CABGpreHAB

Homebased multimodal prehabilitation (CABGpreHAB) for elective patients awaiting CABG surgery – a feasibility study protocol.

Project identification H-24070198/ tillægsanmeldelsesnr: 116943

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List of abbreviations and definitions

AF	Atrial fibrillation
AMI	Acute myocardial infarct
AE:	Adverse event
BMI:	Body Mass Index
BIA:	Bio electrical Impedance Analysis
CABG:	Coronary Artery Bypass Grafting
CAD:	Coronar artery disease
CR:	Cardiac rehabilitation
$DAOH_{30}$	Days alive out of $hospital_{30}$
HRQoL:	Health related quality of life
ICU:	Intensive care unit
ICU-LOS:	Intensive care unit – length of stay
IHD:	Ischemic heart disease
LOS:	Length of stay
MDT:	Multi-disciplinary team conference
MI	Myocardial infarct
NRT:	Nicotine replacement therapy
NYHA:	The New York Heart Association
PAM^{13}	Patient activation measure
PCI:	Percutaneous coronary intervention
PHQ-4	Patient Health Questionnaire for depression and anxiety
QoL:	Quality of life
RCT:	Randomized clinical trial
SD:	Standard deviation
SOC-13	Sense of coherence -13
STAI	The State-Trait Anxiety Inventory
UC:	Usual care
6MWT:	6-minute Walk Test

1. Introduction and background

1.1 Introduction

Advanced age, frailty, comorbidity and physical inactivity are often present in patients with ischemic heart disease (IHD) awaiting coronary artery bypass graft surgery (CABG) surgery.[1] These characteristics, as well as the physiological impact of having surgery are significant homeostatic disturbances where patients postoperatively suffer from physical symptoms and a lack of a return to independence.[2,3] Cardiac surgery invariably induces varying degrees of physiological stress, impacting multiple organ systems, and imposes psychological burden.[4] As increasing age, patient complexity and comorbid burden grow more common in patients undergoing cardiac surgery, innovative strategies are required to alleviate the risk of adverse outcomes.[5] Strategies to improve outcomes from surgery and accelerate return to baseline levels have traditionally focused on the intra-and postoperative period, nevertheless the waiting period before surgery might offer an opportunity for improving the safety and outcome of the surgical intervention and improve patients' motivation in postoperative rehabilitation and recovery time.[6,7]

1.2 Background

IHD constitutes a significant cause of mortality and morbidity globally, and accounts for over four million deaths annually in Europe, placing a great strain on healthcare resources.[8,9] In Denmark, cardiovascular diseases account for the death of one in five individuals, representing the second leading cause of mortality in the country.[10,11] Specifically, IHD was the predominant cardiovascular disease leading to death among Danes in 2021, with an estimated 12,000 deaths attributed to cardiovascular diseases each year.[12] The prevalence of IHD escalates with advancing age and is notably higher in men compared to women, including within the elderly population. In Denmark, approximately 163,000 individuals are currently living with IHD, and approximately 12,000 new cases are diagnosed annually.[13] The economic burden of IHD is substantial, with annual costs for treatment, care, medication, and lost productivity estimated at approximately 5.5 billion DKK. [14,15] IHD results from atherosclerosis in the coronary arteries, reducing blood flow to the heart muscle. This condition, also known as coronary artery disease (CAD), causes arterial narrowing, which can lead to angina, blood clots, and myocardial infarction (AMI), commonly known as a heart attack.[16] Diabetes, hypertension, and dyslipidemia are known to be major cardiovascular risk factors influenced by unhealthy lifestyle behaviors such as smoking, alcohol consumption, physical inactivity, and a diet high in calories and trans-fat acid. Smoking known as one of the main risk factors for developing IHD causes every year 3000 new cases of IHD in Denmark.[17] An unhealthy lifestyle plays a fundamental role in the development of cardiovascular disease (CVD), requiring emphasis and attention,[18] while impacting both health outcomes and quality of life. Importantly, these risk factors are modifiable, offering substantial potential for reducing CVD risk through both primary and secondary prevention strategies.[9] Standard treatment in multivessel disease

in patients with IHD is revascularization by coronary artery bypass graft (CABG) surgery, a well-recognized, treatment to relieve symptoms of angina, improve exercise capacity, quality of life and survival.[19,20] In 2021 a total of 1195 isolated CABG-procedures were performed at the four heart surgery centers in Denmark.[21] Out of these were 580 carried out at The Department of Cardiothoracic Surgery at Rigshospitalet, either as an elective or acute procedure.[22] CABG is acknowledged as "state of the art,"[23,24] and is one of the most frequently performed cardiac surgeries in the Western world associated with better long-term survival compared to PCI in most regions in the world.[25] Despite advances in surgical techniques, anesthesiology and perioperative care[4] postoperative complications, including infections, hemorrhage, arrhythmias, graft failure, atrial fibrillation, pneumonia, renal injury, and cerebrovascular events, are associated with an elevated risk of both early and late mortality and all-cause rehospitalization, particularly within 90 days of CABG.[26]

1.2.1 Waiting for elective CABG surgery

Most patients scheduled for elective CABG surgery wait at home and undergo little or no physical training or other interventions in the lead up to their operation. Evidence shows that patients deteriorate functionally and psychologically during this period prior to surgery.[1,27] Furthermore, studies show that the time spent waiting for cardiac surgery is a period of great uncertainty for the patient. There appears to be heightened anxiety regarding physical activity, mainly because of their current cardiac conditions or diagnosis.[27,28,29] Subsequent physical inactivity characterized by sedentary behavior and lifestyle may add to the underlying IHD and this has been recognized as one of the coronary artery disease's major risk factors.[30] In line with this results from the Heart Centre's cross-sectional study conducted in the fall of 2018 and 2019, involving 130 hospitalized cardiac surgery patients, reported low activity level during the four weeks preceding their surgery indicating sedentary lifestyle in the weeks leading up to their cardiac surgery.[31] Studies show that a decrease in physical activity quickly leads to a decline in physical fitness and reduces the physiological capacity to withstand the side effects of surgery.[27,32] Studies show that ischemic heart patients awaiting surgery often have difficulty maintaining a normal level of physical activity, which in turn leads to reduced oxygen uptake and loss of muscle mass.[30] Symptoms such as fatigue, shortness of breath, and fear of angina pain can prevent the patient from being physically active.[28,29] Additionally, anxiety and depression can contribute to reduced motivation to be physically active during the waiting period before surgery.[28] Moreover, resent research revealed that the prevalence of sarcopenia in older patients at cardiac rehabilitation (CR) after cardiac procedure is high (35 %), and remains high at follow-up (23%) and indicates correlations with poor functional capacity.[33] Ensuring that patients are in optimal nutritional health before undergoing CABG surgery is crucial, as it is an important driver for clinical outcomes in this population. Malnutrition, defined as an unintended nutritional intake imbalance (not necessarily a decreased intake),

is evident in 20 % of patients before cardiac surgery associated with increased morbidity and mortality.[34,35] Malnutrition before surgery has been associated with longer length of stay (LOS) in the intensive care unit (ICU) and higher rates of postoperative cardiovascular and infectious complications.[36,37] Further smoking and alcohol overconsumption are well known risk factors for a complicated recovery after CABG-surgery including delayed wound healing, pulmonary complications, and mortality.[38] Moreover preoperative alcohol abuse and misuse are likely causes of subclinical myocardial dysfunction, immunosuppression, and decreased hemostasis – increasing the risk of hemodynamic instability, infection, and bleeding.[39,40]

