

Preventive **Heart** Rehabilitation in patients
undergoing *elective* **O**pen heart surgery to prevent
Complications and to improve **Q**uality of life
(Heart-ROCQ)

*A Prospective Randomized Open controlled trial,
Blinded End-point (PROBE)*

(December 2016)

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A non-blinded randomized controlled trial>'

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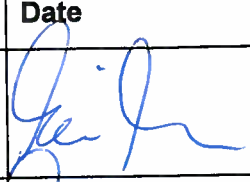

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)
PRE+POST CR program	Pre- and postoperative cardiac rehabilitation program
POST CR program	Postoperative cardiac rehabilitation program
CABG	Coronary artery bypass grafts
POCD	Persisting post-operative cognitive dysfunction
CR	Cardiac rehabilitation
PROBE	A Prospective Randomized Open controlled trial, Blinded End-point
RCT	Randomized controlled trial
TAVI	Transcatheter aortic valve implantation
RAND-36_v2	The Medical Outcome Study 36-item General Health Survey
6MWT	The six minutes walking test
VO2max	Maximal oxygen uptake
PICU	Prolonged stay at the intensive care unit
STS	Times sit to stand test
PHQ-9	Patient health questionnaire nine
GAD-7	The Generalized Anxiety Disorder- 7 item scale
PCQ	The iMTA Productivity Cost Questionnaire
MCQ	The iMTA Medical Cost Questionnaire
ICER	Incremental Cost Effectiveness Ratio
SWA	The Sensewear GECKO mini-armband
IPQ-R	The validated revised illness perception questionnaire
CSA	Cardiac self-efficacy scale
QALY	Quality Adjusted Life Year
EQ-5D-5L	EuroQol five dimensions questionnaire

SUMMARY

Rationale: Patients undergoing cardiac surgery are at risk of developing perioperative complications and major adverse cardiac events, mainly related to both their preoperative status and type of surgical procedure. Postoperative exercise based cardiac rehabilitation (CR) is an effective therapy to prolong survival and improve quality of life. However, little is known about the effect on post-operative complications, quality of life and return to work of a combined pre- and post-operative CR program encompassing physical therapy, dietary counseling, psychological support and life style management compared to a CR program, which is provided only after cardiac surgery.

Objective: to determine whether a pre- and postoperative (PRE+POST) CR program improves the short (up to three months) and long term outcomes (up to one year) of the cardiac surgery (i.e. reduction in postoperative surgical complications, readmissions to hospital and major adverse cardiac events in conjunction with improvements in the physical component of health related quality of life), when compared to postoperative CR only (POST).

Study design: A Prospective Randomized Open controlled trial, Blinded End-point. Patients are randomized between two standard care CR programs. One group will start a POST CR program after surgery. The other group will be randomized to a combined PRE+POST CR program.

Study population: Patients (age > 18 years) admitted for elective coronary bypass surgery, valve surgery and/or aortic surgery

Main study parameters/endpoints: The primary outcome is a composite weighted endpoint of postoperative surgical complications, re-admissions to hospital, major adverse cardiac events and health related quality of life (two domains: physical functioning and physical problem), at three months and one year after surgery. Endpoints are determined by an independent endpoint committee, blinded to the group allocation. Secondary, the study focuses on physical health (cardiorespiratory fitness, muscle strength and functional status), psychological health (feelings of anxiety and depression), work participation, economics, lifestyle risk factors (physical activity and smoking behavior), self-efficacy and illness representations.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The risks of the study measurements are minimal, because all studied parameters are observational, non-invasive and in part are part of care as usual. Questionnaires and physical tests are conducted. Eligible patients are asked to fill in six validated questionnaires additional to standard care for three to four times (baseline, one day before surgery, 3-4 months and one year after surgery). In addition, four questionnaires (KATZ, PHQ-9, GAD and Rand-36_v2) are collected in standard care as standard care procedure ('Meetbaar Beter') and are repeated for one to two times. Furthermore, patients are asked to perform four physical tests (6 minutes walking test, grip and leg strength and sit to stand test), which can be conducted in 45 minutes. These tests are performed throughout the rehabilitation program and after surgery at 3-4 months and after one year. Some tests are conducted in the context of the CR program.

1. INTRODUCTION AND RATIONALE

While mortality due to cardiovascular disease has declined over the last decades in Europe, cardiovascular diseases still account for one of the highest burdens of disease, also in the Netherlands. Over 15,000 coronary artery bypass grafts (CABG), valve and aortic surgeries are performed in the Netherlands each year¹. The risk of post-operative complications is high. Approximately 18% of the procedures is complicated by infections²⁻⁵, ~30% by delirium^{6,7} and ~15% by persisting post-operative cognitive dysfunction (POCD)^{8,9}. There is evidence that individuals with poor dietary habits (present in ~80%), or with physical inactivity (present in 67%), or who are older (mean age at operation is ~69 years) are at higher risk for complications after cardiac surgery^{1,10-15}.

A major part of cardiac surgery procedures is conducted electively and patients have to wait four to six weeks for the surgery. A preoperative waiting period can increase psychological stress and feelings of anxiety^{16,17}. Indeed ~30% of the patients experience feelings of anxiety and depression prior to surgery and ~20% experience these feelings after surgery¹⁸. The consequences of anxiety and psychological stress on the autonomic nervous system (e.g. increased heart rate, blood pressure, cortisol and arginine vasopressin levels¹⁹) may induce an undesirable increase in myocardial oxygen demand. Moreover, psychological stress has been associated with increased immune reactivity, poor wound healing and deterioration of cardiovascular function²⁰⁻²². Furthermore, Arthur and colleagues (2000)²³ showed an ongoing decrease in functional status in patients on the waiting list for cardiac surgery. Thus, a waiting period may contribute to increase the risk of complications, whereas this period can also be used to improve patients preoperative status.

Loss of both, mental and physical function following cardiac surgery is a frequent problem among elderly. After surgery, patients are bed ridden for at least five days. Declining percentages of 11-15% in muscle strength and aerobic capacity have been reported after 10 days of bed rest in older and middle-aged healthy adults^{24,25}. To maintain function and prevent dependency of care it is important to preserve and/or restore the level of muscle strength and aerobic capacity. This is of particular important when aging has already decreased the reserves of the physiological systems²⁶. In addition, less physically fit patients are exposed to an increased risk on cardiac death^{12-14,27}. Prevention of postoperative disabilities and complications can be beneficial to decrease health care costs. With 9.3% the treatment of cardiovascular disease is still one of the largest expenditures of health care in The Netherlands (2007 total health care costs were ~74 billion euro)²⁸.

A cost-effective therapy that is suggested to improve the pre- and post-operative condition of the patient is cardiac rehabilitation (CR). CR has the aim to influence favorably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions²⁹. Pre- and postoperative CR have been suggested to be effective to reduce postoperative pulmonary complications, duration of hospital stay, mortality, cardiovascular events and to improve quality of life^{23,30-35}. The largest benefits have been observed for patients undergoing valve surgery and CABG^{34,35}. Furthermore, CR provides an opportunity to a successful return to work. Approximately 80% of patients return to work within one year after an acute coronary syndrome event³⁶.

Nowadays, CR is an essential part of regular care for this patient group in the Netherlands. A CR program is reimbursed by all insurance companies when a patient is referred by a cardiologist. The type of the CR program and the timing of the start of the program vary among hospitals. The European Association for Cardiovascular Prevention and Rehabilitation defines three phases of CR: phase I, in hospital program; phase II, an early

post-discharge program wherein "structured and closely monitored exercise, psychoeducational activities and lifestyle changes are encouraged intensively" and phase III, long-term maintenance programme³⁷. Many hospitals in the Netherlands provide a phase II CR program and patients start thus their CR-program only 3-4 weeks after surgery³⁵. A rehabilitation program that starts before surgery and focuses on optimizing physical and psychological status is possibly more effective in reducing short- and long-term complications than a preoperative waiting period without physical and psychological support. Recently, a combined pre- and postoperative rehabilitation program has been implemented by the UMCG (hereafter named as the PRE+POST CR program). Whereas the preoperative phase consists of an outpatient CR program and the postoperative phase of an in- and outpatient CR program. The Heart-ROCQ study program is designed to study the effectiveness of the PRE+POST CR program compared to a regular Dutch phase II rehabilitation program focusing only on post-surgery outpatient rehabilitation (hereafter named as a POST CR program).

