Patient-reported outcomes after cardiac surgery

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Things that really matter

Fredrike Blokzijl

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CONTENT

CHAPTER 1

GENERAL INTRODUCTION

Origin of cardiothoracic surgery

During the late 19th and early 20th centuries, surgery to correct cardiac trauma or existing cardiac conditions was considered to be highly experimental (1). In 1913 Alexis Carrel performed the first coronary bypass surgical procedure on a dog, with use of a carotid artery segment as a bridge between the aorta and left coronary artery (1). His operation encountered great resistance from his colleagues, nevertheless he predicted that coronary bypass could be performed on humans in the foreseeable future. It took almost 50 years until the first successful coronary bypass operation was performed by Robert Hans Goetz in 1960 (1). In the subsequent years more and more people underwent coronary artery bypass grafting (CABG). Meanwhile, other cardiac conditions like valve stenosis and atrial septal defects were successfully treated with open-heart surgery and the department of cardiovascular- and thoracic surgery was founded.

Current status and developments

Nowadays, cardiovascular disease (CVD) is the number one cause of death worldwide and the number two cause of death in Europe (2). In 2018, 37.769 people in the Netherlands died due to cardiovascular disease, with an average age of 78 years for men and 84 years for women (3). Due to improvements in operative techniques along with general advances in medicine (i.e. secondary prevention after myocardial infarction), people with CVD are becoming older, leading to an elderly population undergoing cardiac surgery. More than half of the cardiac surgery interventions are being performed in patients older than 75 years and this group is rising over time (4).

Together with an aging patient population, the importance of outcome measures has shifted from the physician's perspective toward the patient's perspective (5). Patient Reported Outcomes (PROMS) such as symptom relief, quality of life or satisfaction with care, are reported directly by the patient without interpretation by a physician or other medical professional (6). These types of outcome measures are better met with measures of *patient-centered* outcomes, because they are of particular concern to the patient (7). The World Health Organization defines Quality of Life (QoL) as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (8). It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment (8). QoL encompasses not just the absence of disease but the presence of physical, mental and social well-being, judged by the person himself and is therefore subjective. QoL has become an increasingly important aspect in medicine and social sciences over the last years. Currently, QoL is regarded as a quality indicator by hospitals and other healthcare institutions because it provides information on the experience of patients and can therefore improve quality of care.

Although the first publications on QoL post cardiac surgery date from the beginning of the 1970s (9,10) and QoL is often addressed in the ESC/EACTS treatment guidelines for cardiac disease (11,12), the evidence base for postoperative patient-reported outcome measures including QoL after cardiac surgery, is still in its infancy and needs to be strengthened (13–15). Studies are needed to provide doctors and other allied healthcare professionals with reliable data to evaluate potential harms and benefits of a cardiac surgical treatment on QoL and other patient-reported outcomes. Subsequently patients and their families can be informed on the harms and benefits of a treatment during preoperative counseling to enable shared-decision making. Shared-decision making is an approach where clinicians and patients share the best available evidence when faced with the task of making decisions and where patients are supported to consider options, to achieve informed preferences (16).

AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on the impact of cardiac surgery on patient's daily lives by studying QoL and several other patient-reported outcomes after cardiac surgery. The overarching aim of this thesis is to contribute to the knowledge of patient-reported outcomes after cardiac surgery. Three major questions are addressed in this thesis:

1. What is the influence of cardiac surgery on patient-reported outcomes such as quality of life and return to work?
2. Do patients undergoing cardiac surgery, benefit from cardiac rehabilitation in terms of patient-reported outcomes?
3. Are elderly patients more at risk of a decreased quality of life after surgery?

The following chapters deal with different aspects of these three questions. In **chapter 2** results of cardiac rehabilitation after cardiac surgery on various outcomes are reported in a systematic review. In **chapter 3** the results of an observational study on quality of life among elderly patients compared to younger patients one year after CABG are described. **Chapters 4 and 5** involve the results of a multicenter study on quality of life among patients in different age groups after CABG or surgical aortic valve replacement. **Chapter 6** comprises a qualitative study describing the experiences and opinions of patients and their spouses on return to work after CABG. **Chapter 7** reports the outcomes of a prospective study on the prevalence of postoperative cognitive dysfunction and the association with quality of life after CABG. In **chapter 8** the protocol for the Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life (HEART-ROCQ-study) is described. Finally, **chapter 9** provides a general discussion of the study results, their clinical implications and addresses possible directions for future research.