1.2.2 Recommendation and guidelines

The adoption of routine preoperative optimization strategies for patients awaiting CABG surgery has so far been limited although the Health Authority's "Recommendations for Cross-Sectional Pathways for People with Heart Disease," suggest that the multi-diciplinary team (MDT) conference's conclusion should also include a plan for preoperative preparation to improve postoperative outcomes and increase rehabilitation potential.[41] In Denmark, patients have historically been waiting weeks for heart surgery but it fluctuates. Patients are called for heart surgery approximately two to four weeks before, where they either remain hospitalized or are discharged home during the waiting period. The patient receives written informational material about the process before and after CABG surgery. For patients who are fully examined and referred for CABG surgery, there will be an intermediate period. In this period it is recommended that the patient is prepared for the procedure and that the rehabilitation potential is strengthened through physical activity, thereby reducing the loss of function before subsequent rehabilitation. In addition to optimization of medication and chronic conditions, patients should be offered, smoking and alcohol cessation, nutritional support, and physical training according to individual need.[41]

Evidence suggest smoking cessation at least four weeks before CABG surgery reduces the risk of major postoperative pulmonary complications such as reintubation, atelectasis and pneumonia.[42] The reccomendations by The Danish Health authority is smoking cessation six weeks before surgery.[43] Similar to smoking cessation, abstinence from alcohol is not treated as a prerequisite for surgery, but reccomendations from the Danish Health Authoriry recommend zero alcohol intake four weeks before surgery.[44] The European Society for Clinical Nutrition and Metabolism guidelines recommend an increased intake of protein before surgery to reduce the physiological stress response after surgery.[45]

1.2.3 Prehabilitation in patients with IHD awaiting elective CABG surgery.

Prehabilitation is a newly introduced term that reflects a proactive process of enhancing an individual's functional capacity between diagnosis and scheduled surgery, intending to improve the patient's capacity to withstand the upcoming physiologic stress of surgery and thus avoid complications.[46] This period of awaiting

surgery is proposed as a "window of opportunity" to address poor nutritional status, low physical fitness, and high emotional distress.[47,48] The role of multimodal prehabilitation combining exercise training, nutritional optimization, and psychological support, in patients with IHD awaiting CABG surgery is sparse[49] and unknown in a Danish setting. We conducted a scoping review[50] of prehabilitation in elective CABG surgery patients in accordance with JBI methodology for scoping reviews,[51,52] in May 2023. We updated the systematic literature search in Medline (PubMed), Embase (Ovid) and Cochrane Central in February 2024 to identify new studies on the topic. This scoping review[50] examined prehabilitation interventions to optimize outcomes after elective CABG surgery and found that available evidence is mostly based on small studies with high heterogeneity. Prehabilitation before CABG-surgery has been described as a combination of exercise training, education, and social support affecting patients` physical and psychological readiness for surgery intended to reduce postoperative complications and LOS.[6,53,54] To ensure that patients undergoing elective CABG surgery benefit from prehabilitation, there is a need for methodologically rigorous clinical trials and comprehensive knowledge synthesis. These efforts are necessary to identify optimal strategies for patient selection, intervention design, adherence, and the duration of interventions.[50] Additionally, existing evidence indicates that prehabilitation programs should be tailored and centered around individual patient needs.[55] Recently a meta-analysis examining the effects of exercise-based prehabilitation in cardiac surgery patients on various perioperative outcomes, as compared to standard care, demonstrated significantly improved post-surgery six-minute walking distance, reduced LOS, and a decreased risk of postoperative atrial fibrillation (AF) in patients aged 65 years or younger.[7] Furthermore a systematic review confirmed improvement in functional capacity and declines in in postoperative complications and LOS.[56]

This support prehabilitation as integrated into cardiac surgical planning[57] towards optimizing patients before surgery and potentially enhance surgical outcomes. However, it also concludes that the ideal prehabilitation regimen remains uncertain, particularly in terms of the significance of dietary modifications and psychological preparations for surgery, the benefits of which are not yet fully understood in cardiac surgical patients.[57] Nevertheless, a formalized prehabilitation program focusing on prehabilitation for cardiac surgery patients has not yet been established in Denmark. We propose that patients awaiting elective CABG surgery who receive a home-based multimodal prehabilitation intervention, in addition to usual care (UC), will show improvements in physical activity, functional capacity, mental health, and quality of life postoperatively. These improvements may also positively impact health behavior, health outcomes, length of hospital stay, and days alive out of the hospital after surgery. Additionally, as far as we know no previous studies have investigated a home-based multimodal prehabilitation intervention program within this patient population in Denmark, while recent findings in a scoping review[50] provides a comprehensive summary of strategies that will be applied when developing a prehabilitation program for patients awaiting elective CABG surgery for

optimizing physical capacity, lifestyle behaviors, mental health, and nutritional status in preparation prior to CABG surgery.[50] Before a larger randomized controlled trial (RCT) can be conducted, a feasibility study is required to determine if a larger trial is possible, and if so, outline the optimal design features.[58] It can be described as complex interventions according to the UK Medical Research Council, why conducting a feasibility study as part of the process from developing to implementation is recommended.[59]

2. Study aim and objectives

This CABGpreHAB feasibility study is conducted to evaluate the feasibility of delivering a homebased multimodal prehabilitation intervention for patients awaiting elective CABG surgery with the purpose to optimize a subsequent full-scale RCT:

2.1 Primary objective

The primary objective of this feasibility study is to determine if it is feasible for patients awaiting elective CABG surgery to participate in a preoperative homebased multimodal prehabilitation intervention. We will evaluate this through completion of the following objectives:

- Assess the proportion of eligible patients that are recruited into the study.
- Assess the suitability of inclusion and exclusion criteria by examining recruitment data.
- Explore reasons for non-consent to study participation.
- Assess the acceptability of the study to patients by measuring recruitment and retention to the study and thorough qualitative interview responses.
- Assess the acceptability of the intervention through qualitative interviews and retention rates during the study.
- Assess adherence to and completion of the intervention (i.e. do participants adhere and work through all components of the intervention) and explore engagement and satisfaction with the interventions by qualitative interviews.
- Assess the proportion of patients lost to follow-up after study entry.
- Assess safety of the interventions.
- Explore the appropriateness of outcome measures, completion rates and assess response to questionnaires through qualitative interviews.
- Evaluate the logistics of delivering a home-based tele-exercise training intervention through qualitative interview responses from both health care professionals and patients.
- Determine the “prehabilitation window” (length of time between MDT-conference and CABG surgery)

2.2 Secondary objective:

The secondary objectives will evaluate if the multimodal prehabilitation intervention has an impact on preoperative and postoperative outcomes. For this we will collect data on study outcomes to assess levels, variation, and changes over time, which can inform sample size for the future RCT, as shown in **Table 1**. section 7.2