To the best of our knowledge, this is the first study comparing the effectiveness of these two implemented rehabilitation programs on postoperative surgical complications and major adverse cardiac events. Most studies investigated the effect on preoperative CR or postoperative CR, but did not investigate the effect of preoperative CR and postoperative CR. The combination of a pre- and postoperative CR program may influence the effectiveness. To answer the question which CR program is the most effective it is necessary to perform a randomized controlled trial (RCT). Subsequently, an RCT assessing the best available CR programs will enhance our understanding on the effectiveness and potential mechanisms of CR. The results of this study may advance the CR guidelines and may provide cardiologists and other health professionals with evidence to facilitate their decision about the timing and content of a rehabilitation program for specific subgroups. Furthermore, this study may improve event free survival, functional and physical capacity and active lifestyle in cardiac surgical patients. An economic evaluation can provide information on the cost-effectiveness of this new health care intervention compared with the existing alternative. A societal perspective of this economic evaluation is chosen, meaning that not only health-care costs but also patient and lost productivity costs are taken into account. Quality adjusted life years (QALYs) will be calculated to evaluate the benefits gained in terms of quality and quantity of life.

1.1 OBJECTIVES

The primary aim of this study is to determine the effectiveness of a pre- and post-operative (PRE+POST) cardiac rehabilitation program compared to a phase II cardiac rehabilitation program that is provided only post-operative (POST), three months and one year after elective cardiac surgery. The effectiveness is primary measured with a composite endpoint of two subdomains of health related quality of life (physical functioning and physical problem), surgical complications, readmissions to hospital and major adverse cardiac events). The preoperative phase of the PRE+POST CR program consists of a outpatient CR program and the postoperative phase of an in- and outpatient phase. The postoperative phase of the POST CR program consists of an outpatient phase.

Secondary, this study is designed to evaluate the effect of the CR programs on:

- Prolonged stay at the intensive care, the occurrence atrial fibrillation and re-thoracotomies (*Complications and events*)
- Cardiorespiratory fitness, muscle strength and functional status (*Physical health*)
- Feelings of anxiety, depression and quality of life (*Psychological health*)
- Work participation
- Economic evaluation: health care costs and work-related costs
- Physical activity and smoking consumption (*Lifestyle risk factors*)
- self-efficacy and illness representations (*Potential mediators*)

The hypotheses are that patients who follow the PRE+POST CR program will benefit in terms of improved preoperative status, self-efficacy and illness perceptions compared to POST patients who follow postoperative CR only. In addition, PRE+POST patients may adopt a healthier lifestyle compared to patients who follow a POST CR program. This may prevent postoperative surgical complications, readmissions to hospital and major adverse cardiac events in conjunction with improvements health related quality of life, physical and psychological health. Furthermore, we expect that the PRE+POST CR program will be cost-effective in terms of a reduced health care use and an earlier return to work after cardiac surgery.

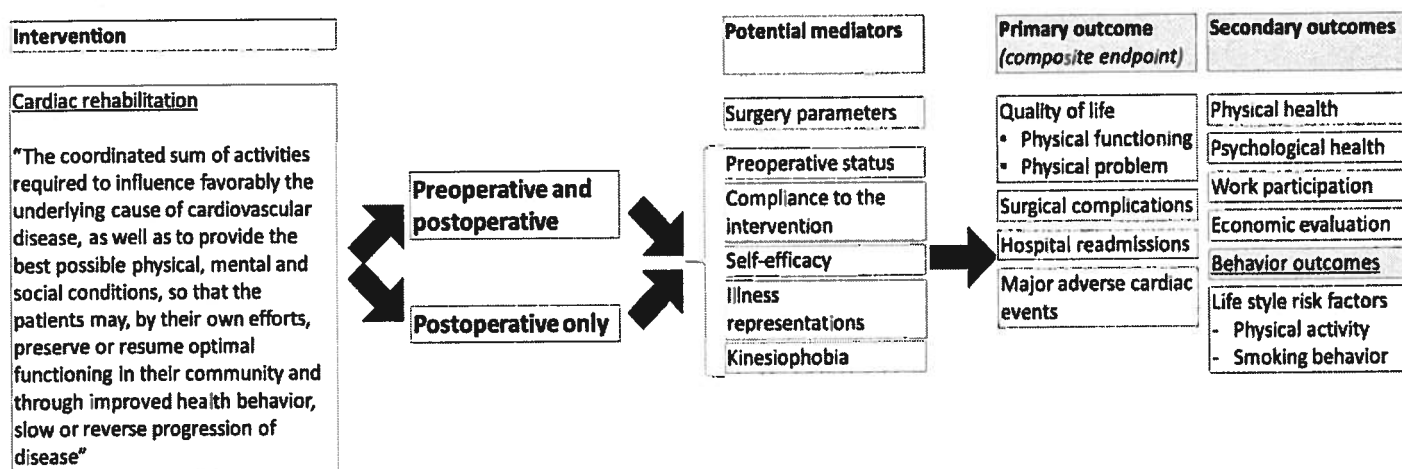


Figure 1: Intervention components, potential mediators and outcomes of the Heart-ROCQ study.

2. STUDY DESIGN

This prospective randomized open controlled trial (Figure 2) is executed in cardiac patients undergoing a thoracic surgery procedure in a single center (UMCG). Double blinding (researcher and participants) is not possible because of logistic reasons. However, the primary endpoint is evaluated by an independent end-point committee, blinded for group allocation.

Randomization

Patients are randomized to two groups. One group will start a regular phase II CR program after surgery and are considered as the POST group. The other group will be randomized to a combined pre-and postoperative rehabilitation program (the PRE+POST CR program). The latter group is considered as the PRE+POST group. The PRE+POST group follows the CR program in the UMCG, location Beatrixoord. The POST group will receive the CR in the referred hospital. All hospitals provide a basic postoperative outpatient CR program, which is generally accepted care in the Dutch health care system. These CR programs are based on the multidisciplinary guidelines cardiac rehabilitation 2011 of the association of Dutch Cardiac Rehabilitation³⁸. The inclusion period is estimated to last 3.5 years, based on the power analyses (Section 3.4). The total study duration will therefore be 8.5 years (including follow-up of mortality up to five years). Patients are treated according to the intention to treat principles.

