.9	-0.18
Sit-To-Stand test	310	1.09 (-0.34; 2.52)	0.13	5.0	0.22
HADS anxiety	310	-0.59 (-1.50; 0.32)	0.20	4.0	-0.15
HADS depression	310	-0.43 (-1.33; 0.46)	0.34	3.8	-0.11
Binary outcomes	**n**	**OR (95% CI)**	**p-value**		
HADS anxiety (8+)	310	0.62 (0.29; 1.29)	0.20		
HADS depression (8+)	310	0.46 (0.22; 0.97)	0.04		
HeartQol (>median)					
HeartQol global	310	0.78 (0.45; 1.35)	0.37		
HeartQol emotional	310	0.93 (0.42; 2.09)	0.86		

Table 3. Mean values and standard deviation (SD) of HADS-anxiety and HADS-depression in experimental group and usual care group

Secondary outcomes	n	Group	Admission	Discharge	Four weeks after surgery
HADS anxiety, (±SD)	310	Experimental	5.4 (4.3)	5.7 (4.0)	3.5 (3.4)
		Usual care	6.0 (4,5)	5.8.(4.3)	4.3 (3.7)
HADS depression, (±SD)	310	Experimental	4.0 (3.5)	5.8 (3.7)	3.7 (3.2)
		usual care	3.9 (3.5)	5.7 (4.1)	4.3 (3.7)

Table 4. Results of per-protocol analysis in a general univariate linear model with primary and secondary outcomes. The estimates are the mean difference in outcome and odds ratio between experimental group and usual care group.

Primary outcome	n	Estimate (95%CI)	p-value	Cohen´s d
6MWT	209	41.1 (8.0; 74.3)	0.02	0.40
Secondary outcomes	**n**	**Estimate (95%CI)**	**p-value**	**Cohen´s d**
SF-12 mental	209	1.84 (-1.80; 5.49)	0.32	0.17
SF-12 physical	209	-1.50 (-4.69; 1.70)	0.36	-0.16
Pittsburgh Sleep QI	209	-1.49 (-3.02; 0.04)	0.06	-0.31
Örebro MSQ	209	-3.54 (-6.92; -0.17)	0.04	-0.34
Sit-To-Stand test	209	1.87 (0.04; 3.70)	0.046	0.36
Binary outcomes	**n**	**OR (95%CI)**	**p-value**	
HADS anxiety (8+)	209	0.56 (0.20; 1.52)	0.25	
HADS depression (8+)	209	0.46 (0.17; 1.27)	0.13	
HeartQol (>median)				
HeartQol global	209	0.76 (0.36; 1.61)	0.48	
HeartQol physical	209	0.70 (0.34; 1.41)	0.32	
HeartQol emotional	209	0.87 (0.42; 1.82)	0.72	

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Paper VI

Non-adherence: a challenge for phase one rehabilitation after coronary artery bypass surgery; Secondary results from the SheppHeartCABG trial

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Abstract

Objectives: This paper relates non-adherence to phase one rehabilitation after coronary artery bypass surgery to sociodemographic and clinical baseline data.

Methods: Patients admitted for CABG (n=326) from two sites were randomized to comprehensive phase one rehabilitation plus usual care versus usual care alone with 152 patients (mean age 65 ± 9 years; 132 men) allocated to the experimental group. Four weeks intervention included exercise training and psycho-educational consultations including a mindfulness audio. Adherence was defined as >50% participation.

Results: 31% (n=48) of the patients were non-adherent to the in-hospital exercise training programme and 53% (n=81) after discharge. Females were less non-adherent to the in-hospital training, but the degree of non-adherence increased after hospitalisation (20% (4/20) to 70% (14/20)). Non-adherence to mindfulness was 87% (132/152) in hospital and 70% (106/132) after discharge. Males not using mindfulness were 85% (112/132) in hospital and 70% (92/132) thereafter. Non-adherence to psycho-educational consultations was 5 (3%), of whom 4 (80%) were men. Patients with university level education were more adherent to exercise training during hospitalization than patients with lower educational level (odds ratio=3.14 (95% confidence interval (CI); 1.16-8.51), p=0.02). Diabetic patients were more non-adherent to exercise training after discharge (3.74, (1.54-9.08), p=0.004) as were overweight patients (0.37(0.17—0.80), p=0.01).