3. Method

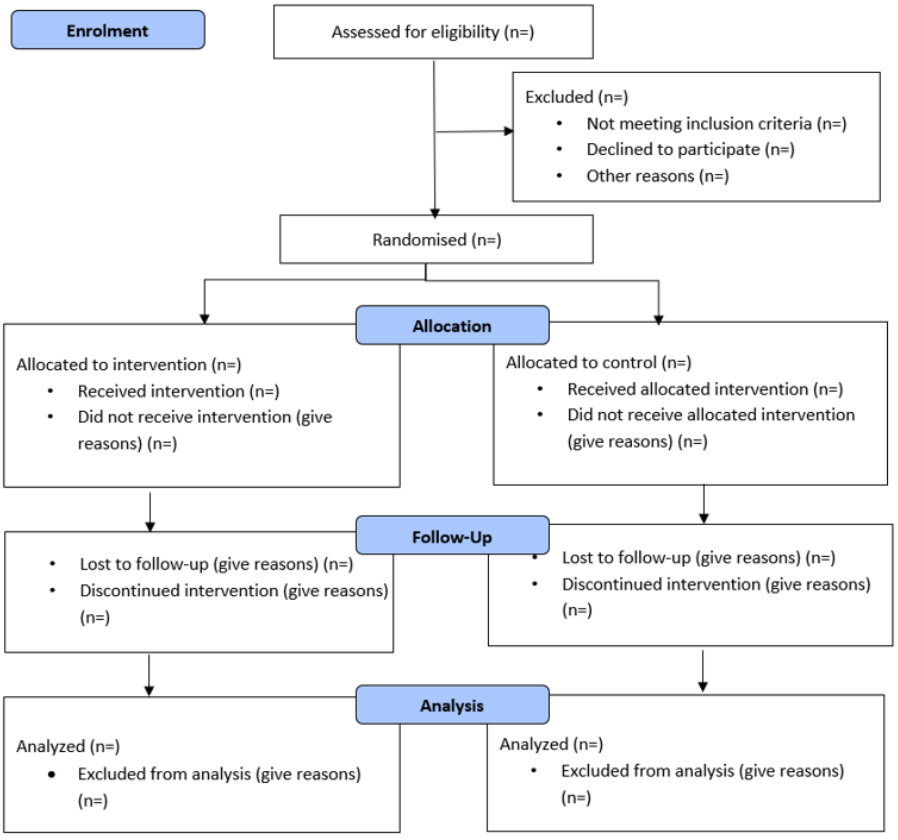
3.1 Study design

The CABGpreHAB feasibility study is designed as a randomized pilot study, aiming to assess the feasibility of a multimodal prehabilitation intervention plus usual care versus usual care alone in patients awaiting elective CABG surgery. It is an investigator-initiated study designed as an open-label, single-center randomized controlled feasibility study (allocation ratio 1:1) with blinded outcome assessment, designed to assess the method proposed for use in a larger RCT. This protocol follows guidance from Standard Protocol Items: Recommendations for interventional Trials (SPIRIT).[60] The CABGpreHAB study will be registered at www.ClinicalTrials.gov before initiation.

3.2 Inclusion and screening procedure

Patients referred to elective CABG surgery who are deemed eligible due to inclusion criteria will be identified and assessed for eligibility by the responsible surgeon after the MDT-conference as shown in **Figure 1.**

Figure 1. CONSORT[61] diagram to illustrate flow of participants through the study.



3.3 Randomization

Following baseline assessment, randomization will occur in a 1:1 ratio, stratified by age, gender (men, women), and EuroSCORE (indicative of disease severity), assigning participants either to the intervention group or to usual care. Randomization is completed using the web-based tool Randomizer for Clinical Trials.

3.4 Blinding

Due to the nature and conditions of prehabilitation, the interventions are open, making it impossible to blind the interventions to the staff and patients.[61] However, all physical testing, data collection, and administration will be conducted by blinded staff. Statistical analysis of outcomes and the conclusions derived from these analyses will also be performed in a blinded manner. The study results will be analyzed by an independent statistician, and the research group will interpret the results. The conclusions will be prepared in two versions before the allocation code is broken, with each version assuming alternately that one arm is the intervention: one version will assume that arm A is the intervention, and the other will assume that arm B is the intervention.

3.5 Participant timeline

After the MDT conference eligible patients identified from the elective waiting list for CABG-surgery are invited to participate. When they have contended, they will be allocated to either CABGpreHAB plus usual care or usual care alone. The intervention will be launched immediately after inclusion in the study. At baseline a face-to-face introduction and counselling will take place at the preoperative clinic at the Department of Cardiothoracic surgery Rigshospitalet. There will be assessment at baseline, the day before surgery (ending of the intervention period) and on day 30 post surgery. All study participants will wear the accelerometer from the screening phase until the day preceding the procedure, and again postoperatively until the day of discharge and for 30 days thereafter as illustrated in **Figure 2.**

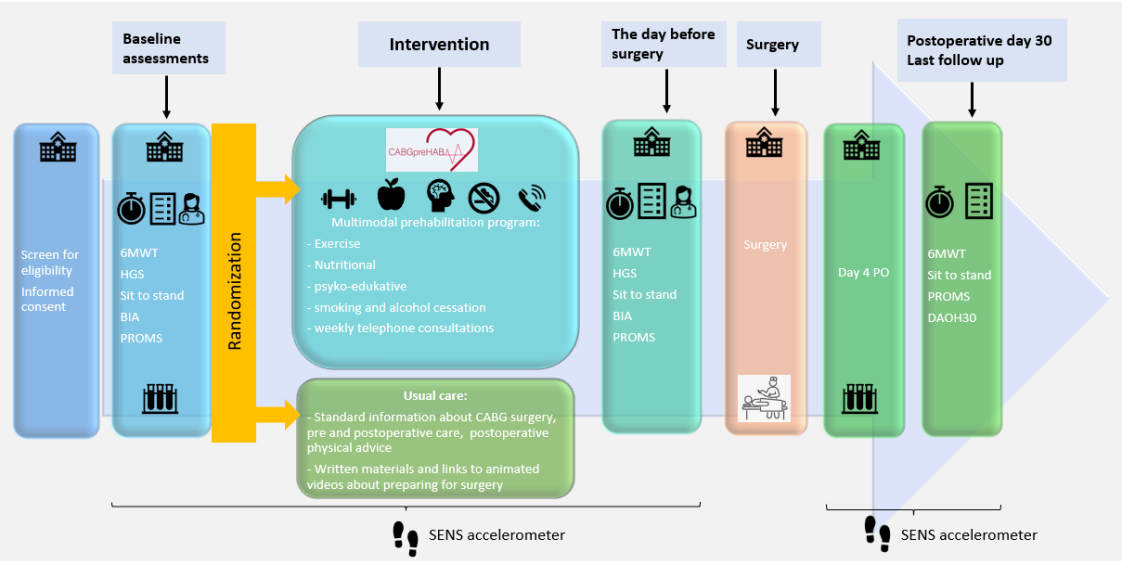


Figure 2. Graphical illustration of the study design

3.6 Sample size and power

As the primary aim of this study is to evaluate feasibility, there is no formal requirement for a formal power calculation.[62] Sample sizes between 24 and 50 have been recommended.[63,64] A sample size of 25 patients in each group was chosen as it seems reasonable to provide outcome data in a small sample, and at the same time a sample size large enough to investigate the additional aspects that are being assessed for feasibility[65] informing a future power calculation for a full-scale RCT.

4. Selection and allocation of participants

Following the MDT conference in the department of Heart and Lung Surgery, Rigshospitalet the responsible surgeon screen for eligibility by comparing patients' referral against the inclusion and exclusion criteria as described in this protocol section 4.1. If the patient is deemed eligible after screening, they will receive an invitation in e-Boks to be contacted for a brief information about the study. If they accept this invitation, the patient will be contacted by telephone by a responsible clinician in the project, and if the patient is interested to hear more, written information material about the study will be send by e-Boks or regular post. The patient will be informed that participating is voluntary, that they have the right to bring a bystander for the oral information, which will take place when they meet for the planned visit in the pre-clinic some days later. If patients haven't got the invitation about information in E-boks the responsible surgeon will introduce the study for eligible patients and present patients with the written information at the meeting in the pre-clinic . The oral information will be given with no external interruptions and will be given in a language easily understood without technical or value laden terms. The patient will receive a full explanation of the study design and study procedures, and information about usual care. This information interview is performed by the principal investigator or in her absence by a designated delegate. Consent to participation is given on the basis of written and oral information. Prior to consent, it must be ensured that a potential participant has been given sufficient time to consider his or her participation and minimum 24 hours. However, potential participants can sign earlier if they wish. An informed consent form must be signed and dated by the participant prior to participation in the trial. A copy of the form is provided to the participant. The principal investigator and her designated delegates can receive the signed consent form. When the written informed consent is received, the study specific procedures such as test, randomization and other study related procedures will take place.

