Heart rehabilitation in patients awaiting open-heart surgery targeting complication prevention and quality of life improvement
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Chapter 6

Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life (Heart-ROCQ) – Study protocol for a prospective, randomised, open, blinded endpoint (PROBE) trial
Abstract

Introduction: The rising prevalence of modifiable risk factors (e.g., obesity, hypertension, and physical inactivity) is causing an increase in possible avoidable complications in patients undergoing cardiac surgery. This study aims to assess whether a combined preoperative and postoperative multidisciplinary cardiac rehabilitation (CR) programme (Heart–ROCQ programme) can improve functional status and reduce surgical complications, readmissions and major adverse cardiac events (MACE) as compared with standard care.

Methods and analysis: Patients (n = 350) are randomised to the Heart–ROCQ programme or standard care. The Heart–ROCQ programme consists of a preoperative optimisation phase while waiting for surgery (three times per week, minimum of three weeks), a postoperative inpatient phase (three weeks) and an outpatient CR phase (two times per week, four weeks). Patients receive multidisciplinary treatment (e.g., physical therapy, dietary advice, psychological sessions and smoking cessation). Standard care consists of six weeks of post-surgery outpatient CR with education and physical therapy (two times per week). The primary outcome is a composite weighted score of functional status, surgical complications, readmissions and MACE, and is evaluated by a blinded endpoint committee. The secondary outcomes are length of stay, physical and psychological functioning, lifestyle risk factors, and work participation. Finally, an economic evaluation is performed. Data are collected at six time points: at baseline (start of the waiting period), the day before surgery, at discharge from the hospital, and at three, seven and 12 months post-surgery.

Ethics and dissemination: This study will be conducted according to the principles of the Declaration of Helsinki (V.8, October 2013). The protocol has been approved by the Medical Ethical Review Board of the University Medical Center Groningen (no 2016/464). Results of this study will be submitted to a peer-reviewed scientific journal and can be presented at national and international conferences.
Introduction

The leading cause of death in Western countries is ischaemic heart disease⁴. One of the treatments for severe ischaemic heart disease is cardiac surgery. The risk of postoperative complications related to cardiac surgery is substantial; pulmonary complications (up to 33%), delirium (~26%) and arrhythmias (~30%) have been reported to occur²⁴. These complications are associated with prolonged hospitalisation, increased adverse events (i.e., readmission, stroke, myocardial infarction and mortality), reduced health-related quality of life (HR-QoL) and higher healthcare costs⁵–¹⁰. Patients with poor dietary habits (present in ~80% of the candidates for cardiac surgery), who are physically inactive (~45%), who smoke (22%), or who experience depression and/or anxiety disorders (~30%) are at higher risk for postoperative complications and are at risk for lack of functional benefits after cardiac surgery⁸,¹¹–¹⁹.

Over the last decades risk factors such as age, obesity, diabetes, hypertension and dyslipidaemia have steadily increased in patients undergoing cardiac surgery²⁰,²¹. Despite their adverse effects on treatment outcomes, reducing the burden of modifiable risk factors is currently not part of standard clinical care before and after cardiac surgery. Before cardiac surgery, patients often have a preoperative period of several weeks on the waiting list in which they receive little or no guidance. This waiting period has been associated with increased psychological stress, feelings of anxiety and reduced functional status²²,²³. With respect to inactivity during hospitalisation after cardiac surgery, research has shown that during the 8–11 days of hospitalisation, patients spent the majority of their time sitting or in a supine position²⁴,²⁵. In-hospital physical inactivity is a predictor of a longer hospital stay and rehospitalisation²⁴,²⁶,²⁷. It causes a decrease in muscle strength and aerobic capacity, both fundamental in the performance of activities of daily living²⁸,²⁹. This reduced physical capacity may seriously impact independence, especially since these patients are often elderly and the functioning of their entire physiological system is already reduced³⁰.