Conclusions: This study demonstrated wide acceptance of psycho-educational consultation in patients who had undergone coronary artery bypass grafting while their adherence to physical rehabilitation was low especially efter discharge from hospital and the possibility to attend a mindfulness programme was found irrelevant.

Keywords: Adherence, rehabilitation, coronary artery bypass grafting, exercise psycho-education.

Trial registration: www.clinicaltrials.gov identifier; NCT02290262

INTRODUCTION

Open heart surgery represents both a physical and mental strain[1-3] and cardiac rehabilitation is important for return to everyday life[4]. Yet some patients do not regard rehabilitation as necessary.[5] It is evident that patients benefit from outpatient rehabilitation (phase two rehabilitation)[6] and may also benefit early after discharge (phase one rehabilitation) after coronary artery bypass surgery (CABG).[7,8]

To benefit from cardiac rehabilitation, adherence is important, but low adherence to treatment is common and has implications for treatment cost and effectiveness. The World Health Organization (WHO) defines adherence as, "the extent to which a person's behavior corresponds with agreed recommendations from a healthcare provider."[9] Physical training is safe even early after surgery[10] but non-adherence is a challenge for phase one rehabilitation.[11] Research has focused on phase two rehabilitation adherence for post-CABG patients[11] and has identified "belief in own capability" (self-efficacy) in relation to exercise training to increase adherence.[12] Furthermore, belief in the effectiveness of cardiac rehabilitation is a predictor of adherence.[13]

Results from the randomized clinical trial SheppHeartCABG (Shaping outcomes by Exercise Training and Psycho-education in Phase One for Heart Patients) showed no differences between experimental group (exercise training and psycho-education) and the usual care group on the primary outcome, the Six Minute-Walk Test (6MWT) four weeks after surgery. Maybe a low level of adherence to the programme could explain the negative results since a per-protocol analysis showed a significant effect of rehabilitation on 6MWT and a Sit-to-Stand test for participants who adhered to the intervention.

To improve outcomes it is important to characterize patients who do not adhere to the intervention. The objective of this paper was to explore non-adherence to intervention components related to sociodemographic and clinical baseline data during phase one rehabilitation after CABG.

MATERIAL AND METHODS

A total of 326 patients referred for coronary artery bypass surgery were randomized to comprehensive phase one rehabilitation versus usual care in the SheppHeartCABG randomized controlled trial. Sixteen dropped out during the intervention or did not grant permission for use of their data. Of the 310 remaining patients, 152 were allocated to the experimental group (132 men) at a mean age of 65 years (SD±9.1). Sociodemographic data were age, sex, habitation status, occupational status and educational level. Clinical data were body mass index (BMI), New York Heart Association (NYHA) classification, Left Ventricular Ejection Fraction (LVEF), diabetes mellitus (DM) and smoking. Prescribed medication was received from medical records at baseline after signed consent.

Intervention

Patients undergoing first-time CABG were randomized 1:1 to comprehensive phase one rehabilitation plus usual care versus usual care alone (Figure 1). The comprehensive rehabilitation programme included both exercise training and a psycho-educational consultation. Four weeks exercise training began at admission and lasted until four weeks after surgery. A physiotherapist led the programme including both in-hospital and outpatient exercise training. The in-hospital programme included respiratory therapy, neck and shoulder exercises, walking, and cycling. After discharge the programme consisted of daily resistance training and walking.

The psycho-educational programme began on the day of admission and included three in-hospital nurse consultations and one outpatient telephone nurse consultation three weeks after surgery. Psycho-education involved information and education on managing life after CABG, including both physical and emotional responses. The perspective was holistic to establish a joint approach to disease management and coping inspired by Parse's Human Becoming practice methodology.[15] The consultations included a brief mindfulness intervention developed for the trial. Patients were introduced to mindfulness during the first consultation by a short exercise and instructed to use an audio mindfulness programme between consultations. The psycho-educational component was led by six nurses experienced in care of CABG patients.

According to guidelines patients in both arms of the trial received usual care involving pre- and post-operative information provided by physicians, nurses and physiotherapists. Perioperative nursing included an introduction to post-operative pain and nausea medications, pain assessment, and post-operative activities.

Outcomes measures

Adherence to the intervention was defined in the protocol as completing at least 75% of the exercises, mindfulness sessions and consultations.[16] However, only one participant adhered to the programme at that level. Consequently adherence was accepted if at least 50% of the exercise sessions and psycho-educational consultations were completed. The argument for changing adherence was pragmatic. Adherence to the exercise training intervention was evaluated by the patients' reported exercise diary and by the psycho-educational intervention recordings obtained at each consultation. The number of sessions depended on the hospital length of stay.