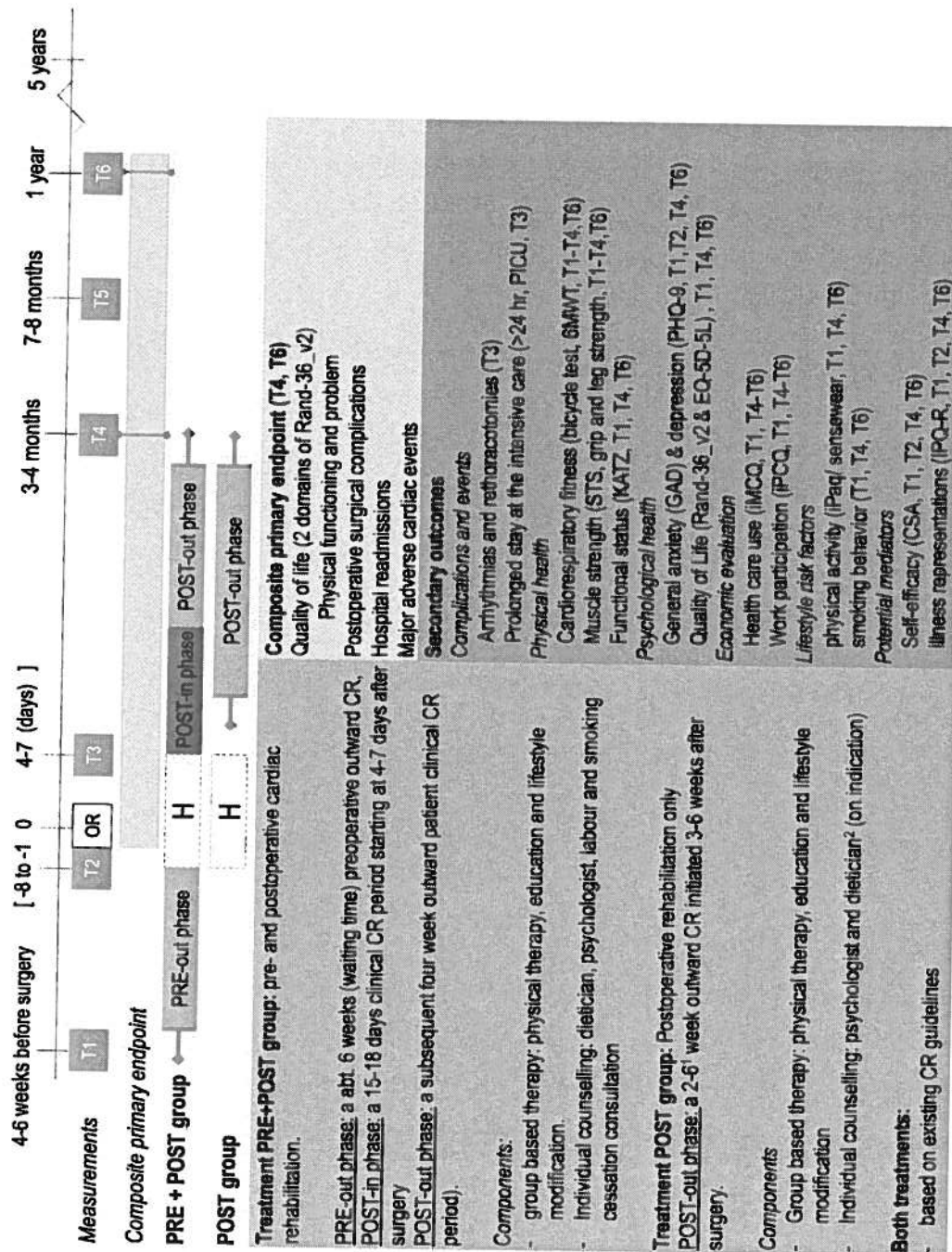


Figure 2: Research design of the randomized controlled trial. The phases of the CR programs and times of measurement are shown relative to the moment of surgery. T1 and T2 are preoperative measurements, T3, T4, T5 and T6 are postoperative and follow up measurements. Mortality is screened up to 5 years after surgery. H= hospital stay; OR = operation.

Measurements of physical tests and questionnaires

Patients will be asked to fill in short questionnaires and perform physical tests at six measurement time points (Figure 2). The first measurement is conducted when patients are admitted for the surgery (T1). The second measurement is one day before surgery (T2). The third measurement is four to seven days after surgery (or when the drain has been taken out and patient is able to walk (whichever of the two is last, T3). The fourth measurement is three to four months after surgery (T4), the fifth measurement is seven to eight months after surgery (T5) and the sixth one year after surgery (T6).

Screening outcomes

Prolonged mechanical ventilation, delirium, lung infection, atrial fibrillation and readmissions and prolonged stay at the intensive care are measured in the period between surgery and when patient meets the UMCG discharge criteria.

The UMCG discharge criteria are:

- 1) no drain, no external pacemaker lead, no infusion or oxygen present,
- 2) stable clinical conditions (stable lab results, X-ray and haemodynamic parameters),
- 3) Able to perform basic ADL-activities (i.e. going independently to the toilet).

Hospital admissions are screened in period between 30 days after surgery and one year after surgery. Deep wound infections and re-thoracotomies are screened up to 120 days after surgery. Surgical and percutaneous interventions, myocardial infarction and CVA are screened up to one year after surgery. All-cause mortality is screened up to five years after surgery.

3. STUDY POPULATION

3.1 Population (base)

Patients admitted to the department of Thoracic Surgery of the UMCG for:

- coronary artery bypass graft surgery
- valve surgery
- aortic surgery
- or a combination of the surgeries mentioned above

3.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age \geq 18 years
- Accepted for elective coronary bypass surgery, valve repair/replacement or aortic surgery (or combined) under general anesthesia

3.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients accepted for transcatheter aortic valve implantation (TAVI)
- Patients undergoing congenital heart surgery
- Aortic descendens or dissections surgery
- Elite athletes
- Co-morbidities that prevent participation in one or more program elements (e.g. disorders to the nervous or musculoskeletal system that limits exercise capacity, severe COPD (GOLD class 3-4), addiction to alcohol or drugs/ serious psychiatric illness) or when it is undesirable to exercise (e.g. cardiomyopathy/morrow).
- Other treatment planned that possibly will interrupt the program (for example on a waiting list for an organ transplantation, preoperative endocarditis or planned chemotherapy for cancer etc.)
- Unable to read, write and understand Dutch

3.4 Sample size calculation

The composite weighted score consists of a summary score for worsening in functional status and the number of postoperative surgical complications, readmissions to the hospital and major adverse cardiac events (Table 2). The primary endpoint is partly adapted from the A-HeFT study³⁹.

The mean weighted score is estimated on 1.0 with a standard deviation of 0.9. This estimation is based on historical data of the UMCG (postoperative surgical complications and mortality), the Fitness Study - an on-going pilot study in the UMCG among the same population - (functional status), two literature studies: Iribarne et al., 2014⁴⁰ (hospital readmissions) and Serruys et al., 2008⁴¹ (stroke and percutaneous interventions) and Meetbaar Beter database (re-interventions and myocardial infarction). A decrease of 0.3 means on average a decrease of one complication/event or worsening in functional status in 30% (or 10-20% decrease in major cardiac events or death) of the patients, which is considered to be clinically relevant. A group of 286 patients (143 in the PRE+POST group

and 143 in the POST group) achieve 80% power to detect a difference in the weighted score of 0.3, when alpha is set on 0.05.

The number of eligible patients is estimated to be 170 per year. We expect that 100 patients (60%) per year will be enrolled in the study. Therefore the estimated inclusion period is 3.5 years ($n=350$). In the total sample size ($n = 350$) a withdrawal of $\pm 20\%$ is incorporated. Because the mean score is estimated on different sources, different interim analyses are performed (section 7.4). Based on the interim analyses, the sample size can be adapted to ensure power.

4. TREATMENT OF SUBJECTS

Subjects are randomized between two different types of standard care cardiac rehabilitation programs. No treatment elements are added to these programs for research purposes. Table 1 gives an overview of the current CR programs.

PRE+POST group

Patients who are randomized to the PRE+POST group receive a CR program consisting of three phases. 1) A preoperative optimization phase (3x p/wk, 4-6 weeks, before surgery), 2) a postoperative in-patient phase (15 to 18 days in rehabilitation center, second weekend at home) and, 3) an outpatient patient clinical rehabilitation phase (2x p/wk, 4 weeks). During each phase, patients will visit a physical therapist (group sessions of inspiratory muscle training (IMT), strength training, aerobic cycling and breath, cough and relaxation sessions), a dietician and a psychologist to optimize general health and receive advice on lifestyle, anxiety and stress management. Two additional components are coaching to stop smoking and coaching to return to work. These additional components are available for patients who smoke and/or are still working.

POST group

Patients who are randomized to the POST group receive an out-patient CR program after surgery. In general, this program starts three to six weeks after discharge (phase II). According to the guidelines³⁸ the CR program starts always with one or more intakes to determine the situation and targets of the individual patient in a standardized way. The content of the cardiac rehabilitation program is determined based on the situation and targets of the patient. As a consequence the length and content between patients can differ. However in general, patients always start with an exercise program, which is supervised by a physical therapist for about six weeks (twice a week). If targets are not reached the cardiac rehabilitation program can be prolonged. On indication support of psychological and/or dietary consult is added. Some hospitals (e.g. Martini ziekenhuis) have their own dietary support, in other hospitals (e.g. UMCG, Ommelanden hospital in Delfzijl and Wilhelmina hospital in Assen) the patient is referred to a dietician in the primary care. In the UMCG, the length of the outpatient CR-program can be prolonged to a maximum of sixteen weeks. The UMCG provides additional psychological support, if necessary. Additional dietary support is not included in the out-patient CR program; patients are referred to a dietician in the primary care.

Cross overs

In some circumstances patients can be referred to another rehabilitation program. For example when the recovery or surgery is complicated by a CVA or when patients develop severe heart failure. In these situations patients are referred by their supervising physician to specialized rehabilitation programs, such as neurologic rehabilitation of another inpatient rehabilitation program. These patients will be considered as cross overs and data will be handled according to 'intention-to-treat' analyses.