Patients will be eligible if they comply with the inclusion criteria in line with previously used criteria.[66,67] Exclusion criteria are listed below.

4.1 Inclusion criteria

- Planned to have elective isolated first-time CABG surgery.
- 18 years or older
- Two weeks or more prior to surgery
- Speaks and understands Danish.
- Gives written informed consent.

4.2 Exclusion criteria

- Patient with unstable angina pectoris and/ or MI during the last two weeks.
- Left main stem stenosis >50%
- Left ventricular ejection fraction < 35%
- Significant ventricular arrhythmia
- Orthopedic or neurologic preconditions precluding exercise training.
- Inability to attend the prehabilitation program due to physical limitations.
- Patients who have cognitive deficits that would disqualify prehabilitation.
- Severe heart failure, NYHA Class IV
- Lack of capacity to consent

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant

Participants in the study can freely withdraw their informed consent at any time and be treated according to the department's standard procedures. Patients will be excluded from the study if they withdraw their consent and will be informed that withdrawal from the study will not affect their future treatment. If possible, the reason for withdrawal will be obtained and reported. The patient is not obligated to give reasons for withdrawal. Patients who leave the study will be asked for permission to continue to collect data and to use already collected data. If the patient gives permission, he/she will be included in the final analysis. Only if the patient refuses the use of already collected data, all data relating to him/her, will be destroyed.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

The project team reserves the authority to halt the participation of any individual involved in the study, primarily in response to adverse events and concerns regarding safety. Additionally, the principal investigator retains the right to conclude the study. Grounds for such termination may encompass inadequate adherence to the study's protocol, challenges in participant recruitment, deviations from the established timeline, and administrative discrepancies.

5. Study site and personnel

5.1 Study site and setting

The CABGpreHAB feasibility study will be carried out in The Department of Cardiothoracic Surgery at The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen.

5.2 Study personnel

In the CABGpreHab study, the interventions are administered by trained specialist nurses specializing in heart surgery and specialized physiotherapists. To execute the interventions effectively, the nursing staff will undergo skills enhancement through training courses and supervised practice, particularly given the nature of the psychosocial interventions involved. The physical exercise program is initiated by physiotherapists with specific expertise in exercise training for patients awaiting CABG surgery. The principal investigator is Ida Elisabeth Højskov, Sune Damgaard is primary responsible physician/surgeon and Dorte Bæk Olsen is project leader.

6. Study interventions

All included patients will receive standardized surgical processes and perioperative care under existing protocols for preoperative patient education.[23,68]

6.1 Control intervention/Usual care

Participants assigned to the control group will receive usual care including standard information about CABG surgery, pre- and postoperative care, and postoperative physical activity advise.[68] Patients are informed about date of surgery along with information in secure mailbox (e-Boks) after the MDT conference. The date for surgery is tentative, and there will always be some risk of postponed surgery for the elective patient due to emergency heart surgery. Patients are either admitted the day before surgery or weeks before in our pre-ambulatory clinic in the Department of Cardiothoracic Surgery at Rigshospitalet. They receive written materials and links to animated videos about preparing for surgery is available for all patients undergoing elective CABG surgery.[69-71] The day before surgery the patient is informed by their heart surgeon and the last assessment and preparation for the surgery takes place in the ward. The patients have also been given information about the surgery and the postoperative period during their pre ambulatory visit weeks before surgery. This preparation includes counselling with a multi-disciplinary team, including a nurse from the department, a physiotherapist, cardiothoracic anesthesiologist, and surgeon. During this preoperative counselling session, the nurse assesses nutrition status, as well as smoking and alcohol habits. The nurse also invites the patient to talk about the situation of being a heart patient awaiting surgery. Preoperative anxiety is assessed with The Apais tool to encouraged patients to talk about uncertainty and further needs for information. The nurse also provides information related to postoperative expectations such as the ICU, the

operation room, and issues related to the postoperative period in the department, such as pain, arrhythmia, pulmonary issues, coughing, early mobilization and so on. Furthermore, if patients are consuming high levels of alcohol, we contact the "social care nurse at Rigshospitalet", who can plan with the patient to be abstinent before surgery. This preoperative preparation where patients and significant others are invited to participate is a well-established practice in the Department of Cardiothoracic Surgery following protocols and guidelines in the field.[23,68]

6.2 Multimodal prehabilitation interventions (CABGpreHAB)

Patients randomized to the multimodal prehabilitation programme will besides usual care as described above receive preoperative interventions that consists of:

6.2.1 Exercise intervention

During the initial assessment patients will be taught how to perform the exercises to complete at home during the intervention period. The exercise intervention is supervised by skilled physiotherapists and delivered via Infinity Connect app and a webcam[72] at Rigshospitalet to a group of approximately 4–8 patients who exercise at home and communicate via a tablet. Each session is 60 min, i.e., 40 min of exercise and 20 min of patient education, three times per week for the prehabilitation period. The exercises used in the program are identified and selected amongst exercises used in previous exercise intervention studies and involves larger muscle groups with 50/50% exercises for upper and lower extremities, respectively.[73] The exercises are executed in four sets to achieve peripheral muscle fatigue and secondary dyspnea/breathlessness. Each set is carried out in a predefined period of 20 to 40 s with a maximum number of repetitions performed, i.e., 8 to 25 repetitions depending on the patients exercise capacity and motivation, but with the aim of 12 to 20 repetitions.[73,74] In practice the training intensity is determined by using the self-rated Borg Scale, moderate intensity RPE 11-15, 50-60% VO_2peak.[74]

The first week serve as a familiarization phase with the purpose to adapt to exercising, adjusting, and optimizing load and to avoid musculoskeletal overload injuries. Monitoring physical activity and providing motivation through phone calls weekly will be enhanced by incorporating a novel accelerometer system, offering activity level feedback (SENS innovation)[75] to guide healthcare staff. Participants in the intervention will be instructed to perform daily exercise tasks such as brisk walking and sit-stand exercises. Additionally, motivational phone calls will be made to participants in the intervention group, while healthcare staff will receive feedback on these patients, aiding to guide them in achieving their activity goals. Patients will also be asked to complete a diary describing physical activity outside the programmed session, included in a patient booklet. All study participants will wear the accelerometer from the screening phase until the day preceding the procedure, and again postoperatively until the day of discharge and for 30 days

thereafter.[76,77]The technology platform provided to the patients includes a tablet and an accelerometer device to facilitate exercise training sessions and data collection.

6.2.2 Nutritional intervention

The aim of the nutritional part of the intervention is avoidance of sub-optimal pre-operative nutritional intake. All participants will receive the pre-operative nutritional advice as part of usual standard of care. In addition, all participants in the intervention arm will be encouraged to follow these guidelines as part of the adherence support. The usual care regarding nutritional advice in the period before CABG surgery include weight maintenance, intake of energy and protein rich food items as well as micronutrients with focus on a daily intake of B and C vitamins. The patients are advised to plan their meals if the appetite is low to ensure a sufficient intake of protein and energy before the surgery which is considered more important in the pre-operative period than following the general advice regarding consumption of vegetables etc. Energy and protein rich supplements are also suggested for patients with low appetite to promote an energy and protein rich diet in the pre-operative period. Nutritional risk will be assessed at baseline and preoperatively using the NRS-2002 total score which is already part of usual care.[78] After screening with NRS-2002 patients are categorized as being nutritionally at-risk patients (score>3) or nutritionally not at risk (score<3) according to the total score obtained. Patients not at risk for malnutrition will be provided with nutritional advice according to usual care. In addition to usual care regarding nutrition, not at-risk patients will receive encouragement to follow the nutritional advice as part of adherence support throughout the intervention period. I addition to usual care at-risk patients will be offered protein and energy rich supplements free of charge as well as individualized advice and encouragement as part of adherence support throughout the intervention period.