The goal of cardiac rehabilitation (CR) is to improve the preoperative and postoperative status of patients undergoing cardiac surgery. CR aims ‘to favourably influence the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental, and social conditions’³¹. Postoperative CR is already an essential part of standard care in the Netherlands, although many hospitals in the Netherlands provide a phase II outpatient CR programme, starting three to six weeks after cardiac surgery³²,³³. Benefits of postoperative CR are reported for a variety of cardiac patients³⁴; however, the evidence in patients undergoing cardiac surgery is still lacking with regard to patient-relevant outcomes and mortality³⁵. In addition to postoperative CR, small trials suggested that preoperative CR is effective in reducing postoperative pulmonary complications, duration of hospital stay, improving HR-QoL and physical fitness, and increasing the compliance to postoperative CR²¹,³⁶,³⁷. However, long-term effects and the effects on other complications remain unclear. Furthermore, most studies investigated the effect of preoperative CR or postoperative CR, but not the effect of both CR methods combined. The hypothesis is that a combined preoperative and postoperative CR programme is more beneficial when
compared with a separate preoperative CR programme or a single postoperative CR programme.

The aim of the Heart-ROCQ study is to determine the effect of a comprehensive preoperative and postoperative CR programme (the Heart-ROCQ programme) on functional status, postoperative surgical complications, readmissions to hospital, and major adverse cardiac events (MACE) compared to a regular Dutch postoperative outpatient CR programme (the standard care CR programme). In addition, the effect of the Heart-ROCQ programme on physical and psychological functioning, including HR-QoL, lifestyle risk factors, work participation, and cost-effectiveness, is evaluated in comparison with the standard care CR programme. To assess who will benefit from CR and why the CR programme is effective, moderator and mediator analyses are performed.

**Methods and analysis**

**STUDY DESIGN AND ORGANISATION**

This investigator-initiated, prospective, randomised, open, blinded endpoint trial is executed in a single centre (University Medical Center Groningen [UMCG]). Patients from three referral hospitals (Ommelander Hospital Groningen, Martini Hospital Groningen and Wilhelmina Hospital Assen) who are accepted for cardiac surgery at the UMCG are also approached to participate. Patients are randomly assigned to a combined preoperative and postoperative multidisciplinary CR programme (the Heart-ROCQ group) or a regular phase II outpatient CR programme after surgery (the Standard Care group). Figure 6.1 provides an overview of the study design.

**ETHICAL CONSIDERATIONS AND DISSEMINATION**

This study is conducted according to the principles of the Declaration of Helsinki (V.8, October 2013) and according to the research code of the UMCG. The protocol (V.2, 19 December 2016) has been approved by the Medical Ethical Review Board (METc) of the UMCG (no 2016/464).
The study has been registered at ClinicalTrials.gov (no NCT02984449). If applicable, substantial amendments will be notified to the METc for approval and changes will be written into articles describing the results of the study. Results of this study will be submitted to a peer-reviewed scientific journal and can be presented at national and international conferences.

PARTICIPANTS
Patients (≥ 18 years) admitted for elective coronary artery bypass grafting (CABG), valve surgery, aortic surgery, or combined procedures are eligible. Patients accepted for congenital procedures, transcatheter aortic valve implantations, aortic dissections, or aortic descending repair are excluded. Other exclusion criteria are: inability to participate in all programme elements of the Heart-ROCQ programme due to disorders of the nervous or musculoskeletal system that limit exercise capacity, chronic obstructive pulmonary disease with Global Initiative for Chronic Obstructive Lung Disease criteria classification 3 or 4, addiction to alcohol or drugs, a serious psychiatric illness (i.e., recently experienced psychosis, bipolar disorder, diagnosis of schizophrenia, serious cognitive, or neurological problems, and acute suicidal ideations or behaviour), or when it is undesirable to exercise (i.e., hypertrophic cardiomyopathy, unstable angina, advice from cardiologist); any treatment which is planned during one of the CR programmes and which is expected to interrupt attendance to the CR programme (e.g., planned organ transplantation, preoperative endocarditis, planned chemotherapy and so on); playing a sport at the (inter)national level; and being unable to read, write or understand Dutch.