Statistical methods and strategy of analysis

Baseline sociodemographic and clinical data differences between adherent and non-adherent patients were tested using Pearson χ^2 test for categorical variables. To test association between non-adherence to exercise training and sociodemographic and clinical data, multivariate logistic regression were used to estimate odds ratio (OR) for training during hospitalization and training after discharge adjusted for age, sex and LVEF. The sociodemographic data age, occupational status and educational level, NYHA class, and LVEF were dichotomised. Data were analysed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

Patients gave their informed written consent after receiving verbal and written information. All data were treated in confidence and patients were assured anonymity. The trial followed the recommendations of the latest Declaration of Helsinki and was approved by the regional Ethics

Committee (no. H-4-2014-109) and the Danish Data Protection Agency (no. 30-1309). The trial was registered at ClinicalTrials.gov (ID NCT02290262).

RESULTS

Non-adherence related to sociodemographic and clinical baseline data see Table 1.
In the experimental group 48 (31%) were non-adherent to the exercise training programme during hospitalization. Patients not participating in outpatient exercise training were 81 (53%) with females showing a lower value than men (20%, 4/20) in hospital with an increase to 70% (14/20) out of hospital. Non-adherence to mindfulness was 87% (132/152) in-hospital and 70% (106/132) after discharge. Male patients not using mindfulness were 112 (85%) in hospital and 92 (70%) after discharge. In contrast only 5 (3%) were non-adherence to the psycho-educational consultations of which 4 (80%) were men.

Baseline sociodemographic data and clinical characteristics of the experimental group tested for adherence/non-adherence differences are presented in Table 2. Non-adherence during hospitalization was associated with educational level and with diabetes. Occupational status and use of beta-blockers during hospitalization were also different among adherent and non-adherent patients to exercise training. After discharge differences in the use of anti-diabetic and analgesic medication were found, while there were no differences in age, sex, NYHA class and LVEF.

Those patients who had obtained a university degree (xx years) were more adherent than others (odds ratio=3.14, (95% confidence interval (CI); 1.16-8.51), p=0.02) adjusted for age, sex and LVEF (Table 3) and diabetic patients were more non-adherent to exercise training after discharge than patients without diabetes (3.74 (1.54-9.08), p=0.004). Accordingly, the use of anti-diabetic medication was associated with non-adherence to exercise training after discharge (5.49 (1.78-16.97), p=0.003). Also patients with prescribed beta-blocker medication were more non-adherent to exercise training during hospitalisation than patients not using such medication (0.40 (0.17-0.97), p=0.04). Patients with normal weight were more adherent to exercise training after discharge than patient with overweight (0.37 (0.17-0.80), p=0.01).

DISSCUSSION

This study represents the largest experimental sample from a randomized controlled trial on CABG patients participating in a phase one rehabilitation programme, but two thirds of the patients did not adhere to the programme. Non-adherence to exercise training increased from in-hospital to out-patient training while non-adherence to psycho-education was low, but extremely high to mindfulness. Patients without university level education, diabetes and overweight patients demonstrated non-adherence. In summary, the adherence to cardiac rehabilitation was low which calls for new means to increase patient attendance. Some of the findings in this study are modifiable factors that need to be addressed. No literature on phase one rehabilitation describes clinical and sociodemographic factors associated with non-adherence. Therefore phase two rehabilitation is included in the discussion.

Non-adherence to exercise training was lower in-hospital than after discharge. Patients were assessed daily by physiotherapists for the first three post-operative days and presence of healthcare professionals influences patients' participation in rehabilitation.[17] In contrast the outpatients did exercise training on their own.

Adherence to the psycho-educational component was high, but mindfulness was poorly practiced between consultations. Neither male nor female patients adhered to the mindfulness component in-hospital, but male patients doubled their mindfulness activity after hospital discharge. Men and women have similar benefits from cardiac rehabilitation,[18] but women are less often referred to cardiac rehabilitation than men[19] and have a particularly low rate for participating in cardiac rehabilitation.[20] Patients participating in phase two rehabilitation has a high risk of not completing rehabilitation programmes.[21,22] This study emphasises the need for potential investigating of association between sex and non-adherence.