6.2.3 Psycho-educative intervention

The intervention seeks to enhance preparedness for CABG surgery through individualized assessment and review of psychosocial factors that may influence treatment outcomes and quality of life. Mental health such as emotional well-being and stress reduction will serve as primary foci of this psycho-educative intervention inspired by Antonovsky' s salutogenetic theory known as Sense of Coherence (SOC).[79] The SOC is composed of three key components: comprehensibility, manageability, and meaningfulness. According to Antonovsky, a strong SOC enables individuals to view stressors as less threatening and more manageable, thereby promoting resilience and health. Depending on the patients' SOC, when going through a negative life event as living with IHD awaiting CABG surgery, the intervention aims to support in terms of understanding and involve the availability of the patients' resources to deal with these events. By identifying appropriate resources to cope with stress and encourage the patient to use these resources, making the waiting period before heart surgery more understandable, manageable, and meaningful. Involving SOC-enhancing content

in this intervention we are inspired by theory of psycho-educative programs.[80, 81] Nurses play a pivotal role in delivering psychosocial support to patients undergoing cardiac surgery[82] and in this intervention it will be provided by trained nurses, who will engage in counselling sessions aimed at equipping patients with coping strategies to mitigate stress, anxiety, and depression.[83] The preoperative baseline consultation will take place in a quiet room in the ward and last for about 30-45 minutes. An inspirational guide will form the basis for the consultations. There will be consultation: at study inclusion, and once a week (by phone) in the waiting period until the day before surgery, The participants will be given a phone number to the responsible project nurse, who can be contacted in a certain period on working days.

6.2.4 Smoking cessation intervention

In this intervention, patients will receive guidance on smoking cessation. During these sessions, a nurse will educate the patient about the detrimental effects of smoking on the development and progression of ischemic heart disease, emphasizing the negative impact of smoking on their health, particularly before surgery, where smoking cessation is strongly recommended.[84] As part of the intervention, patients will be encouraged to contact the municipal smoking cessation coordinators to arrange a meeting and receive further support. The smoking cessation program will include counselling sessions at baseline and weekly phone call sessions, along with the provision of nicotine replacement therapy (NRT). NRT will be provided in the form of transdermal patches for moderate to heavy smokers, supplemented with individualized doses of chewing gum or lozenges, following current guidelines.[85] NRT will be distributed during the baseline counselling session. The objective of the program is to achieve an 80% reduction in smoking quantity (cigarettes per day) before surgery or complete cessation.

6.2.5 Alcohol cessation intervention

The approach to support patients in zero alcohol intake before surgery is rooted in the recommendations from the Danish Health Authority and the patients are encouraged to completely avoid alcohol intake if the patient is assessed a risky drinker (drinking more than 4 alcohol items per day).[86] A simple guide of questions and advice will be developed for the adherence support to register challenges and encourage adherence to support minimizing/avoiding alcohol intake. Assessment, counseling, and support sessions will be organized with the social nurse at Rigshospitalet for patients exhibiting hazardous drinking behaviors.

After the initial face-to-face meeting in the pre-clinic participants will receive three web-based sessions with a physiotherapist and one telephone counselling with a nurse per week during the intervention period. Detailed protocols for the face-to face counselling and web-based and telephone calls will be developed before the outset of the study.

7. Study outcome measures

In this CABGpreHAB feasibility study we will explore two types of outcomes: feasibility outcomes and explorative clinical outcomes.

7.1 Primary outcome

Feasibility outcomes include:

Recruitment and retention rates. The recruitment rate will be determined by the number of individuals who participate in the study out of those who are eligible/admissible but refused to participate. First, we will evaluate the number of patients we are able to include in the study during the inclusion period. A proportion of 60% or more of patients awaiting elective CABG surgery who are eligible for the study is acceptable. Retention will be assessed by the percentage of participants who remain in the study from beginning to end of study (30 days post-surgery).

Attrition rates. Attrition is defined by the number of individuals who give consent to participate in the study but drop out before the end of the intervention period, regardless of group allocation.

Fidelity. Fidelity of delivery of the webcam-based exercise training intervention will be assessed qualitatively by 8-10 semi-structured interviews the day before surgery by a research nurse.

Adherence rates. Adherence to the interventions will be measured by using the number of telephone counselling and tele-exercise sessions delivered out of the theoretical number that could have been delivered based on the surgical wait time of each participant. Adherence to the homebased tele-exercise training sessions and telephone counselling by evaluating the number of sessions applied in the intervention group. This will be collected by patient recorded physical activity logbook, by weekly phone calls and completed by accelerometer data. Adherence with the prehabilitation program will be assessed against the target of individuals achieving > 70% of the prescribed exercise program (self-reported) + during the study follow-up with phone calls. Inclusion in the CABGpreHAB study must be attractive to at least 30% of eligible patients who meets the inclusion criteria. The interventions must be widely accepted, with at least 70% of included participants completing 70% or more of the planned sessions in the intervention group. This will be assessed by interviews addressing reasons for withdrawals from the study and at which stage of the study these occur.

Safety: Safety of the intervention will be determined based on the number and nature of adverse events (AE), which is defined as any discomfort or symptoms of angina pectoris that will prevent a patient to take part in the physical tele exercise sessions or symptoms that require medical attention. Adverse event (AE), serious AE (SAE), serious adverse reaction (SAR), and suspected unexpected serious adverse reaction (SUSAR) will be monitored during the trial counting the number of occurrences. In addition to the physiotherapist

taking note of any undesirable effect during and after the tele session or phone counselling with the project nurse, all participants are asked to report any symptoms that was not consistent with their usual physical condition presentation as a result of exercise sessions.

For a lager RCT trial to be deemed feasible, feasibility outcomes need to be attained, meaning that more than 60% of eligible patients will participate and at least 52% of the intervention group will receive more than 60% of the intended interventions.[87]

7.2 Secondary outcome

Secondary outcomes shown in **Table 1**. will assess the patients' responses to the multimodal prehabilitation programme and data will be collected on the following explorative outcomes shown in **Table 2,** measured at baseline, the day before surgery and 30 days after discharge.