STUDY ENROLMENT, RANDOMISATION AND REGISTRY
Figure 6.2 shows the flow chart of the Heart-ROCQ study. Patients on the waiting list of the thoracic surgery department and meeting the study criteria for type of surgery are asked by their cardiologist to participate. The cardiologist provides the patients with study information and an invitation to meet the researcher at the preoperative consultation. At the preoperative consultation, the researcher will obtain informed consent and conduct the baseline measurements. Eligible patients who have signed informed consent and performed the baseline measurements are randomised to the Heart-ROCQ group or Standard Care group. Randomisation (concealed group allocation in REDCap, random blocks of 2–4, 1:1 ratio) is stratified for weight of the surgery (isolated CABG, single non-CABG [i.e., replacement or repair of part of aortic or valve], two procedures or three procedures), gender and age (≥ 65 and < 65 years). Prior to the start of the study, the randomisation lists were created (using the ‘ralloc’ function of Stata/SE, V.13.0) and imported into the secure data collection tool REDCap (V.73.2), by an independent researcher. Medical staff and researchers are not blinded to group allocation due to logistic reasons. The primary endpoint is evaluated by an independent endpoint committee blinded to group allocation.

Patients who are not willing to participate are asked to give written consent for using data that are collected during routine care. The data are collected in the Heart-
Assessed for eligibility via screening the waiting list of thoracic surgery (n=)

Excluded: Type of surgery (n =)*
*TAVI (n=), Congenital (n=), Aortic descendens (n=), Dissections (n=)

Consultation cardiologist (n=)

Receive written information describing study trial (n=)

Excluded: Not motivated to participate (n=)
Not able to participate due to logistics (n=)

Accepted invitation for intake (n=)

Excluded: No-show at intake (n=)

Intake (n=)

Excluded: Unable to participate in CR program (n=)
Other treatment (n=)
Sport at (inter)national level (n=)
No Dutch language (n=)

In- and exclusion criteria (n=)

Excluded: No informed consent (n=)

Informed consent (n=)

T1: Baseline measurement (n=)

Randomized (n=)

Heart-ROCQ group (n=)

Standard care group (n=)

Lost to follow up (n=)

Lost to follow up (n=)

PRE-out CR phase

T2: 1 - 8 days before surgery (n=)

T2: 1 - 8 days before surgery (n=)

Lost to follow up (n=)

Lost to follow up (n=)

POST-in en POST-out CR phase

T3: 4 - 7 days after surgery (n=)

T3: 4 - 7 days after surgery (n=)

Lost to follow up (n=)

Lost to follow up (n=)

POST-out CR phase

T4-T6: 3 months, 7 months and 1 year after surgery (n=)

T4-T6: 3 months, 7 months and 1 year after surgery (n=)

Lost to follow up (n=)

Lost to follow up (n=)

Analysed (n=)

Intention to treat

Analysed (n=)

Intention to treat

Analysed (n=)

Per protocol (supplementary)

Analysed (n=)

Per protocol (supplementary)

Figure 6.2 Flow chart of the Heart-ROCQ study. CR: cardiac rehabilitation; TAVI: transcatheter aortic valve implantation.
ROCQ study registry to increase insight into potential differences between patients who participated in the study and patients who did not. The Heart-ROCQ registry will thus provide more insights into the generalisability of the results. Data from this registry are not used for the primary statistical analyses.

**INTERVENTION**

**Heart-ROCQ group**

The Heart-ROCQ group receives a CR programme at the Center for Rehabilitation of the UMCG (Beatrixoord location, which is located six km from the hospital of the UMCG) consisting of three phases. The first phase is an outpatient preoperative optimisation phase during the waiting period (three times per week, minimum of three weeks). The second phase is a postoperative inpatient CR phase (three weeks, weekdays only) followed by the third phase, an outpatient CR phase (two times per week, for four weeks). During each phase, all participants receive physical therapy including group sessions of inspiratory muscle training, strength training, aerobic cycling, breathing, coughing and relaxation. In addition, patients have an assessment with a dietitian and a psychologist and take part, when indicated, in individual sessions to optimise their health. In addition, different group education sessions are organised regarding coping with stress, awareness of risk factors, and maintaining a healthy lifestyle. Two additional modules, namely coaching to stop smoking and to return to work, are available for patients who, respectively, smoke or are employed. A detailed description of the CR programme is given in the online supplementary information.