Table 1: Overview of the current cardiac rehabilitation programs

Postoperative cardiac rehabilitation program (POST group)	Pre- and postoperative cardiac rehabilitation program (PRE+POST group)
<p><i>Preoperative:</i> - An unsupported waiting period</p> <ul style="list-style-type: none"> - Patient attends single, 3 hr cardiac assessment with nurse practitioner, anesthesiologist and thoracic surgeon - Patient waits at home 	<p><i>Preoperative: PRE-out phase</i> An outpatient cardiac rehabilitation phase (three times a week)</p> <ul style="list-style-type: none"> - Patient attends single, 3 hr cardiac assessment with nurse practitioner, anesthesiologist and thoracic surgeon - Patients health status and lifestyle will be assessed by the intake of the psychologist, physical therapist and dietician <p><i>Physical therapy</i></p> <ul style="list-style-type: none"> - Inspiratory muscle training (IMT, 3x p/wk, 6 cycles of six repetitions, 60-80% of maximum inspiratory pressure). - Aerobic cycle ergometry (3x p/wk, 25 min, moderate intensity (rate perceived exertion (RPE) of 3 on a Borgscale 0-10) - Resistance training (3x p/wk, 1-3 cycles of 10-15 repetitions, 50-80% of estimated 1RM, on six fitness apparatus) and cardio fitness (3x p/wk, 10 min, moderate intensity (RPE of 3 on a Borgscale 0-10) - Two sessions of body awareness (2x30 min) - Two group educations about basic training principles and forced expiration technique and huff- and cough techniques. <p><i>Psychological counseling</i></p> <ul style="list-style-type: none"> - Group education about coping with stress, dealing with the situation and risk factors. <p><i>Dietary advise</i></p> <ul style="list-style-type: none"> - Individual session at the beginning of the waiting period - Group education about cardiovascular risk factors and dietary intake - Individual sessions with psychologist/dietician on indication - Involvement of partner/relatives during group and individual sessions <p>Smoking consultation on indication</p>
<p><i>Surgery and hospitalization</i></p> <ul style="list-style-type: none"> - Admission to hospital, one day before surgery - Hospitalization till UMCG discharge criteria are met. <p>(possible transfer to other hospital after four to seven days)</p>	<p><i>Surgery and hospitalization</i></p> <ul style="list-style-type: none"> - Admission to hospital, one day before surgery - Hospitalization till UMCG discharge criteria are met. - Transfer to rehabilitation center when discharge criteria are met

Postoperative cardiac rehabilitation program (POST group)	Pre- and postoperative cardiac rehabilitation program (PRE+POST group)
<p><i>Week 2-4 after surgery:</i> -</p> <ul style="list-style-type: none"> - Further recovery at home (no support) 	<p><i>Week 2-4 after surgery: POST-in phase</i></p> <ul style="list-style-type: none"> - 15 to 18 days clinical cardiac rehabilitation period <p><i>Physical therapy</i></p> <ul style="list-style-type: none"> - Individual sessions (twice a day) <p>When exercise tolerance of patient is acceptable:</p> <ul style="list-style-type: none"> - IMT (1x p/wk under supervision, 2x p/wk on their own, 6 cycles of six repetitions, up to 80% of maximum inspiratory pressure)* - Aerobic cycle ergometry (daily, up to 25 min**, RPE 3) - Resistance training (daily, and cardiofitness (3x p/wk, 10 min, moderate intensity (RPE of 3 on a Borgscale 0-10) - Weekly, a 30 min session of body awareness <p><i>Dietary advice and psychological counseling</i></p> <ul style="list-style-type: none"> - Group education about handling with the heart surgery and strategies to prevent re-intervention or cardiac events - Individual session with the psychologist and dietician and psychological sessions in the first week after surgery - Individual sessions with psychologist/dietician on indication <p>Smoking and labor consultation on indication</p>
<p><i>Starting approximately 3-6 weeks after surgery: POST-out phase</i></p> <ul style="list-style-type: none"> - Two to six week outpatient patient clinical rehabilitation period (A phase II rehabilitation program, based on the Dutch guidelines)³⁸ <p><i>Physical therapy</i></p> <ul style="list-style-type: none"> - One to three times a week supervised sport activity - Patients are encouraged to plan one sport activity by themselves. <p><i>Group education</i></p> <ul style="list-style-type: none"> - two to four group educations about risk factors and retaining a healthy lifestyle. <p><u>On indication:</u></p> <ul style="list-style-type: none"> - Prolongation of program to max. 16 weeks (8 to 12 weeks on average) - Psychological counseling¹ - Dietician¹ 	<p><i>Starting approximately 5 weeks after surgery: POST-out phase</i></p> <ul style="list-style-type: none"> - Four week outpatient patient clinical rehabilitation period (three times a week) <p><i>Physical therapy</i></p> <ul style="list-style-type: none"> - Two times a week supervised sport activity*** - Patients are encouraged to plan one sport activity by themselves. - Two group educations in which patients will make a plan for exercise in home situation and discuss the experiences of this plan. <p><i>Life style management module</i></p> <ul style="list-style-type: none"> - Two group sessions about retaining a healthy lifestyle after rehabilitation supervised by a psychologist and dietician. (starting at the end of clinical phase or begin outpatient patient clinical rehabilitation period) - Individual dietetics or psychological sessions on indication <p>Smoking and labor consultation on indication</p>

*IMT training ends when the intensity of the last preoperative training is reached; ** Depending on patients exercise tolerance; *** the following sports are included: aerobic cycle ergometry, sports and games, resistance training/ cardio fitness and swimming; ¹Not available in each hospital

4.1 Investigational product/treatment

NA

4.2 Use of co-intervention (if applicable)

NA

4.3 Escape medication (if applicable)

NA

5. INVESTIGATIONAL PRODUCT

NA

6. NON-INVESTIGATIONAL PRODUCT

NA

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome is a composite weighted score of functional status, postoperative surgical complications, re-admissions to hospital and major adverse cardiac events at three months after surgery and one year after surgery. Each event, complication or worsening in functional status are considered as a score of 1 to 3 points. These points are summed to calculate the total score. Table 2 gives an overview of the primary endpoint. Functional status will be assessed with two health domains of the Medical Outcome Study 36-item General Health Survey (RAND-36 version 2): physical functioning and physical health problems. These two scales and the other six scales are evaluated separately as secondary outcomes.

7.1.1 Secondary study parameters/endpoints (if applicable)

The secondary endpoints are divided into seven domains: complications/ events, physical capacity, psychological health, -economic evaluation, lifestyle risk factors and potential mediators. In table 4 an overview is provided of the primary and secondary outcomes and the required amount of time to conduct the measurements.

Complications and events

The incidence of the parameters of the composite endpoint are analysed separately as secondary endpoint (Table 2). In addition, all-cause mortality will be defined in cardiac death and non-cardiac death. Table 3 shows the definitions of the other secondary complications and events.

Physical health

Cardiorespiratory fitness will be measured by the six minutes walking test (6MWT). This submaximal walking test mimics efforts in everyday life of patients with coronary artery disease, because most of the daily life activities are performed submaximally. In addition, a walking test is close to a real life situation, since walking is an important activity of daily living. A strong correlation ($r = 0.82$, $p < 0.001$) with VO_{2peak} was shown by Tueller and colleagues (2010)⁴², however other studies found a modest correlation between the 6MWT and maximal oxygen uptake (VO_{2max} , 0.6-0.7)^{43,44}. From a meta-analysis strong evidence was found that the 6MWT was responsive to change in clinical status following cardiac rehabilitation⁴⁵. However, an increase in percentage between 2-8% should be taken into account, when the test is repeated⁴⁵. In addition, cardiorespiratory fitness is measured using results of the bicycle tests (oxygen uptake, heart rate and work load) which are performed in the context of the cardiac rehabilitation programs.

Muscle strength will be assessed with two hand dynamometers. Grip strength will be bimanually measured with a Jamar^R Hydraulic Hand dynamometer as measure for muscle strength of the upper extremities. Normative data of the grip strength test and 6MWT have been reported by Tveter and colleagues (2014)⁴⁶.

For measuring isometric muscle strength (knee extension) the Q force is used⁴⁷. It consists of a chair with an attached, adjustable fixed leg brace at the front. It has three sensors, which are located in the brace to determine the generated force in Newton, the angle between the horizontal chair surface and the brace and the distance between the force transducer and the rotation axle of the brace in millimeter. Rails are attached at the left and

right bottom of the seat to which the brace is connected so that both the left and right leg can be tested (Figure 3).