Belief in the efficacy of rehabilitation is a predictor of adherence.[11,13] Likewise, expectations can affect outcomes. Expectations are both positive and negative, depending on whether a patient believes that cardiac rehabilitation makes a difference.[23] Patients need to understand why rehabilitation is important and about ≥50% of prescribed sessions are not attained by patient during cardiac rehabilitation[11], and the number might even be higher. [24]

An association between overweight and not completing cardiac rehabilitation is known[25,26] and overweight can be the reason for being physically inactive. Overweight is a predictor for not completing phase two cardiac rehabilitation programme.[27] Furthermore, an association between diabetes and non-adherence to exercise training was identified. Yet, in other studies patients with diabetes seem to be more adherent to a cardiac rehabilitation programme than patients with other co-morbid diseases.[28,29] This could not be found in the current study. Finally, non-adherence could also be explained with intake of beta-blockers, as beta-blockers can have negative influence on exercise tolerance.[30]

The findings showed patients with a high educational level were more adherent to exercise training than patients without such degree as known for patient with myocardial infarction[31,32] and indicates that special attention is needed to improve adherence to cardiac rehabilitation in those patients with a low level of education. Thus, sociodemographic and medical variables impact adherence to cardiac rehabilitation.[11]

Study strengths and limitations

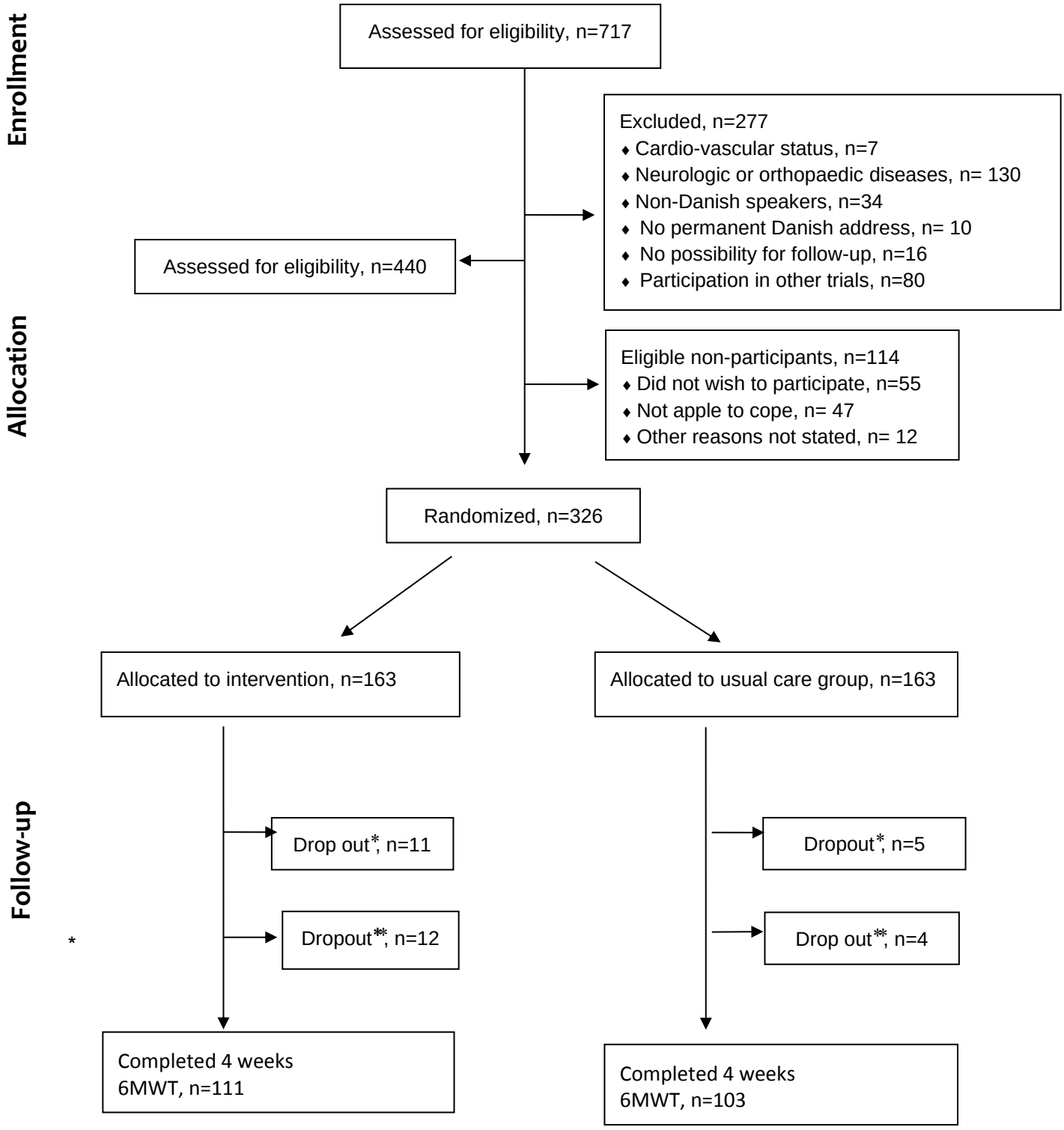
This study is a post-hoc analysis based on phase one rehabilitation for CABG patients. The sample reflects the sex ratio in the CABG population with fewer females which affects statistical power to address sex issues. Patients were included consecutively in an unselected CABG population with a reasonable number of exclusion and inclusion criteria securing external validity. The trial applied central stratified randomisation securing against selection bias and blinded assessment statistical analysis, reducing detection and interpretation bias. There was a relatively high inclusion rate to the trial. Patients participating in a clinical trial might be affected in terms of their physical and mental health by contact with health professionals.