**Standard Care group**

In the Netherlands, the current standard of care consists of a phase II outpatient CR programme, which is conducted at the referred hospital. In general, this CR programme starts three to six weeks after discharge from the hospital and lasts for six weeks. The programme consists of four educational sessions (regarding risk factors and retaining a healthy lifestyle) and physical therapy (two times per week: 30 min. cycling together with 30 min. sports and games, relaxation therapy, or strength training). Furthermore, patients can be referred to a psychologist or a dietitian when needed. The content of this CR programme is based on the Dutch CR guidelines.

**COMPOSITE PRIMARY ENDPOINT: FUNCTIONAL STATUS, COMPLICATIONS AND EVENTS**

The primary outcome is a composite weighted score of functional status, postoperative surgical complications, readmissions to the hospital, and MACE. Each event is scored (ranging from 1 to 3 points) separately. Table 6.1 shows an overview of the primary outcome and the scoring system. The scores of all events are combined to calculate a total score. Only the most serious complication is counted per event (e.g., when a percutaneous coronary intervention [score 1] is complicated by a stroke [score 2], the score will be 2 and not 3 \([1 + 2]\)).
The concept of the composite weighted score is adapted from the African–American Heart Failure Trial\textsuperscript{41}. Functional status is assessed through two health domains of the Medical Outcomes Study 36-item General Health Survey (RAND–36 V.2)\textsuperscript{42}: physical functioning and physical health problems. The primary endpoint is evaluated at three months (T4) and one year (T6) after surgery (Figure 6.1). Deep wound infections and surgical re-explorations are screened up to 120 days, after surgery. Other postoperative surgical complications are measured in the period between the surgery and when a patient meets the UMCG discharge criteria (Table 6.2). Hospital admissions are checked between baseline and one year after surgery. To prevent bias (since the Heart-ROCQ group follows the inpatient CR phase after surgery), hospital admissions between the day of admission before surgery and 30 days after surgery are not included when determining the (calculated) primary endpoint.

SECONDARY OUTCOMES

Complications and events
All individual components of the composite endpoint regarding the complications and events will be analysed separately as secondary outcomes. Table 6.3 summarises the definitions of the secondary complications and events, including at the time of screening. All documents concerning the composite primary endpoint and the secondary complications are encrypted and subsequently adjudicated by the independent endpoint committee. The endpoint committee consists of four members (cardiologists and cardio–thoracic surgeons), who are not employed in the UMCG and are blinded to group allocation.

Questionnaires and physical tests
Table 6.4 shows the physical tests and questionnaires of the secondary outcomes regarding physical and psychological health, lifestyle risk factors, and the economic evaluation. Physical tests and questionnaires are completed at six assessment points (Figure 6.1). The preoperative measurements (T1 and T2) are conducted at the start (preoperative consultation) and the end (1–8 days before surgery) of the waiting period. The third measurement (T3) is performed when patients meet the UMCG discharge criteria (Table 6.2). The follow-up measurements (T4, T5, and T6) are at three, seven, and 12 months after surgery. Patients are asked to fill in questionnaires online or when requested on paper, prior to the visits for the physical tests. All adverse events reported spontaneously by the patient or observed by the investigator are recorded. In addition, serious adverse events are reported to the METc. Data are stored in REDCap and on a secure drive at the CardioResearch department in the UMCG. Two times per year, the study is monitored by a trained research monitor from another department of the UMCG. Details of procedures, data collection, management and monitoring can be found in the Trial Master File of the Heart–ROCQ study (can be obtained by the investigators). On 12 June 2018, the study was audited and certified for ISO 9001: 2015 independently by DNV GL.
**Table 6.1 definitions and score of the components of the composite primary endpoint**