Table 1. The patient related tests and outcome measures

Outcome variable	Measurement Instrument	What is the argument for this test or instrument?
		TESTS
Exercise capacity	**6MWT**	(6MWT) measures total walking distance completed in six minutes.[88] Functional exercise capacity assessed as change from baseline by using the (6MWT) according to the American Thoracic Society guidelines.[88]
Muscle strength	**30 seconds sit-to stand**	Strength and endurance in leg assessed as change from baseline by 30 sec sit-to stand test.[89]
Muscle strength	**Hand grip strength**	The Hand grip strength measures the upper-body physical function assessed by hand grip strength using a hand-held dynamometer.[90] Frailty assessed from baseline by Hand grip strength.
Body composition	**BIA**	*Bio-electrical Impedance Analysis (BIA)* estimates values for each body percentage, fat mass, fat-free mass, muscle mass and bone mass and total body water are assessed measuring bioelectrical impedance in the body using a Bioelectrical Impedance Analyzer.[91]
Nutritional status	**NRS 2002 + BMI, weight, height**	Nutritional Risk Screening 2002 (NRS 2002) screening tool is a validated tool attributes scores of different levels of nutritional status to patients based on weight loss, BMI, and food intake, considering disease severity (degree of stress metabolism) and age. It is a toll recommended for detection of undernutrition and the risk of its development in hospital settings. Nutritional status assessed as changed from baseline.[78] Body mass index BMI[92] at baseline,
Daily physical activity score	**SENS® motion accelerometer**	The SENS motion® system consist of a single-use miniature, waterproof tri-axial accelerometer, and a dedicated smart phone application. The accelerator will be placed on the lateral side of the patient's thigh at the assessment initial with a small waterproof Band-Aid. The participants will be asked to wear the SENS-accelerometer continuously for minimum four weeks during the intervention period and again post-surgery until end of follow up 30 days post index surgery. Physical activity assessed as changed from baseline by accelerator SENS innovation device.[75]
		QUESTIONAIRES
Physical activity	**Copenhagen City Heart study**	Self- reported physical activity assessed from baseline by question from Copenhagen City Heart study.[93] *A question: " How physically active are you now?"* from the Copenhagen City Heart study will be used to grade the participants physical activity in four levels (level 1-4 , i.e., 1= almost entirely sedentary, 2= light physical activity (PA) for 2-4 h per week, 3= light PA>4 h per week or more vigorous PA for 2-4 h per week, 4= more vigorous PA >4 h per week or regular heavy exercise or competitive sports several times per week.
HRQOL	**SF-12**	The SF-12 is a 12-item version of the SF-36 and is a brief, reliable measure of overall health status that generates both a physical and a mental component score. The questionnaire measures eight domains of health: physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Scores are calculated for each domain and aggregated into the mental component score (MCS) and the physical component score (PCS). The SF-12 is a suitable questionnaire in studies with large sample sizes having severe constraints on questionnaire length and in studies focusing on patient-based assessment of physical and mental health.[94] Health-related quality of life (HRQL) assessed as changed from baseline by Short Form 12 (SF-12).[94]

Heart-specific QoL	**HeartQoL**	The HeartQoL questionnaire measures health-related quality of life in patients with ischemic heart disease, specifically angina, myocardial infarction, or ischemic heart failure. The questionnaire consists of 14 items and provides two subscales; a 10-item physical subscale and a 4-item emotional subscale which are scored from 0 (poor The HeartQoL questionnaire measures health-related quality of life) to 3 (The HeartQoL questionnaire measures health-related quality of life better). A global score is available if needed. Asks patients to remember how their heart condition has bothered them in the past four weeks. The HeartQoL questionnaire measures health-related quality of life allows clinicians and researchers to (a) assess baseline The HeartQoL questionnaire measures health-related quality of life, (b) make between-diagnosis comparisons of The HeartQoL questionnaire measures health-related quality of life and (c) evaluate changes in The HeartQoL questionnaire measures health-related quality of life in patients undergoing interventions to improve patient HRQL.[95]
Anxiety	**State-Trait Anxiety Inventory**	The State-Trait Anxiety Inventory (STAI) is a widely used psychological tool designed to measure two distinct types of anxiety. STAI consists of 40 items and is divided into two sections, each containing 20 items. The State-Trait Anxiety Inventory (STAI) is a widely used psychological assessment tool designed to measure two types of anxiety in adults: state anxiety (S-Anxiety) and trait anxiety (T-Anxiety)**.** State Anxiety (S-Anxiety) reflects a temporary emotional state or condition characterized by subjective feelings of tension, apprehension, and nervousness. This type of anxiety fluctuates and is typically influenced by situational factors. The STAI measures how anxious an individual feels "right now, at this moment." Trait Anxiety (T-Anxiety) refers to a stable personality characteristic, indicating a general tendency to perceive situations as threatening and respond with anxiety across time and circumstances. It reflects a person's baseline level of anxiety in daily life. The STAI consists of 40 self-report items: 20 items assess state anxiety (e.g., "I feel calm," "I feel nervous"), and 20 items assess trait anxiety (e.g., "I am a worrier"). Respondents rate their agreement with each statement on a 4-point Likert scale.[96]
Depression	**PHQ-4**	Patient Health Questionnaire for depression and Anxiety (PHQ-4) includes four questions, scored on a 4-point Likert scale ranging from 0 (“not at all”) to 3 “nearly every day). The questions are: 1. Depression (2 items from PHQ-9): Little interest or pleasure in doing things. Feeling down, depressed, or hopeless. Anxiety: (2 items from GAD7): Feeling nervous, anxious, or on edge. Not being able to stop or control worrying. Scoring: Each question is scored from 0-3, leading to a total score range of 0-12. The total score helps to classify the overall level of psychological distress: 0-2: Minimal or none, 3-5: mild, 6-8: Moderate, 9-12: Severe.[97]
Sense of coherence	**SOC-13**	The SOC-13 (Sense of Coherence-13) is a brief version of the Sense of Coherence scale developed by Aaron Antonovsky to assess an individual's ability to manage stress and maintain health. It measures three core dimensions: 1. Comprehensibility: The extent to which life is perceived as structured and understandable. 2. Manageability: The belief that one has the resources to cope with life’s demands. 3. Meaningfulness: The degree to which life is seen as meaningful and worth engaging in. The SOC-13 contains 13 items scored on a 7-point Likert scale, with higher scores indicating a stronger sense of coherence and better stress resilience.[98]

Self-efficacy/self-management	**PAM_{13}**	The PAM_{13} (patient activation measure) is a 13-item survey, assesses an individual's knowledge, skill, and confidence for self-management. It categorizes patients into four levels based on their activation score, which ranges from a lack of understanding of the need for active participation in health (level one) to challenges in maintaining positive health behaviors over time (level four).The questionnaire consists of 13 questions, where each question is a statement. Respondents indicate on a scale from 1-4 how much they agree with the given statement (1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree). All scores are then summed and divided by the number of answered questions, resulting in a score between 13-52. The score is then placed into one of four activity levels below, where level 1 is the lowest.[99]
Smoking status	**Self-reported**	Smoking status assessed as change from baseline. The number of participants successfully quitting smoking out of all active smokers
Alcohol intake status	**Self-reported**	Alcohol intake status assessed as change from baseline. The number of participants successfully quitting alcohol consumption out of all participants consuming alcohol.
Patient characteristics	**Self-reported**	Age, gender, educational level, employment, civil status
CR status	**Self-reported**	Last follow up (30 days post index surgery) questionnaire ask about status for: Participating in CR
Other outcomes DATA		
Adverse Events	**Patient record**	Measuring outcomes related to adverse advents for ensuring patient safety
Complications PO	**Patient record**	Complications such as pneumonia, atelectasis, hemorrhage, cardiac arrythmias, delirium
ICU-LOS/LOS	**Patient record**	Indicator of how well patients are recovering post-surgery and may indicate complications.
$DAOH_{30}$	**Patient record**	$DAOH_{30}$.[100,101] Days alive and out of hospital is a composite measure that can be calculated based on available variables and proposed as a reliable surgical endpoint. DAOH integrates several clinical outcomes, including death and hospital readmission.
Biomarkers	**Patient record**	Hgb, albumin, kreatinin, CRP planned as standard blood work at baseline and post intervention.

Abbreviations: BMI: Body Mass Index; BIA: bio electrical Impedance Analysis, CR: cardiac rehabilitation; $DAOH_{30}$: Days alive out of $hospital_{30}$; HRQoL: Health related quality of life; ICU: Intensive care unit; ICU-LOS: intensive care unit – length of stay; LOS: length of stay; NRS 2002: Nutritional Risk Screening 2002; PO: post operative; PAM_{13}: Patient activation measure; PHQ-4: Patient Health Questionnaire for depression and anxiety; SF-12: Short form survey.

8. Data collection

Clinical and sociodemographic data as well as patient-reported outcome measurements will be collected for both groups at baseline, the day before surgery, and 30 days post-surgery as shown in **Table 2**.