IMPLICATIONS

The study showed the need for examining ways to increase adherence to phase one rehabilitation after CABG. The level of non-adherence to the exercise training programme was lowest during hospitalisation. The consultation part of the psycho-educational approach made sense for the patients. An explanation could be the holistic approach in which the patients were involved in

deciding topics/items for the consultation and making decisions. In contrast, non-adherence to the mindfulness component was high both in hospital and after discharge. Low adherence level might indicate importance of profound instructions and follow-up. The findings regarding educational level, overweight and diabetes should receive attention combined with the use of psycho-educational consultation when designing interventions in order to increase adherence in phase one rehabilitation after CABG surgery.

Figure 1. Consolidated Standard of Reporting Trials (CONSORT) flow diagram. Flow of patients in the SheppHeartCABG trial.



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**Dropout: dropped out and wanted to extract their data from the trial
***Dropout: dropped out from the trial with acceptance to use data.

Table 1. Sociodemographic and clinical baseline characteristics of the experimental group for those adherent and non-adherent to the programme.

	Total experimental group (n= 152)	Experimental adherent (n= 51)	Experimental non-adherent (n= 101)
Age in years, mean (±SD)	65 (9.1)	65 (7.7)	65 (9,7)
Male, n (%)	132 (87)	46 (90)	86 (85)
Female, n (%)	20 (13)	5(10)	15 (15)
Cohabitation status,			
Single/divorced/widowed	32 (21)	8 (16)	24 (23)
Married/domestic partner	120 (79)	43 (84)	82 (77)
Occupational status			
Active employment, n (%)	61 (41)	25(49)	36 (37)
Pensioner, n (%)	86 (57)	25 (49)	61 (60)
Early retirement, n (%)	4 (3)	1 (2)	3 (3)
Person on job release scheme, n (%)	1 (1)	0 (0)	1 (1)
Educational level			
Vocational level, n (%)	69 (45)	22 (43)	47 (47)
College, n (%)	36 (23)	11 (22)	25 (25)
University, n (%)	34 (22)	15 (30)	19 (19)
None, n (%)	2 (1)	1 (2)	1 (1)
Undisclosed, n (%)	11 (7)	2 (4)	9 (9)
Body mass index[1]			
< 18.5 (kg/m2), n (%)	1 (1)	0 (0)	1 (1)
≥ 18.5 < 25 (kg/m2), n (%)	39 (26)	22 (43)	17 (17)
≥25 < 30 (kg/m2), n (%)	64 (42)	19 (37)	45 (45)
>30 (kg/m2), n (%)	47 (31)	10 (20)	37 (37)
Undisclosed, n (%)	1 (1)	0 (0)	1(1)
Type of heart disease			
Ischemic heart disease, n (%)	40 (30)	10(20)	30 (30)
Morbus cordis artiosclerosis, n (%)	63 (41)	21 (41)	42 (42)
Others, n (%)	3 (2)	1 (2)	2 (2)
Undisclosed, n (%)	45 (30)	19(37)	26 (26)
NYHA class[2]			
NYHA class I, n (%)	44 (39)	24 (47)	20 (20)
NYHA class II, n (%)	53 (35)	14 (27)	39 (39)
NYHA class III, n (%)	31 (29)	7 (14)	24 (24)