<table>
<thead>
<tr>
<th>FUNCTIONAL STATUS</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening in physical functioning (domain score of health-related quality of life, RAND-36 V.2)*</td>
<td>1</td>
</tr>
<tr>
<td>No change or improvement in physical functioning*</td>
<td>0</td>
</tr>
<tr>
<td>Worsening in physical problem (domain score of health-related quality of life, RAND-36 V.2)*</td>
<td>1</td>
</tr>
<tr>
<td>No change or improvement in physical problem*</td>
<td>0</td>
</tr>
<tr>
<td>A clinically relevant worsening is classified as minimal change according to Wyrwich and colleagues (2004)*3</td>
<td></td>
</tr>
</tbody>
</table>

(SERIOUS) ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No serious adverse event.</td>
<td>0</td>
</tr>
<tr>
<td>Prolonged mechanical ventilation</td>
<td>Mechanical ventilation longer than 24 hours.</td>
</tr>
<tr>
<td>Lung infection</td>
<td>(1) A new lung radiographic infiltrate and (2) two signs that the infiltrate is of infectious origin – that is, (a) fever: body temperature &gt; 38°C or &lt; 36°C; (b) leukocytosis – white cell counts &gt; 10x10⁹/L or &lt; 4x10⁹/L; (c) positive sputum culture; and/or (d) decline in oxygenation</td>
</tr>
<tr>
<td>Delirium</td>
<td>(1) A DOS* score ≥ 3 at hospital ward and/or (2) diagnosis confirmed by a psychiatrist, geriatrist or supervising specialist according to the DSM-IV criteria resulting in treatment with medication</td>
</tr>
<tr>
<td>Readmissions to intensive care unit</td>
<td>Unrelated to a secondary endpoint</td>
</tr>
<tr>
<td>Deep wound infection</td>
<td>Deeper tissues are affected (muscle, sternum and mediastinum) and must include (1) surgical drainage/refixation or (2) an organism is isolated from culture of mediastinal tissue or fluid, or (3) antibiotic treatment because of sternum wound.</td>
</tr>
<tr>
<td>Readmissions to hospital</td>
<td>An unplanned hospital stay with different dates of admission and discharge with a medical indication (i.e., clinical signs and symptoms or change of treatment).</td>
</tr>
<tr>
<td>Any cardio-thoracic surgical interventions</td>
<td>Graft or valve failure, CABG, valve, aortic, or other cardiac surgery.†</td>
</tr>
<tr>
<td>Any percutaneous interventions</td>
<td>PCI, TAVI and so on.</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>According to the third universal definition of myocardial infarction.‡</td>
</tr>
<tr>
<td>Cerebral vascular accident / stroke</td>
<td>Acute neurological event of at least 24 hours in duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT, MRI or pathological confirmation.</td>
</tr>
<tr>
<td>Sudden death survivor</td>
<td>The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, and ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.</td>
</tr>
<tr>
<td>Death</td>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>

Total score = sum of physical status and SAEs at three months and one year (worst score of each event)

In gray, postoperative complications can be scored ones. *Compared with baseline. †According to the definitions of the ‘Begeleidingscommissie Hartinterventies Nederland’. ‡Thygesen and colleagues (2012)*44. CABG: coronary arterial bypass graft; DOS: delirium observation screening scale; DSM: diagnostic and statistical manual of mental disorders; PCI: percutaneous coronary intervention; RAND-36 V.2: Medical Outcome Study 36-item General Health Survey; SAE: serious adverse event; TAVI: transcatheter aortic valve implantation.
Potential moderators

Preoperative risk profile (i.e., Euroscore II, medical history, lifestyle risk factors, and physical, and mental status), surgery parameters, and demographics are collected from the medical record and baseline measurements. The content of the CR programme is described in terms of compliance, duration of CR programme, type of treatment, frequency, and training load (i.e., for bicycle training: external workload, *Not measured between the day of admission before surgery and 30 days after surgery because of POST-in phase of the Heart-ROCQ programme; †Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) will be classified as cardiac death; CABG: coronary artery bypass grafting; ICU: intensive care unit; PCI: percutaneous coronary intervention; T4: follow-up at three months after surgery; T6: follow-up at 12 months after surgery.

Table 6.2 Discharge criteria of the University Medical Center Groningen

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 activity of daily living activities (i.e., going independently to the toilet).