Table 2: definitions of the composite weighted primary endpoint

Functional status	Score
Worsening in physical functioning (<i>domain score of health related quality of life, rand36_v2</i>)	1
No change or improvement in physical functioning	0
Worsening in physical problem (<i>domain score of health related quality of life, rand36_v2</i>)	1
No change or improvement in physical problem	0
An clinical relevant worsening is classified as minimal change according to <i>Wyrwich et al., 2004</i> ⁴⁸	
(Serious) Adverse Events	
No serious adverse event	0
Prolonged mechanical ventilation (<i>Mechanical ventilation longer than 24 hours during initial postoperative ICU stay</i>)	1
Lung infection (<i>Positive sputum culture in the period between the surgery and when patient meets discharge criteria</i>)	1
Delirium (<i>In the period between the surgery and when patient meets discharge criteria: 1) A DOS score ≥ 3 at hospital ward AND/OR 2) A positive ICU-CAM score (i.e. feature 1 plus 2 and either 3 or 4 present) at the intensive care by stay > 1 day AND/OR 3) Diagnosis confirmed by a psychiatrist, geriatrist or supervising specialist according to the DSM-IV criteria</i>)	1
Re-admissions to intensive care unit (<i>In the period between the surgery and when patient meets discharge criteria</i>)	1
Deep wound infection (<i>deeper tissues are affected (muscle, sternum and mediastinum) and must include: 1) surgical drainage / refixation OR 2) an organism is isolated from culture of mediastina tissue or fluid OR 3) antibiotic treatment, because of sternum wound</i>) (up to 120 days)	2
Re-admissions to hospital (<i>The number of an overnight hospital stay in the period between 30 days after surgery and one year after surgery</i>)	1
Any cardiothoracic surgical interventions (<i>graft- or valve failure, CABG, valve, aortic or other cardiac surgery</i> ¹)	2
Any percutaneous interventions (<i>PCI, TAVI, etc.</i>)	1
Myocardial infarction (<i>According to the third universal definition of myocardial infarction</i> ²)	2
Cerebral vascular accident (CVA)/stroke (<i>Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT or MRI or pathological confirmation.</i>)	2
Death (<i>all-cause mortality</i>)	3
Total score = sum of physical status en serious adverse events	

¹According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland'; ²Thygesen et al., 2012; ICU: Intensive care unit; CABG: coronary arterial bypass graft; PCI: percutaneous coronary intervention; TAVI: transcathetic aortic valve implantation

Table 3: definitions of the secondary complications and events

Parameter	Definition
Atrial fibrillation	New onset of atrial fibrillation requiring medical treatment or cardioversion in the period between the surgery and when patient meets discharge criteria**
PICU	An ICU stay larger than 24 hours
Re-thoracotomy for bleeding/tamponade	Surgical incision into the sternum as a result of a bleeding or tamponade (<i>up to 120 days after surgery</i>) a) acute: presented within 24 hours after surgery b) late: presented after 24 hours after surgery
Re-thoracotomy dehiscence	Aseptic wound dehiscence (<i>up to 120 days after surgery</i>)
All cause re-admissions to hospital	The number of overnight hospital stays in the period between 30 days after surgery and one year after surgery for any reason
Cardiac re-admissions to hospital	The number of overnight hospital stays in the period between 30 days after surgery and one year after surgery with a directly related cardiac cause
All cause hospitalization days	Total number of days of hospitalization in the period between 30 days after surgery and one year after surgery for any reason
Cardiac hospitalization days	Total number of days of hospitalization in the period between 30 days after surgery and one year after surgery with a directly related cardiac cause
Cardiac death	Any death due to proximate cardiac cause (e.g. Myocard infarct, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure related deaths, including those related to concomitant treatment*
Non-cardiac death	All death with a non-cardiac cause

PICU: prolonged stay at the intensive care unit; *specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) will be classified as cardiac death; **A spontaneous transient period of atrial fibrillation, without any consequences for the patient is not mentioned as an event.

Functional muscle strength of the lower extremities will be assessed by the 'ten times sit to stand' test (STS). This test measures mainly muscle strength of the lower extremities and shows a correlation 0.5-0.6 with a combined score of specific lower limb strength measures (i.e. strength of a hip extension during a leg press, knee extension, and ankle plantar flexion, Jones et al., 1999). The modest correlation is possibly because performance on the STS test may also be influenced by other components like balance and reaction time⁴⁹. The STS has a high test-retest reliability in patients enrolled in cardiac rehabilitation (ICC =0.87)⁵⁰.

The Katz Index of Independence in Activities of Daily Living assesses functional status as a measurement of the client's ability to perform activities of daily living independently. The Index ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. The scoring system has a range of 0 to 6 points, and a higher score indicates more dependency in performing daily

functioning^{51,52}. The Katz is validated by Reijneveld and colleagues (2007)⁵³. This questionnaire is also included in the routine preoperative assessment.

Psychological health

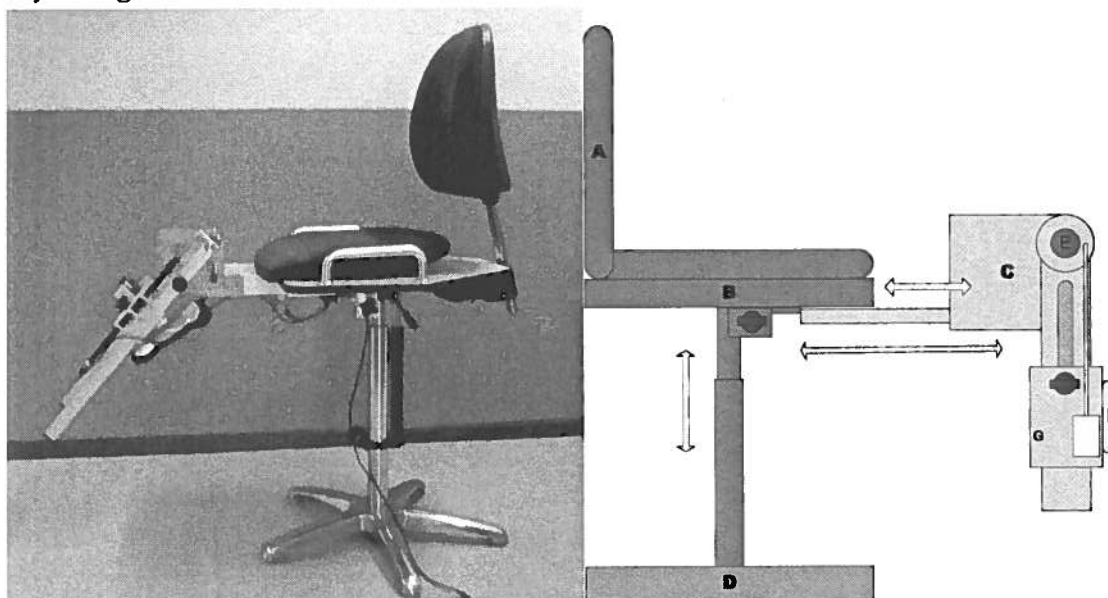


Figure 3: sagittal view of the Q-Force.

A	Back support	E	Inclinometer
B	Sitting area	F	Force transducer
C	Leg socket	G	Length transducer
D	Pedestal		

Depression is measured using the Patient Health Questionnaire Nine (PHQ-9). It includes nine items, which are the nine symptoms of depression according to the DSM-4. A PHQ-9 score >10 has a sensitivity of 88% and a specificity of 88% for major depression⁵⁴. The test-retest reliability is excellent (ICC correlation = 0.81-0.96) and is a responsive depression outcome measure in older adults⁵⁵. Most patients are able to complete the Patient Health Questionnaires in several minutes with no assistance. Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks and 1 of the symptoms is depressed mood or anhedonia. Other depression is diagnosed if 2, 3, or 4 depressive symptoms have been present at least "more than half the days" in the past weeks, and 1 of the symptoms is depressed mood or anhedonia. The level of depression severity can be measured by adding together the item scores (score 0 for 'not at all', score 1 for 'several days', 2 for 'more than half the days', and 3 for 'nearly every day'). Löwe and colleagues (2004)⁵⁵ conclude that a PHQ-9 change score of 5 or greater reflects a clinically relevant change.

To assess the presence of general anxiety the Generalized Anxiety Disorder- 7 item scale (GAD-7) is used. This questionnaire is based on the DSM- IV criteria and it can be self-administered. The questionnaire has a good internal consistency (Cronbach- α =0.92) and test-retest reliability (ICC= 0.83)⁵⁶. The score of all seven items range from 0 (Not at all) to 3 (Nearly every day). The total score is the sum score of the seven items (range 0 to 21). The total score is categorized in to four severity groups: minimal/no anxiety (0-4), mild (5-9), moderate (10-14), or severe (15-21). The optimum cut-off value of GAD at 10 points has shown a sensitivity of 89% and a specificity of 82%⁵⁶.