NYHA class IV, n (%)	2(1)	0 (0)	2 (2)
Undisclosed, n (%)	22 (14)	6(14)	16 (16)
LVEF [3]			
Normal (50-70), n (%)	112 (74)	40 (78)	77 (73)
Under normal (36-49), n (%)	30 (20)	9(18)	21 (20)
Low (<35), n (%)	9 (6)	2 (4)	7 (7)
Undisclosed, n (%)	1 (1)	0(0)	1 (1)
Smoker			
Current smoker, n (%)	20 (13)	5 (10)	15 (15)
Previous smoker, n (%)	79 (52)	27 (53)	52 (5)
Non-smoker, n (%)	53(35)	19(36)	35 (33)
Diabetes Mellitus			
Type I, n (%)	6 (4)	1(2)	5 (5)
Type II, n (%)	29 (19)	4 (8)	25 (25)
Undisclosed, n (%)	1 (1)	0(0)	1 (1)
Prescribed medication			
Blood pressure-lowering drugs, n (%)	89 (59)	30 (59)	59 (58)
ACE inhibitor, n (%)	27 (18)	8 (16)	19 (19)
Beta-blocker, n (%)	43 (28)	16 (31)	27 (27)
Calcium antagonist, n (%)	33 (22)	11 (22)	22 (22)
Antiarrhythmic, n (%)	3 (2)	2 (4)	1 (1)
Antiplatelet drugs, n (%)	127 (84)	44 (83)	83 (82)
Diuretic, n (%)	27 (18)	5 (10)	22 (22)
Anti-diabetic, n (%)	24 (16)	2(4)	22 (22)
Statin, n (%)	126 (83)	45 (88)	81 (80)
Antidepressant, n (%)	9 (6)	2 (4)	7 (7)
Pain reliever, n (%)	21 (14)	2(4)	14 (14)
Sleeping medicine, n (%)	5 (3)	1(2)	3 (3)

[1]BMI; Body Mass Index; [2]LVEF Left Ventricular Ejection Fraction [3]NYHA; New York Heart Association Functional Classification

Table 2. Socio-sociodemographic and clinical baseline data related to differences in adherence and non-adherence to the separate intervention components.

Experimental group	**< 50% Exercise training during hospita-lisation** *n=48 (31%)*	**P-value**	**< 50% Exercise training after discharge** *n= 81 (53%)*	**P-value**	**< 50% Mindfulness during hospita-lisation** *n=132 (87%)*	**P-value**	**< 50% Mindfulness after discharge** *n=106 (70%)*	**p-value**	**< 50% Psycho-educational consultations** *n=5 (3%)*	**P-value**
Age in years,										
> 65 years	19 (31)	0.95	30 (48)	0.31	51 (82)	0.16	43 (69)	0.93	1 (2)	0.34
<65 years	28 (31)		51 (57)		81 (90)		63 (70)		4(4)	
Sex										
Male, n (%)	43 (33)	0.26	67 (51)	0.11	112 (85)	0.06	92 (70)	0.98	4 (3)	0.64
Female, n (%)	4 (20)		14(70)		20 (100)		14 (70)		1(5)	
Cohabitation status										
Single/divorced/Widowed, n (%)	11 (34)	0.70	21 (66)	0.15	28 (87)	0.90	20 (62)	0.32	2 (6)	0.29
Married/domestic partner, n (%)	37 (31)		60 (50)		104 (87)		86 (72)		3 (3)	
Occupational status										
Active employment, n (%)	20 (34)	0.04	27 (43)	0.05	55 (89)	0.57	44 (71)	0.78	0 (0)	0.06
Retried, n(%)	25 (30)		54 (60)		77 (86)		62 (69)		5 (6)	
Educational level										
Vocational level/college, n (%)	41 (35)	0.04	64 (55)	0.52	100 (86)	0.36	83 (71)	0.56	4 (3)	0.87
University, n (%)	6 (17)		17 (49)		32 (91)		23 (66)		1(3)	
NYHA class[1]										
Unknown, n (%)	9 (19)	0.15	12 (57)	0.64	16 (76)	0.27	17 (81)	0.23	2 (10)	0.21
NYHA class I +II n (%)	26 (26)		50 (50)		87 (88)		70 (71)		2 (2)	
NYHA class II+III, n (%)	13 (27)		19 (59)		29 (91)		19 (60)		1 (3)	
LVEF[2]										
Normal, n (%)	38 (28)	0.73	69 (51)	0.22	116 (87)	0.78	93 (69)	0.81	4 (3)	0.57
Low, n (%)	9 (50)		12 (66)		16 (89)		13 (72)		1(6)	
BMI[3]										
Normal, n (%)	12 (25)	0.71	15 (37)	0.01	36 (88)	0.83	28 (68)	0.81	28 (68)	0.84
Overweight, n (%)	36 (32)		66 (60)		96 (87)		78 (70)		78 (70)	
Diabetes Mellitus										
Yes, n (%)	10 (29)	0.83	26 (77)	0.02	29 (85)	0.76	56 (67)	0.76	1 (3)	0.90
No, n (%)	37 (31)		55 (46)		103 (87)		83 (70)		4 (3)	
Smoker										
Smoker, n (%)	7 (24)	0.38	17 (59)	0.52	26 (90)	0.62	21 (72)	0.72	0 (0)	0.27
Non-smoker, n (%)	40 (31)		64 (52)		106 (86)		85 (69)		5 (4)	