Table 6.3 Definitions of the secondary complications and events

<table>
<thead>
<tr>
<th>DEFINITIONS</th>
<th>TIME OF MEASURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Surgery to T3</td>
</tr>
<tr>
<td>New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion.</td>
<td></td>
</tr>
<tr>
<td>Prolonged ICU stay</td>
<td>Initial stay</td>
</tr>
<tr>
<td>When the number of calendar days is two or more from ICU admission to discharge.</td>
<td></td>
</tr>
<tr>
<td>Readmissions to hospital</td>
<td>Baseline to T6*</td>
</tr>
<tr>
<td>The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (i.e., clinical signs and symptoms or change of treatment).</td>
<td></td>
</tr>
<tr>
<td>a) Directly related to a cardiac cause.</td>
<td></td>
</tr>
<tr>
<td>b) Not directly related to a cardiac cause.</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation days</td>
<td>Baseline to T6*</td>
</tr>
<tr>
<td>Total number of days of hospitalisation.</td>
<td></td>
</tr>
<tr>
<td>a) Directly related to a cardiac cause.</td>
<td></td>
</tr>
<tr>
<td>b) Not directly related to a cardiac cause.</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Baseline to 5 years after surgery</td>
</tr>
<tr>
<td>Any death due to proximate cardiac or cardiovascular cause (e.g., myocardial infarct, low-output failure, fatal arrhythmia, death secondary to a cerebral vascular accident, pulmonary embolism, ruptured or dissecting aortic aneurysm, or other vascular diseases), unwitnessed death, and death of unknown cause, and all procedure related deaths (e.g., PCI, CABG), including those related to concomitant treatment†.</td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>Baseline to 5 years after surgery</td>
</tr>
<tr>
<td>Any death not covered by the above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.</td>
<td></td>
</tr>
<tr>
<td>CONCERNING SAFETY</td>
<td></td>
</tr>
<tr>
<td>Surgical re-exploration for bleeding/ tamponade</td>
<td>Surgery to T4</td>
</tr>
<tr>
<td>Surgical incision into the sternum as a result of a bleeding or tamponade.</td>
<td></td>
</tr>
<tr>
<td>a) Acute: presented within 24 hours after surgery.</td>
<td></td>
</tr>
<tr>
<td>b) Late: presented after 24 hours after surgery.</td>
<td></td>
</tr>
<tr>
<td>Surgical re-exploration dehiscence</td>
<td>Surgery to T4</td>
</tr>
<tr>
<td>Aseptic wound dehiscence.</td>
<td></td>
</tr>
</tbody>
</table>

*Not measured between the day of admission before surgery and 30 days after surgery because of POST-in phase of the Heart-ROCQ programme; †Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) will be classified as cardiac death; CABG: coronary artery bypass grafting; ICU: intensive care unit; PCI: percutaneous coronary intervention; T4: follow-up at three months after surgery; T6: follow-up at 12 months after surgery.
Potential mediators

Illness perceptions (i.e., patients’ mental representations of their illness based on different sources of information) are measured with three subscales (personal control, treatment control, and consequences) of the Revised Illness Perception Questionnaire\textsuperscript{60}. These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress\textsuperscript{61}. The Cardiac Self-efficacy (CSE) Scale\textsuperscript{59} is used to measure CSE (i.e., patients’ confidence to perform a specific task related to cardiac disease).
STATISTICAL ANALYSES

Sample size
Assuming a normal distribution, the mean weighted score of the primary endpoint is estimated on 1.0 with an SD of 0.9 at 1 year after surgery. This estimation is based on historical data of the UMCG, an unpublished ongoing pilot study in the UMCG, the Dutch registration database62 and data reported in literature6,63–65. A decrease of 0.3 is expected in the Heart-ROCQ group, based on previous studies comparing CR with standard care36,64,66 (i.e., no CR), and is considered to be clinically relevant (i.e., on average a 30% decrease in complications/events or worsening in functional status, or 10–20% decrease in MACE or death). To detect this decrease and achieve 80% power (significance level of 5%), a group of 286 patients (143 in the Heart-ROCQ group and 143 in the Standard Care group) is needed. To incorporate a withdrawal of ±20%, a total sample size of 350 is needed at baseline.