Quality of life will be assessed with the RAND-36 version 2. This validated questionnaire with a good reliability includes nine health domains: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional functioning, mental health, vitality, pain, general health, and perceived health change⁵⁷. Outcomes at each dimension will be defined on a scale between 0 and 100; a higher score means a better health. The questionnaire is part of the routine preoperative assessment.

Economic evaluation

The iMTA Productivity Cost Questionnaire (PCQ) will be used to measure productivity losses of paid work and unpaid work. The PCQ is a generic instrument developed to quantify health-related productivity losses for use in economic evaluations. It is largely based on previously available instruments and builds on the current scientific state of play in productivity cost measurement and valuation⁵⁸.

Health-care utilization will be measured by using the iMTA Medical Cost Questionnaire (MCQ) at baseline and after 3-4, 7-8 and 12 months of follow-up. The MCQ is a generic instrument for measuring medical costs. The MCQ includes questions related to frequently occurring contacts with health care providers⁵⁹. To improve the feasibility and reliability, both recently developed questionnaires (PCQ and MCQ) were 'translated' into simple language by a specialized agency. Additionally, a feasibility study was performed to assess the comprehensibility of the questions in practice⁵⁸.

The EQ-5D-5L will be used to estimate the quality-adjusted life years (QALY's). A QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance⁶⁰.

The EQ-5D-5L is a standardized and validated instrument for describing and valuing health-related quality of life developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic evaluation⁶¹. The EQ-5D consists of two elements. The first element is a descriptive system including five dimensions: mobility, self-care, usual activities, pain & discomfort and anxiety & depression. The respondent is required to rate his own health on these five dimensions. Each dimension has five levels: no problems, some problems, moderate problems, severe problems and extreme problems/unable to. The second element is a rating of the respondent's own current health state on a vertical, visual analogue scale where the endpoints are labeled 'Worst imaginable health state' (0 points) and 'Best imaginable health state' (10 points)⁶¹. Utility values for the EQ-5D-5L will be calculated based on the new Dutch tariff⁶².

Lifestyle risk factors,

Physical activity is assessed using the Sensewear GECKO mini-armband (SWA) and the long version (27 questions) of the International Physical Activity Questionnaire (iPAQ)⁶³. The SWA is worn on the upper arm and collects a variety of physiologic data through multiple sensors (a three-axis accelerometer, heat flux sensor, near-body ambient temperature sensor, and galvanic skin response sensor) to give a profile of physical activity. The reliability and validity is investigated in different studies⁶⁴⁻⁶⁶

The iPAQ assesses physical activity undertaken in the prior 7 days, across 4 subcategories: (1) job-related physical activity; (2) transportation-related physical activity; (3) housework, house maintenance, and caring for family and (4) recreation, sports. In addition it includes a category about sedentary activity. Per category, the patient is asked to report the frequency (days per week) and duration (time usually spent per day) of moderate-intensity physical activity, vigorous-intensity physical activity, walking activities, bicycling, and time spent sitting. The iPAQ questionnaire has a good test-retest reliability (Spearman's rho of 0.8)⁶³. Criterion validity of the self-report iPAQ against a CSA accelerometer is moderate (Spearman's rho of 0.3), which is comparable to most other self-reported physical activity questionnaires⁶³. From the data MET-minutes/ week can be calculated by weighting each type of activity by its energy requirements. There are three levels of physical activity (low, moderate and high) to classify the groups⁶⁷. Smoking behavior and history will be assessed with five questions.

Potential mediators

Illness perception is measured with the validated revised illness perception questionnaire (IPQ-R), which is based on the Leventhal's Self-Regulatory Model⁶⁸. The questionnaire contains the following dimensions: identity, timeline, consequences, personal control, treatment cure control, illness coherence, emotional representation, and causes. The dimensions of IPQ-R showed a test-retest reliability with correlations ranging from 0.46 to 0.88. In patients with myocardial infarction a good internal consistency was shown (alpha = 0.73 to 0.94). For this study the subscales personal control, treatment control, and consequences are included. These scales are chosen because of their contribution to psychological distress^{69,70}.

The cardiac self-efficacy scale (CSA) was developed by Sullivan and colleagues (1998)⁷¹ to measure self-efficacy in addressing the challenges posed by coronary disease. Patients are asked 16 items to rate: 'how confident are you that you know or can...' on a five-point Likert scale (0= not at all, 1= somewhat confident, 2 = moderately confident, 3 = very confident, 4 = completely confident). The scale has demonstrated a high internal consistency (Chronbach's alpha = 0.87-0.90). In addition, the scale has shown good convergent and discriminant validity in relation to outcomes as quality of life, functional status and anxiety.

Table 4: Overview and time indication of the primary and secondary outcomes.

				Operation Room						
		T1	T2		H	T3	T4	T5	T6	T7
	Duration (min)	Accepted for CS	-8 to -1 Day			4-7 days	3-4 months	7-8 months	1 year	5 years
Procedures										
Sign informed consent	45	X								
Check in/exclusion criteria		X								
Medical history		X								
Demographics		X								
Composite weighted outcome										
Functional status		*			X		X		*	
Postoperative surgical complications		X								
Hospital readmissions ²		X					X		X	
Major adverse cardiac events		X			X		X		X	X ¹
Secondary outcomes										
Events and complications										
Atrial fibrillation					X					
PICU					X					
Physical capacity										
6MWT	25	#	#				X		X	
Muscle strength	20	X	X			#	X		X	
Functional status (KATZ)	5	*	*			X	X		X	
Psychological health										
Depression (PHQ-9)	5	*	X				X		*	
General anxiety (GAD)	5	*	X				X		*	
Quality of life (Rand-36 v2 & EQ-5D-5L)	12	*	*				X	X	*	
Economic evaluation										
Health care use (MCQ)	15	X					X	X	X	
Work participation (PCQ)	10	X					X	X	X	
Lifestyle risk factors										
Physical activity (iPAQ/ Sense Wear)	10	X					X		X	
Smoking behavior	5	X					X		X	
Potential mediators										
Illness representations (IPQ-R)	5	X	X				X		X	
Self-efficacy (CSA)	5	X	X				X		X	
Standard care (min)		52				45	-	-	22	
Study patients (min)		117	63				124	25	102	

¹ Only all-cause mortality; ²Start screening at 30 days after surgery; * Measured in standard care; X measures added for study patients; # measures added for study patients, but are standard care if patient is randomized to pre- and postoperative CR; CS: Cardiac surgery; H: the period between the surgery and when patient meets discharge criteria; PICU: prolonged stay at intensive care unit; 6MWT: six minutes walking test;

7.1.2 Other study parameters (if applicable)

Other study parameters, to routinely collected measures, include:

- Baseline characteristics (such as age, gender, weight, length, wrist/hip ratio, marital status, living situation, education level, occupation, medical history, co morbidities, anxiety for surgery, waiting time)
- Surgery parameters that may influence primary and secondary study parameters (such as type of surgery, use of cardiopulmonary bypass, surgery duration, cross-clamp time, use of internal mammary graft)
- Results of routinely collected blood tests and hospital stay
- Performed training load (duration, type, frequency and intensity) during the CR program
- Compliance to the CR programs, referred hospital and travel distance to rehabilitation center (this may influence the compliance of the CR program).

7.2 Randomisation, blinding and treatment allocation

Patients are randomly assigned to one of two CR programs in a 1:1 ratio. Allocation to the PRE+POST group or POST group will occur after baseline measurements. Blocked randomization is used to ensure continued inclusion rates in both CR programs.

Randomization is stratified for type of surgery (CABG, AVR, AVR+CABG and other), gender and age (≥ 65 years and < 65 years). Medical staff and researchers are not blinded, because of the complex logistics of the PRE+POST CR program.

7.3 Study procedures

Inclusion into the study

Elective patients (waiting period > 5 weeks)

After informing the patients about the surgery the cardiologist checks the inclusion criteria. All eligible patients are informed about the study. If patients express an interest in study participation a patient information letter and informed consent is provided (attachment E1). The researcher will screen the patient for exclusion criteria and asks the patient to give informed consent during routinely preoperative examination. The maximum time between the appointment with the cardiologist and preoperative examination is 14 days; during this period the patient has time for reflection. There will be sufficient time for questions during the meeting with the researcher. In addition, patients are informed that they can withdraw from the study at any time without consequences. The measurements of T1 are performed if the patient meets the study criteria and informed consent is signed. Random allocation is performed after T1 measurements.