TABLE 2 Schedule of enrollment, intervention, and assessment

Timepoint	Enrollement Allocation Eligibility	Baseline assessment	Min 2 weeks Homebased Prehabilitation	The day before surgery	Surgery	4 days PO	30 days post index surgery
	T_{-1}	T_0	T_1	T_2	T_3	T_4	
Eligibility screening	X						
Informed consent, enrollment		X					
Medical history[1], social demographics[2]		X					
Intervention + Usual care			X				
Primary Outcome							
Feasibility		X	X	X			X
Secondary Outcomes							
6MWT (functional capacity)		X		X			X*
BIA + NRS-2002 (baseline only)		X		X			
Hand grip strength		X		X			
Sit to stand (fysisk frailty)		X		X			X*
SENSE® Daily activity score		X	X	X		X	X
Copenhagen City Heart study		X					
SF-12 (HRQoL)		X		X			X
HeartQoL (Heart-specific QoL)		X		X			X
STATE-Anxiety + Trait-anxiety (baseline only)		X		X			X
PHQ -4		X		X			X
SOC-13		X					
PAM_{13}		X		X			X
Tobacco uses status		X		X			X
Alcohol use status		X		X			X
Adverse events			X				
Other Outcomes							
PO complications[3]							X
ICU -LOS /LOS							X
$DAOH_{30}$							X
Participating in CR							X
Hgb, Albumin, CRP, creatinine		X				X	

[1] Euroscore II, LVEF, NYHA class, BMI, height
[2] Age, gender, marital status, occupational status, educational level,
[3] AF, re-operation, pneumonia, delirium, deep sternal infection, stroke. *Test foretages enten på Rigshospitalet eller lokalt på hjemsygehus.
Abbreviations: $DAOH_{30}$: Days alive and out of hospital; CR: Cardiac rehabilitation; PO: postoperative; AF: Atrial fibrillation; ICU-LOS: intensive care unit length of stay; LOS: length of stay; NRS-2002: Nutrition Risk Screening; PAM_{13}: Patient activation measures; PHQ-4: Patient Health Questionnaire; SOC-13: Sense of Coherence-13.

8.1 Data from questionnaires

The questionnaires are self-administrated and will be completed electronically in REDCap a web-based data capture tool[103] which meets the data legislation for logging. The study participant will receive an email with link to a website through which questionnaires can be completed. The e-mail contains a login and password for the trial participant's access. If patients do not complete the questionnaire electronically, the paper questionnaires will be handed out to the patient, and independent study personal then enters the responses into REDCap. Participants will complete the questionnaires at all three time points: baseline, the day before CABG surgery after the intervention, and 30 days post-surgery. The filled-out questionnaires typed in REDCap and responses will be stored in a secure folder with limited access ("lovbeskyttet mappe").

8.2 Data from patient records

Preoperative relevant information, including patient name and age as well as details about the patient's heart diagnosis and medical status (such as Euroscore II, LVEF, and NYHA class), will be reviewed from the patient record (SP) without consent by the responsible heart surgeon to inform the study about eligibility of patients referred to elective CABG surgery. Additionally, and with consent, postoperative complications, such as infections and arrhythmias, along with any adverse events occurring during the intervention period, will be documented from the patient record. Information on the length of stay (both ICU-LOS and overall, LOS) and the number of days alive out of the hospital within 30 days will be calculated using data from both the patient record and Danish registers. Data will be retrieved from the national electronic record system (E-journal) by an electronic healthcare software (Epic, Madison, WI, USA), which secures a complete enrolment and follow-up as the recording is a requirement for economic reimbursement. All data is processed and stored confidentially, and personal data will always be handled in accordance with the Danish Data Protection Act and the General Data Protection Regulation. Data are stored pseudo-anonymously in a separate approved and secure database (Capital Region REDCap), which only the doctors, research assistants and project nurses of the study will access using person-specific log-in and password. An anonymous trial number are used as patient identification in the REDCap database. The key linking the study-id with the personal id is kept separately from the study data with limited access controlled by the study investigator or designee. Authority and obligations are documented in the log of delegation of responsibility in the trial. The patient's records will be reviewed by study related personnel to assess clinical and safety endpoints. The informed consent gives the investigator and possibly control authority direct access to data from the patient's journal. These are used to view information on the participant's medical condition necessary for the conduct of the study and for self-control, quality control and monitoring. The patient is informed about this and gives informed consent to this when entering the study. If a potential participant declines to participate in the project, we will request permission to collect information regarding their age, gender and current medical status pertinent to their admission for CABG surgery and only if a written informed consent is obtained.

8.3 Data from Danish registries

A register-based follow-up after 30 days will be used to evaluate $DAOH_{30}$. The study will use data from the following registers: The National Patient Register and The Causes of Death Register.

8.4 Biological material

All blood analyses are a part of usual care and the routine blood work when meeting for surgery and will be performed according to clinical standards at the hospital and therefore a research biobank will not be established.

9. Analysis

9.1 Statistical methods

Data analysis will be limited to descriptive summary statistics of the proposed endpoints, and calculation of feasibility measures, enrollment rates and dropout rates within a period. The feasibility analysis will be based on the components of process, resources, management, and scientific approach.[58] Process: number of eligible patients for enrollment; Successful recruitment rate, rate of adherence to the interventions at each time point; Rate of loss to follow up; Rates of completed questionnaires; Understanding of the questionnaires. Resources: Time to screen and consent patients, Time to conduct baseline and follow-ups; Identification of any challenges related to randomization or data collection; Identification of potential barriers of the preoperative programme. Management: Identification of any challenges related to randomization or data collection; Identification of potential barriers for the intervention. Scientific approach: Estimates of improvement in patient-reported outcomes compared to usual care, patients' response to topics and content in the programme and identification of potentially patient safety issues. As recommended for the analysis of pilot studies [58] descriptive statistics will be presented as mean and standard deviations (SD) for continuous variables and frequencies and percentages for categorial variables at baseline and follow-ups**.** Collected data on patient characteristics will be presented in tables. Continuous variables will be displayed as mean (SD), while categorical variables will be presented as number (n) and percentage (%). Descriptive statistics will be used to answer the primary study parameter of feasibility. Feasibility will be presented in tables and based on participation rate (n, %), reasons for nonparticipation (n, %, text), adherence to the prehabilitation program (%), dropout rates (%), reasons for dropout (n,%, text), adverse advents (n,%, text). The secondary aim is to evaluate the patients' responses over time in terms of physical activity, muscle strength, functional capacity, body composition, quality of life and symptoms of depression, and anxiety. A repeated measurements analysis will be used to analyze changes over time in continuous variables. *P*- values <0.05 will be considered statistically significant.

10. Ethics

10.1 Ethical considerations

The CABGpreHAB feasibility study will be conducted in accordance with the protocol after approval from the Committees on Health Research Ethics in the Capital Region of Denmark, and according to good clinical practice guidelines. This study will comply with the General Data Protection Regulation (GDPR) and the Data Protection Act. All personal data collected during this study will be handled confidentially and in accordance with EU legislation and data security regulations and legislation (GDPR). The principles of the Helsinki Declaration in its latest form, and the ICH-GCP guidelines will be followed.[103] The protocol will be registered on www.clinicaltrials.gov and registered in Privacy before inclusion of the first participant. Substantial

amendments to the protocol will not be implemented without the appropriate review and approval by the regional ethics committee and the Danish Data Protection Agency, with the exceptions of situations where it is necessary to prevent imminent danger to trial participants. In such cases, the amendment will be reported to the regional ethics committee.

10.2 Adverse events and reactions

10.2.1 Definitions

Following definitions will be used.