Interim analysis
An interim analysis will be conducted when 40% of the included patients have had the measurements 1 year after surgery. The study will be terminated prematurely when the primary outcome of one of the CR programmes is obviously (P < 0.001) different from the other CR programme.

Primary and sensitivity analyses
All endpoints are primarily analysed according to the ‘intention-to-treat’ principles and missing values are counted as worst-case score (nominal variables) or estimated using maximum likelihood estimation (interval variables). As supplementary analyses, the endpoints are analysed on a per-protocol principle with and without using imputation methods for missing values. In all analyses, a two-sided p < 0.05 is considered statistically significant.

The total score of the primary endpoint will be handled as a continuous variable. All continuous variables will be analysed using linear mixed models to determine ‘time x group’ differences. Significant interactions will be further explored using the Bonferroni post-hoc test to determine differences between each time point. Non-parametric tests will be used if the assumptions of normal distribution are violated. More information about the statistical methods and clinical relevance are written in the research protocol (ClinicalTrials.gov : NCT02984449).

Economic evaluation
For the evaluation of healthcare utilisation, standard prices published in the Dutch costs guidelines are used67. To compare the costs with quality-adjusted life years (QALYs), QALYs are estimated with use of the EuroQol Five-Dimensional Questionnaire (EQ–5D–5L)58. Utility values for the EQ–5D–5L are calculated based on the new Dutch tariff68. Results from the analysis are reported as an incremental cost-effectiveness ratio, dividing the difference in effect by the difference in costs. Bootstrap resam-
pling will be performed, and cost-effectiveness acceptability curves will be plotted, to estimate the probability that the Heart-ROCQ programme is cost effective when compared with standard care. A societal perspective is applied.

**STUDY STATUS**

From May 2017 to December 2018, 75 patients were enrolled. In the following years we expect that the enrolment will increase to 85 patients per year. The last patient is expected to be included in July 2021.

**PATIENT AND PUBLIC INVOLVEMENT**

In a pilot study (to be submitted), patient satisfaction and feasibility (in terms of accessibility, compliance, training load and safety) of the Heart-ROCQ programme have been evaluated. Patients were very satisfied with the programme, scoring it 8 out of 10, therefore we did not change the content of the programme. However, patients' rate of perceived exertion was generally quite low and no serious adverse events occurred during the bicycle training. For safety reasons the intensity was not increased. However, in order to estimate the maximum load more accurately and better tailor the programme to the individual, we decided to change one of the stop criteria of the preoperative submaximal ergometry test from 70% to 90% of expected maximal heart rate. Furthermore, our outcomes are, among others, based on the reasons why patients recommended the programme to other patients. For example, patients reported that their self-efficacy and physical capacity were improved, so we added the CSE questionnaire and physical tests to objectively measure these outcomes. In this way the results were taken into account in the further development of the Heart-ROCQ programme and the protocol of this study. The results of this trial will be distributed by various information channels (e.g., websites of cardiac patient organisations, social media). Two to three times a year we provide a newsletter about the progress and (in the end) the results of the study are sent to patients, who are interested.

**Discussion**

The Heart–ROCQ study is the first randomised clinical trial evaluating the effect of a combination of preoperative and postoperative CR programme compared with a postoperative CR programme. Unlike the vast majority of CR programmes in previous studies, the current programme is multidisciplinary targeting different aspects of surgical outcomes in patients undergoing cardiac surgery. Because different aspects are targeted, a composite weighted score will better reflect the treatment benefits than a single outcome. Therefore, the primary endpoint is a composite endpoint of functional status, postoperative surgical complications, readmissions to the hospital and MACE. The components of the endpoint are of clinical importance to patients undergoing cardiac surgery and reflect a comprehensive representation of the recovery of the patient.
Both the ideas of the primary combined endpoint and the weighting of the individual components were derived from other studies\textsuperscript{41,69,70}. Assigning different weights to the components was needed for more accurate comparison. Since the components are not equal in clinical importance, equal weights would lead to inaccurate statistical analysis\textsuperscript{70}. In the current study, the weighted score of HR-QoL is lower (1 point instead of 2 points) to minimise bias due to patients' knowledge of group allocation. Therefore, improvements in quality of life are not counted in the primary endpoint to prevent bias in a positive direction. This also prevents that a score in quality of life and adverse event cancel each other out (e.g., when a patient experiences an improvement in Quality in Life [+2 points] and has a stroke [-2 points] then the total score is 0). The scores of all-cause mortality, stroke, myocardial infarction and revascularisation are in line with the results shown by Tong and colleagues (2013)\textsuperscript{70}. A disadvantage of composite endpoints is that the effect may be driven by complications that occur with the greatest frequency\textsuperscript{71}. Therefore, postoperative complications which occur frequently, such as atrial fibrillation, are evaluated separately as secondary endpoint. The primary endpoint is evaluated by an end-point committee, which is blinded to group allocation and consists of four independent cardiologists and cardio-thoracic surgeons.