Medication[4]										
Blood pressure-lowering drugs, n (%)	27(57)	0.85	45 (51)	0.42	79 (89)	0.40	66 (74)	0.16	4 (4)	0.32
ACE inhibitor, n (%)	8 (30)	0.87	17 (63)	0.27	24 (89)	0.73	16 (59)	0.19	0 (0)	0.29
Beta-blocker, n (%)	8 (19)	0.04	24 (56)	0.70	36 (84)	0.47	29 (67)	0.70	0 (0)	0.15
Calcium antagonist, n (%)	7 (21)	0.18	18 (54)	0.81	27 (82)	0.35	14 (30)	0.10	0 (0)	0.23
Antirytmia, n (%)	1 (33)	0.83	1 (33)	0.48	3 (100)	0.51	1 (33)	0.19	0 (0)	0.72
Antiplatelet drugs, n (%)	39 (31)	0.90	62 (52)	0.46	109 (86)	0.40	89 (70)	0.84	5 (4)	0.31
Diuretic, n (%)	12 (44)	0.09	19 (70)	0.05	24 (88)	0.73	20 (74)	0.59	5 (7)	0.19
Anti-diabetic, n (%)	11 (46)	0.08	20 (83)	0.00	21 (88)	0.92	19 (79)	0.27	0 (0)	0.33
Statin, n (%)	36 (29)	0.17	67 (53)	0.95	109 (86)	0.79	88 (70)	0.95	2 (2)	0.10
Antidepressant, n (%)	2 (22)	0.60	6 (67)	0.41	9 (100)	0.23	6 (66)	0.84	0 (0)	0.57
Pain reliever, n (%)	8 (38)	0.44	10 (48)	0.58	17 (81)	0.39	14 (67)	0,74	3 (14)	0.00
Sleeping medicine, n (%)	2 (40)	0.65	2 (40)	0.54	5 (100)	0.38	4 (80)	0.61	0 (0)	0.68

[1]NYHA; New York Heart Association, [2]LVEF; Left Ventricular Ejection Fraction, [3]BMI; Body Mass Index, [4]Tested for differences in non-adherence/adherence to medication to the separate intervention components.

Table 3. Sociodemographic and clinical baseline characteristics associated with training during hospitalization and training after discharge in CABG-patients participating in a four weeks comprehensive rehabilitation programme. Univariate and multivariate factors associated with training during hospitalization) and training after discharge.