Adverse Event (AE): any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.[104]

Adverse Reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.[104]

Serious Adverse Event (SAE): any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.[104]

Serious Adverse Reaction (SAR): any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.[104]

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the information available to date).[104,105]

10.2.2 Risk and safety issues in the current trial

This feasibility study is expected to cause limited risks, side effects and discomfort. Patients are expected to benefit from the homebased multimodal prehabilitation program before CABG-surgery.

10.2.3 Assessment of adverse advents

The CABGpreHAB feasibility study will be performed according to the GCP guidelines and applicable regulatory requirements and legislation. The trial will be conducted according to the Act. No.593 of June 14, 2011, on Act on Research Ethics Review of Health Research Projects. The investigator will immediately notify the regional ethics committee if there, within the intervention period, occur SAEs, SARs or SUSARs. The report will be accompanied by comments on possible implications for the trial, and notification will be made within 7 days after investigator has knowledge of the event. In case of serious adverse reactions, which are results of the trial, the investigator will provide the regional ethics committee with the information required.

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.

10.2.4 Severity of adverse events

The following variables will be registered if an adverse event happens: Description of the event, beginning and ending of the event, seriousness (mild, moderate, and serious). Possible casual relation to the intervention and actions taken. This will be registered by a project employee and a physician will be involved if a serious event occurs or if required in relation to a moderate adverse event.

10.3 Risks and benefits

The interventions are expected to cause limited risks, side effects and discomfort. Patients are expected to benefit from homebased prehabilitation due to multimodal preoperative preparation before CABG-surgery improving functional capacity, reducing symptoms of anxiety and depression. Individualized and optimized preoperative care through exercise, supportive nursing counselling will be performed by experienced project nurses, physiotherapists and physicians, and patients will not experience any kind of delays or complications related to the interventions or follow-up process due to participation in the project. Before commencing the exercise components of the prehabilitation program, a physiotherapist will assess the participants' physical capacity. Previous studies have demonstrated the safety of preoperative physical exercise programs involving mild intensity training in patients scheduled for CABG surgery.[6,27,106,107] The physical training regimen will adhere to the established recommendations for physical exercise in patients awaiting CABG surgery, ensuring the safety and efficacy of the exercise program.[108,109] Standard blood sampling, which may cause slight discomfort from the needle stick, is expected as part of the procedure.

10.3.1 Risk and timing of surgery

Historically waiting time for elective CABG surgery has usually been several weeks, but it has been fluctuating between few weeks and up to months. The decision regarding the timing of surgery is typically made collaboratively by cardiologists and cardiac surgeons during multidisciplinary team (MDT) conferences.[19] This decision-making process adheres to current clinical guidelines and is influenced by waiting times dictated by local and regional healthcare resources. According to the most recent guidelines published by the American College of Cardiology, the prioritization and assessment of patient risk before surgery are central to MDT discussions.[20]For patients with stable angina, timely surgical intervention is advised to prevent progression to acute coronary events.[110,111] In a Danish context, there is a 30-day recommendation for maximum waiting times for elective CABG surgery.[113]

10.4 Ensuring integrity and privacy of the participant

All patient-related information obtained during the feasibility study will be handled in accordance with the Danish law for protection of personal data ("lov om behandling af personoplysninger")[113] and the Danish health law (" sundhedsloven"). The

10.5 Oral information and informed consent

Prior to consent all participants receive written and oral information about usual care and the interventions included the CABGpreHAB feasibility study, including the Ethics Committee folder "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt".[114] The participant is informed about the right to bring an assessor and the right to consider their participation for a minimum of 24 hours if needed. The oral information of the patient and signing of the informed consent form will be conducted in a closed off room to ensure that the information is given under undisturbed circumstances and are carried out by the investigator or substitute directly involved in the trial, who have the necessary experience and competence. When the information is given, it is emphasized that participation is voluntary. A patient can be withdrawn from the study at any time, if it is the wish of the patient, or if it is medically indicated, as judged by the investigator. Participation in the study is discontinued, if any of the following criteria applies a) the patient's general condition contraindicates continuing the study or b) the patient turns out to be non-eligible patient.

11. Legal and organizational aspects

11.1 Quality control and quality assurance

All data will be entered into a study database for analysis and reporting. Any data captured electronically will be stored electronically in a separate database according to standard procedures at Rigshospitalet. Upon completion of data entry, the databases will be checked to ensure acceptable accuracy and completeness. System backups and record retention for the study data will be consistent with Rigshospitalet' s standard procedures. Source data will be recorded in the electronic patient record or on specific worksheets. An electronic Case Report Form (eCRF) will be constructed for data capture. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRFs.

11.2 Economy

The study is an investigator-initiated trial conceived and conducted by The Department of Cardiothoracic Surgery, The Heart Centre, Copenhagen University Hospital. The idea for the project originated from DBO and the department of Cardiothoracic surgery at the Heart Centre at Rigshospitalet. The trial will be funded by external funds for research in health sciences. All grants will be paid to the financial office at Rigshospitalet and will be used for salaries for the trial staff and other research related to expenses. No compensation is granted to trial participants or transport expenses. None of the persons responsible for the trial have any

financial affiliation with the funds applied for. If such funding is achieved the ethical committees will be informed of the donator, and value of the grant, and the written patient information material will be updated with all donators mentioned. Any received funds will be deposited to a project specific research account, which is administrated by the hospital and under public revision. The CABGpreHAB trial has been supported by research grants from: The Heart Centre research foundation on the amount of 204.000 DKK, Helsefonden 300.000 DKK (ID: 23-B-0122), Trygfonden 600.000 DKK (ID159457) and PhD. Stipendium from Rigshospitalet Forskningspulje. These funds are used for salaries, running costs and equipment during the project period.

11.3 Insurance

According to the Act on right of appeal and compensation within the National Health Service (Act No. 547 of 24 June 2005) all trial participants are covered by the Patient Assurance Association and will be informed about this prior to inclusion. Sponsors, researchers, and trial nurse are covered by the statutory insurance at the hospital.

11.4 Plan for publication, authorship, and dissemination

After approval of the ethics application by the Regional Scientific Committee, The Capital of Copenhagen, the feasibility study will be registered on www.ClinicalTrials.gov before randomization of patients start. Results of the study will be analyzed by an independent statistician, and the results will be interpreted by the research group. The conclusion will be prepared in in two versions, before the allocation code is broken, with the two arms alternately assumed as intervention (one that assumes that arm A is the intervention, and second, that assumes that the arm B is the intervention). Positive, negative and inconclusive results of the CABGpreHAB feasibility study will be published. The final manuscripts emanating from the study will be sent to a “peer reviewed” international journal. Authorship will be allocated using the guidelines for Proposal authorship defined by the international Committee of medical journal Editors and depends on the personal involvement. A minimum of three scientific papers are planed based on CABGpreHAB trial. To reach policy makers, administrators and healthcare professionals, the project will be presented in thoracic surgery, cardiology, nursing, and physiotherapy journals. To gain broader interest, national patient associations will be contacted.

11.5 Trial timeline

The CABGpreHAB feasibility study will begin in May 2025, after approval by the Regional Ethics Committee in the Capital Region, with inclusion of the first participants. The inclusion will end in May 2026 with the last follow-up in June 2026. The end-of-study is defined as the date of the last patient`s follow-up assessment.

12. Organization

The research team comprises a multidisciplinary group with a strong scientific and clinical background. This protocol has been developed through close collaboration among all members of the research group listed below. The primary responsibility for developing the core elements of the multimodal intervention has been undertaken by Christian Have Dall, Rikke Krogh Madsen, Maria Hein Hegelund, Sune Damgaard, Ida Elisabeth Højskov and Dorte Bæk Olsen. Responsibility for data management is placed in Department of Cardiothoracic Surgery, The Heart Centre, Rigshospitalet.

Ida Elisabeth Højskov[1,2] Primary investigator

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