Previous preoperative CR studies were primarily focused on short-term effects; only one preoperative CR study and a few postoperative CR studies have determined long-term effects\textsuperscript{23,35,36,72}. In contrast to previous preoperative CR studies, the Heart-ROCQ study sets out to investigate both short-term and long-term effects of the CR programmes\textsuperscript{23,35,36}. Due to the trends in, among others, increasing age, obesity and physical inactivity, patients undergoing cardiac surgery are becoming more complex. The Heart-ROCQ programme aims to address these issues, which makes the programme clinically relevant for all cardiac surgery patients. Therefore, we chose to include different types of cardiac surgery. Since different moderators and mediators are assessed before, during and after CR, we can explore which factors are associated with better outcomes and which working mechanisms contribute to its effectiveness. These findings may provide a more in-depth understanding of who benefits the most from CR in both the short- and long-term and the underlying mechanisms of CR, which are still not fully understood in patients undergoing cardiac surgery\textsuperscript{35}. In addition, the present study is thought to considerably contribute to the evidence to further develop guidelines for clinical practice, especially regarding the preoperative CR programme\textsuperscript{73}.

The Heart-ROCQ programme is expected to be cost-effective in the long-term, which is also of interest for policymakers and healthcare providers. Therefore, an economic evaluation is performed to assess the cost-effectiveness of CR, since little is known about the cost-effectiveness of CR\textsuperscript{64}. A societal perspective of this economic evaluation is chosen, meaning that healthcare costs and patient-related and productivity-related costs and benefits are taken into account. If the Heart-ROCQ programme is proven to be effective, it might be advisable to include a supportive prevention-oriented waiting period prior to surgery as an integral part of the treat-
ment for patients undergoing elective cardiac surgery. This implies a paradigm shift from curative care following cardiac surgery to an additional preventive care attitude before surgery. Extensions of rehabilitation options in, or in the vicinity of cardiac centres, will then be required.

The Heart-ROCQ study is the first randomised clinical trial comparing the effect of a combined preoperative and postoperative CR programme with a regular Dutch phase II post-surgery outpatient rehabilitation CR programme in a population undergoing elective cardiac surgery. This study is expected to provide new understanding of the effectiveness and underlying working mechanisms of CR, and subsequently to improve value-based healthcare.
Declarations

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AUTHORS’ CONTRIBUTORS
Conception and design of the study: JH, FB, MJLD, MFR, WD, JF, LHVvdW, PVdH and MAM. Methodology: JH, FB, SD, MJLD, MFR and PVdH. Acquisition of data: JH, FB and SD. Writing – original draft, tables and figures: JH. Writing – reviewing and editing: FB, SD, MJLD, MFR, WD, ICCvdH, JF, LHVvdW, PVdH and MAM. Supervision: MJLD, MFR, WD, JF, ICCvdH, LHVvdW, PVdH and MAM. Funding acquisition: JH, SD, JF, LHVvdW, PVdH and MAM. All authors approved the final version of the manuscript.

COMPETING INTERESTS
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Supplementary information

ADDITIONAL FILE 6.1
A detailed description of the Heart-ROCQ programme.

Supplementary information is not printed, but can be found at https://bmjopen.bmj.com/content/9/9/e031738#DC1
References