	Exercise training during hospitalization				Exercise training after discharge			
	Unadjusted		Adjusted[1]		Unadjusted		Adjusted[1]	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age								
< 65 years	0.98 (0.49-1.97)	0.95	0.91 (0.44-1.86)	0.08	0.71 (0.37-1.37)	0.31	0.72 (0.37-1.40)	0.34
>65 years	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Sex								
Male	1.93 (0.61-6.13)	0.26	1.82 (0.56-5.80)	0.31	0.44 (0.16-1.22)	0.11	0.43 (0.15-1.20)	0.11
Female	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Cohabitation status								
Single/divorced/widowed	1.18 (0.51-2-68)	0.70	1.58 (0.65-3.84)	0.31	1.91 (0.85-4.30)	0.12	1.83 (0.78-4.31)	0.16
Married/domestic partner	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Occupational status								
Active employment	1.22 (0.53-2.80)	0.63	1.13 (0.48-2.68)	0.78	0.51 (0.27-0.99)	0.05	0.54(0.24-1.20)	0.13
Retried(1)	1.00 (ref		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Educational level								
Vocational level/college	2.60 (1.01-6.79)	0.05	3.14 (1.16-8.51)	0.02	1.28 (0.60-2.724)	2.71	1.23 (0.57-2.68)	0.60
University(1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Diabetes Mellitus								
Yes	1.10 (0.48-2.52)	0.83	0.96 (0.41-2.26)	0.93	0.27 (0.112-0.64)	0.003	3.74(1.54-9.08)	0.004
No (1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
NYHA class[2]								
NYHA class I +II	1.10 (0.35-3.34)	0.87	1.24(0.38-4.00)	0.72	0.91 (0.30-2.78)	0.87	1.27 (0.39-4.07)	0.69
NYHA class II+III	0.49 (0.21-1.14)	0.10	0.50 (0.21-1.21)	0.13	0.70 (0.31-1.57)	0.83	0.81 (0.35-1.88)	0.62
Unknown	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
LVEF[3]								
Normal	0.39 (0.15-1.07)	0.07	0.41 (0.15-1.12)	0.08	0.53 (0.19-1.50)	0.23	0.48 (0.167-1.36)	0.17
Low	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	

BMI[4]								
Normal	0.90 (0.41-1.97)	0.78	1.04 (0.46-2.32)	0.92	0.39 (0.19-0.82)	0.01	0.37 (0.17-0.80)	0.01
Overweight	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Smoker								
Smoker	0.66 (0.26-1.67)	0.80	1.36 0.52- 3.56)	0.53	0.77 (0.34-1.74)	0.77	1.39 (0.59-3.28)	0.45
Non-smoker	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Medication								
Blood pressure-lowering drugs	0.94 (0.46-1.88)	0.85	0.87 (0.43-1.78)	0.83	0.76 (0.40-1.47)	0.42	0.76 (0.39-1.48)	0.43
ACE inhibitor,	0.92 (0.37-2.30)	0.87	0.81 (0.31-1.10)	0.65	1.62 (0.69-3.81)	0.27	1.81 (0.75-4.36)	0.19
Beta-blocker,	0.41 (0.17-0.97)	0.043	0.40 (0.17-0.97)	0.04	1.15 (0.58-2.34)	0.69	1.27 (0.61-2.62)	0.53
Calcium antagonist,	0.39 (0.17-0.93)	0.39	0.42 (0.22-1.41)	0.22	1.10 (0.51-2.39)	0.81	1.13 (0.51-2.49)	0.76
Antiarrhythmic,	0.79 (0.70-9.0)	0.85	0.56 (0.08-10.87)	0.94	0.43 (0.38-4.87)	0.50	0.27 (0.20-3.76)	0.33
Antiplatelet drugs,	0.94 (0.37-2.37)	0.89	0.90 (0.34-2.32)	0.82	0.72 (0.30-1.73)	0.46	0.76 (0.31-1.85)	0.54
Diuretic,	0.49 (0.20-1.14)	0.10	1.76 (0.68-4.54)	0.25	2.41 (0.98-5.92)	0.054	1.96 (0.74-5.19)	0.17
Anti-diabetic,	2.16 (0.89-5.27)	0.10	2.10 (0.84-.5.16)	0.11	5.49 (1.77-16.97)	0.003	5.49 (1.78-16.97)	0.003
Statin, n (%)	0.54 (0.23-1.30	0.17	0.49 (0.20-1.19)	0.13	1.03 (0.44-2.40)	0.95	0.97 (0.42-2.27)	0.95
Antidepressant, n (%)	1.60 (0.32-8.04)	0.57	0.64 (0.12-3.47)	0.61	0.55 (0.13-2.29)	0.41	1.81 (0.44-7.53)	0.41
Pain reliever, n (%)	1.45 (0.56-3.78)	0.44	1.81 (0.66-5.00)	0.25	1.30 (0.51-3.27)	0.57	0.76 (0.30-1.93)	0.58
Sleeping medicine, n (%)	0.66 (0.11-4.10)	0.66	1.80 (0.28-11.33)	0.53	1.74 (0.28-10.74)	0.55	0.58 (0.09-3.72)	0.56

[1] Adjusted for age, sex and Left Ventricular Ejection Fraction (LVEF), [2]NYHA; New York Heart Association [3]LVEF Left Ventricular Ejection Fraction [4]BMI; Body Mass Index

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