Patients who do not want to participate are asked to give written consent (attachment E1.2) for using data, which are collected during routine care. Patients are asked for this Heart-ROCQ study registry to get insight in the possible bias of the included population and thus the generalizability of the results of the study. Data are not used for the primary statistical analyses.

Baseline measurement (T1)

Rand-36, KATZ, PHQ-9, GAD and the additional questions about smoking are part of the standard care protocol before surgery using an online questionnaire. The physical tests (6MWT and strength tests) are performed and the MCQ, PCQ, EQ-5D-5L, iPAQ, IPQ-R, CSA questionnaires will be provided to the patients when they sign informed consent for participating in the study. In addition, patients are asked to wear the Sense Wear mini-armband (SWA) for one week. They will be asked to return the questionnaires and the SWA before the preoperative consultation (approximately one week later).

Week before surgery (T2) and hospitalization (T3)

Eight days prior to surgery the PHQ-9, GAD, IPQ-R and CSA are provided. Patients are asked to fill in the questionnaires preceding two days before surgery. In standard care patients are admitted to hospital one day before surgery. During this day physical capacity measurements (6MWT and muscle strength) are performed by a researcher, research assistant or physical therapist. These measurements are also performed on day four to seven after surgery (or when the drain is not removed, after the drain is removed).

Three-four months post-surgery (T4)

Approximately 3-4 months postoperatively, patients will be seen by a researcher at the outpatient clinic in the UMCG. During this visit, physical capacity will be tested (muscle strength and 6MWT). One to two weeks before the appointment, the questionnaires (Rand-36_v2, KATZ, PHQ-9, GAD, MCQ, PCQ, EQ-5D-5L, iPAQ, smoking behavior, CSA) are sent to the patients and the patients are asked to fill these in before the appointment. In addition, the SWA is sent to the patients with the question to wear this activity monitor one week prior to the appointment. During the measurement the questions according the primary endpoint are asked.

Seven to eight months after surgery (T5)

Seven to eight months after surgery patients will be interviewed by telephone about their health care use (MCQ), work participation (PCQ) and EQ-5D-5L during the last four months. Research-assistants will perform the interviews.

One year after surgery (T6)

Patients are followed-up by a researcher-(assistant) at the outpatient clinic, during the yearly control appointment of the cardiologist (one year after surgery). During this visit, physical capacity will be tested (muscle strength and 6MWT). Rand-36, PHQ-9 and GAD are part of the standard care protocol one year after surgery using an online questionnaire. As in T4, the questionnaires (KATZ, MCQ, PCQ, EQ-5D-5L, iPAQ, smoking behavior and CSA) and SWA are sent to the patients prior to the measurement. During the measurement the questions according the primary endpoint are asked.

Procedure of primary outcome

Postoperative complications are routinely collected in standard care. These parameters will therefore be derived from medical record and hospital database. At T4 and T6 (3-4 months and one year follow up) patients are asked if they were hospitalized, underwent any cardiothoracic surgical intervention or any percutaneous interventions since the surgery. In addition, they will be asked if they had a myocardial infarction or CVA. The researcher will check documentation at the hospital in which the intervention or treatment was performed, if

patients have had one of these major adverse cardiac events. The rate of mortality will be checked in the municipal administration. The cause of death is reviewed by interrogation of the general practitioner, if patient has died outside of the hospital.

Procedure of secondary outcomes

Secondary complications and events are collected performing the same procedure of the primary outcomes. Questionnaires are provided online or on paper.

Physical tests are performed according to a standardized protocol. The 6MWT is executed on a flat 40-meter long indoor walking track. Patients are asked to walk for six minutes (without running) and are told that the distance is measured. If needed, patients are allowed to use an assistance device and take one or more rest breaks. Verbal encouragement (such as 'you're doing well') are given at the first, third and fifth minute. The time the patient is walking will be given at the second and fourth minute of the test. During the test, the operator walks close behind the patient and is attentive to any clinical manifestations that may influence the test's quality or require stopping prematurely. The walking distance during the test will be recorded. Heart rate and perceived exertion is conducted before and after the test.

Muscle strength is measured in the dominant hand and left leg (if arterial or venue of the hand/leg are used for the bypass of the surgery, the other hand/leg is used, resp. Jamar® Hand Hydraulic Dynamometer and Q Force). To get familiar with the grip and leg test, participants are requested to perform this test once. Patients start the STS test with their back against the chair and their arms folded cross the chest. The researcher asks the patient to stand up and sit down 10 times as quickly as possible. Time is measured from the start to the end, which is when the buttocks touches the chair after the 5th repetition. To get familiar with the test patient have to do two repetitions before the test. For the test a standardized chair is used. The number of repetitions are count when the patient is not able to complete 10 repetitions.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The reason to leave the study will be asked by the investigator; however the patient does not have to mention the reason. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

7.5 Replacement of individual subjects after withdrawal

Patients who withdraw from the study or who are unable to complete the study procedures are not replaced. A drop out of 20% is taken into consideration in the sample size calculation.

7.6 Follow-up of subjects withdrawn from treatment

After randomization, cardiac rehabilitation discontinuation for any reason does not constitute withdrawal from the study. Patients who prematurely withdraw from the study for any reason are asked to return all assessments as indicated in the study overview (Table 4). If the patient does not attend the study visits, follow-up should continue according to the specified schedule by online questionnaires or telephone, except in the case that the patient specifically refuses such follow-up.

7.7 Premature termination of the study

The study will be terminated prematurely when one of the CR programs is obviously ($P < 0.001$) worse or better than the other CR program (after interim analysis).

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, the investigator will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigator will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the measurements of the study. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Events are common among patients who undergo heart surgery (e.g. infections, stroke, and mortality). SAE's that occur during the regular hospitalization phase after the surgery will not be reported to the accredited METC, but will be registered in regular database of the UMCG.

The occurrence of AEs and SAEs are checked and asked at the patient at T2, T3, T4 and T6 by the researcher.

The investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

8.3 Annual safety report

Not applicable

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

No additional risk is expected during the conduction of the measurements. Patients eligibility are in routinely care checked with a cycling test. An ongoing safety surveillance was therefore not deemed necessary.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The primary endpoint is a composite score of functional status, postoperative surgical complications, hospital readmission and MACE. The summary score is calculated for each patient according to Table 2. Missing data on quality of life will be filled with the worst-case score for that component in the analysis. The mean and standard deviation for the summary scores of each group are calculated and handled as a continue variable. Multivariate analyses, inclusive multilevel analyses, are performed to determine time*group differences at three months and one year after surgery.

9.2 Secondary study parameter(s)

Complications and events

The incidence of atrial fibrillation, re-thoracotomies, prolonged stay at the intensive care unit and parameters of the primary endpoint are determined. In addition, group differences are tested by chi-square tests. Group difference for re-admissions to hospital and hospitalization days are tested with the Mann-Whitney test, because these variables are usually positively skewed.

Physical capacity

Outcomes on physical fitness (6MWT and muscle strength) of the preoperative phase (T1, admission to surgery, T2, one day before surgery and T3, 4-7 days after surgery) and the postoperative phase (T4, 3-4 months and T5 one year) are handled as continuous variable.

Functional status will be measured using the Katz ADL Index for six items: bathing, dressing, toileting, transferring, eating and use of incontinence materials. Each item will be scored as either 0 (independent) or 1 (dependent). A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment. Functional decline will be defined as a decrease of at least 1 point on the Katz ADL Index between baseline and follow-up. These scores will be handled as continuous variables. A change of 1 point is considered as clinically relevant.

Psychological health

For the PHQ and GAD, the total scores are calculated as the sum score of the respectively nine and seven items (resp. range 0 to 27 and 0 to 21). Sum scores of the PHQ and GAD are handled as continuous variables. A PHQ-9 change score of 5 or greater reflects a clinically relevant change. For the GAD, a change of 0.5 standard deviation is considered clinically relevant, which is according to the distribution based theory of Cohen.

For quality of life the scores of the eight subscales (physical role, physical functioning, general health, bodily pain, vitality, social functioning, emotional role and mental health) are calculated. In addition the two composite scores (the physical composite summary score and the mental composite summary score) are calculated. These scores and the score of the eight subscales are handled as continuous variable. A clinical relevant difference is defined as a minimal change according to Wyrwich et al., (2004)⁴⁸

Economic evaluation

The iMTA PCQ will be used to measure absenteeism from paid and unpaid work at baseline and at follow-up moments T4, T5 en T6 (3-4, 8 and 12 months). Standard prices for the costs of absenteeism will be used to calculate the work-related costs.

Health-care utilization will be measured by using the iMTA MCQ at baseline and after 3-4, 8, and 12 months of follow-up. Health-care costs include costs of GP care, costs of psychiatric and psychological care, costs of inpatient hospital care, costs of visits to allied health-care professionals such as physical therapists and costs of home care. For the valuation of health-care utilization, standard prices published in the Dutch costs guidelines will be used. This information will be used to compare health-care usage and will be correlated to compare health-care costs between both groups of randomisation. Ultimately, an Incremental Cost Effectiveness Ratio (ICER) will be used, dividing the difference in effect by the difference in costs. Means will be presented, and given the probably skewed nature of the cost data, we will use bootstrap analysis. Bootstrap re-sampling will be performed on the cost and effect pairs in order to calculate confidence intervals. Furthermore, cost effectiveness acceptability curves will be plotted to estimate the probability that the PRE+POST CR program is cost effective compared to the POST CR program. The ICER represents the additional investment needed to achieve one point improvement on the composite outcome (primary outcome measure).

The EQ-5D-5L will be used to calculate QALYs by using the Dutch tariff for the EQ-5D-5L on basis of composite time trade-off (cTTO). This value set has currently been developed and can be used to compute utilities for use in calculating QALYs for economic evaluations in Dutch healthcare⁶².

Lifestyle risk factors

Data collected with the SWA and the IPAQ questionnaire (T1, T4 and T6) are handled as continuous variables. Energy expenditure at different intensities and METs measures of the SWA are exported. For the IPAQ, MET-minutes per week are calculated within each domain (work, transport, domestic and garden, and leisure) for walking (W), moderate-intensity activities (M), vigorous-intensity activities (V). In addition, total scores for walking (W), moderate-intensity activities (M), vigorous-intensity activities (V) and an overall grand total score are calculated. In addition, patients are categorized in three groups (low, moderate and high) according to the IPAQ manual⁶⁷. The sitting question will be handled as an additional indicator variable of time spent in sedentary activity. The incidence of low, moderate and high physical activity and time spent in sedentary activity are measured at T1, T4 and T6. In addition, the prevalence of smokers will be assessed at T1, T4 and T6. For smokers the number of cigarettes are handled as a continuous variable.

Potential mediators

The summary score of the different dimensions of illness representations (IPQ-R) and self-efficacy (CSA) are calculated and handled as continuous variable.

Mean and standard deviation are calculated for continuous variables. Multivariate analyses (inclusive multilevel analyses) are performed to determine time*group differences for the continuous variables. Non-parametric tests are used if distributions are non-normal. In addition, descriptive statistics will be presented in median and (IQ) range. In all statistical analyses, a two-sided $p < 0.05$ is considered statistically significant.

Missing data analysis will be performed, meaning that the amount and nature of missing data will be studied and depending on this, adequate strategies to handle missing data will be applied (e.g. multilevel analyses). Patients are treated according to the intention to treat principles.

9.3 Other study parameters

A multivariate analysis of variance (MANOVA) is performed for continue baseline parameters (age, BMI, anxiety for surgery etc.) and surgery parameters (such as waiting time, surgery duration). Non-parametric tests (mann whitney test or kruskall-wallis test) are used to test differences, when data is not normally distributed and for ordinal variables (such as type of surgery). Possible differences of binary parameters (such as gender) are tested with chi-square test. If baseline differences are found, caution will be taken when interpreting the results of the primary and secondary endpoints and methods may be modified to adjust for difference.

Heart-ROCQ registry

Data of patients who did not participate, but have given written consent for using routinely collected data, are collected in the Heart-ROCQ registry. Data from the Heart-ROCQ registry are not used for the primary statistical analyses. Separate analyses are performed between included study patients and patients of the Heart-ROCQ registry to get insights into the generalizability of the results of this study. These separate analyses consist of a multivariate analysis of variance (MANOVA) (continue routinely collected baseline parameters (e.g. age, BMI, anxiety for surgery etc.), non-parametric tests (mann whitney test or kruskall-wallis test) for non-normal distributed or ordinal variables (e.g. type of surgery) and chi-square tests for binary parameters (e.g. gender). The included study patients are representative when there are no differences shown with the study registry.

9.4 Interim analysis (if applicable)

An interim analysis will be performed when 40% of the included patients have conducted the measurements of T6 (one year after surgery). We will be able to determine the actual observed event rate and effect of the two CR programs. The study will be terminated prematurely when one of the CR programs is obviously ($P < 0.001$) worse or better than the other CR program. If the event rate is lower than anticipated or when there is little chance of showing that one of the CR programs is better or worse we will decide on possible extending the sample size or discontinuation of the study and write an amendment.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 8, October 2013) and in accordance with GCP guidelines and Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

10.2 Recruitment and consent

Information is given by the supervising cardiologist when patient is accepted for the surgery. The patient information letter and informed consent will be provided to patients who are interested in the study. Usually a preoperative examination is planned within 5 to 14 days. This time (maximum reflection time of 14 days) can be used for patients to consider their decision. At the preoperative examination, the investigator or research assistant asks the patients if they have read and understood the patient information letter and informed consent. The researcher will give answers when the patient has questions regarding the study. Patients who express that they would like to participate are asked to sign the informed consent, which is also signed by the researcher. The researcher emphasizes that participation or lack of participation is not influencing their treatment. Furthermore, he will explain that withdrawal from the study is possible at any moment (without any consequences or without having the obligation to tell the reason of withdrawal). Patients are included if the written consent is signed.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not Applicable

10.4 Benefits and risks assessment, group relatedness

As mentioned in the introduction, ~30% of the cardiac surgical patients experience post-operative complications. Sixty percent of the cardiac surgical patients are 65 years or older (mean age 67/71 years (M/F)). Older patients are at higher risk to develop post-operative complications. In addition, lifestyle risk factors (e.g. poor dietary intake, sedentary life style, psychological stress and anxiety and smoking) are common in this population. An increase in anxiety and deterioration of functional capacity has been shown during an unsupported preoperative period. On average, cardiac surgical patients have a post-operative hospitalization period of seven days, which may induce further deterioration of maximal aerobic capacity and muscle strength. Prevention and recovery of these physiological systems are important for maintaining independency, particularly in the elderly population, where reserves of physiological systems are decreasing due to the process of ageing. Preoperative optimization and early rehabilitation treatments possibly improve the above-mentioned issues more compared to a postoperative CR program.

(Potential) Benefits

It is expected that patients experience no benefits when participating in the study.

Risks

No additional risks are expected during the measurements (physical tests). The physical tests can be performed at submaximal aerobic performance and are considered to be safe and feasible in cardiac surgical patients^{33,72}. In standard care a cycling test is performed to ensure patients eligibility to cardiac rehabilitation. This test is performed

before inclusion to the study, patients who are eligible to the CR program are thus able to perform the physical tests performed in this study.

10.5 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO.

The investigator(also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

No additional health care costs are required. Reimbursement for CR after an cardiac intervention is provided by all insurance companies on the condition that a patient is referred by a cardiologist.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be collected by research assistants and (para) medical personal. All research data will be recorded anonymously under a unique study number on a scoring form or in an online environment, which is only available for research assistants and medical personal involved in this study. All data will be transferred to a safe clinical management system (Redcap). All research and medical data will be kept strictly confidential. Only the principal investigator and researchers that are involved in this study will know the code and are able to identify the patient. The data will be kept for 15 years.

11.2 Monitoring and Quality Assurance

Monitoring during the study takes place by a trained research monitor from the UMCG. The frequency will be two times a year. The research monitor will monitor how many patients are included and the number of withdrawal from the study, check the inclusion and exclusion criteria of three patients and the integrity of the research dossier. At last, 1-10% of the informed consents and data will be checked.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator.

Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

11.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The last visit of the patient is one year after surgery, however mortality is screened up to five years after surgery. Therefore, the end of the study is defined as four years after the last patient's visit

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The study will be registered in clinical trials database. No arrangements have been made with any third parties. Results of this study are submitted to a peer reviewed scientific journal and can be presented as a (poster) presentation at a national/international conference. Publication of results of this study will be in compliance with the CCMO publication policy.

12. STRUCTURED RISK ANALYSIS

Not Applicable

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