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Chapter 2

CARDIAC REHABILITATION FOR PATIENTS HAVING CARDIAC SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Cardiac rehabilitation (CR) is recommended for all cardiac patients including patients after cardiac surgery. Since the effect of CR after cardiac surgery has not been well established yet, we conducted a systematic review on the effects of CR for patients after cardiac surgery compared to treatment as usual.

Evidence acquisition: A systematic review of randomized clinical trials (RCTs), quasi-randomized and prospective observational studies in The Cochrane Library, PubMed/MEDLINE and EMBASE was undertaken until October 18th 2017. Adults after any kind of cardiac surgery were included. Primary outcome was all-cause mortality, other outcomes were serious adverse events, health-related quality of life, work participation, functioning and costs/cost-effectiveness. Risk of bias was evaluated and the quality of evidence was assessed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.

Evidence synthesis: Eighteen RCTs and 15 observational studies were included. Low risk of bias was only observed in one observational study. Meta-analysis of RCTs suggested no significant difference of CR compared to control on mortality (random-effects relative risk (RR) 0.93 (95% CI: 0.40-1.81), while observational studies suggested statistically significant beneficial effect associated with CR (random-effects RR=0.49, 95% CI: 0.35 - 0.68). CR did not significantly affect any of the other outcomes. Due to the limited data TSA could not be performed.

Conclusions: The body of evidence does not allow us to reach any reliable conclusions about the effectiveness of CR following cardiac surgery. Future trials need to be conducted with low risks of bias and clearly defined outcomes.

INTRODUCTION

Over the last decades outcome of cardiac surgery has improved due to continued advances in operative techniques, including myocardial protection, and perioperative care (1). International guidelines recommend cardiac rehabilitation (CR) for patients with cardiovascular disease (CVD) to improve functioning and also to slow or reverse progression of disease by healthier lifestyle eventually to reduce morbidity and mortality (2–7). CR is a complex intervention of one or several components including exercise training, education, psychosocial management and/or a behaviour-modification program (4,7,8). It is likely that CR is also beneficial for patients after cardiac surgery although these patients have different diseases and interventions, compared to patients with CVD. More important, it is uncertain which component of CR is beneficial for patients having cardiac surgery including sternotomy. Systematic reviews which have claimed benefit of CR for patients after cardiac surgery have merged heterogeneous populations of cardiac surgery, coronary artery disease and patients with heart failure (9–12).

One recently published systematic review evaluated exercise-based cardiac rehabilitation specifically for patients having heart valve surgery and found that CR may improve exercise capacity (13). Unfortunately, the effect on other outcomes could not be evaluated due to insufficient data. No systematic review has evaluated CR either given pre- or postoperatively in patients having cardiac surgery in general, or has evaluated a wide range of functioning outcomes, quality of life and economic aspects. We conducted a systematic review, with meta-analyses and trial sequential analysis to evaluate effectiveness of CR for patients after cardiac surgery compared to medical treatment as usual. We specifically hypothesized that the physical exercise component of CR may be beneficial in patients having cardiac surgery including sternotomy.

EVIDENCE ACQUISITION

This systematic review was performed following recommendations of The Cochrane Handbook for Systematic Reviews of Interventions (14) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (15,16) (Supplementary Material Table I). The protocol for this review was registered in the international prospective register of systematic reviews (PROSPERO) prior to conduct no. CRD42016051544 (Supplementary Material 2 Text File 1) (17).

Eligibility criteria

We included all prospective comparative studies involving adults (18 years and older) after cardiac surgery irrespective the underlying type of cardiovascular disease and irrespective their age. All types of surgical procedures were included, irrespective their timing (emergency or planned surgery). We evaluated the intervention effect in the overall group and then in subgroups, since the major strength of any meta-analysis is increased power and precision. Most frequently performed procedures in cardiac surgery include coronary artery bypass grafting (CABG), valve repair or -replacement, aortic surgery, or combinations of these.

Comparative studies including combinations of heterogeneous patients, for instance, patients after myocardial infarction and cardiac surgery patients, were considered for inclusion if most participants (≥ 80%) had cardiac surgery.
We assessed the benefits and harms of exercise-based CR for patients having cardiac surgery as we hypothesized that specifically the physical exercise component of CR may be beneficial. We defined "exercise-based" interventions as any kind of exercise training focusing on increasing exercise capacity, in either a supervised or unsupervised program conducted in an inpatient, outpatient, community, or home-based setting. The intervention was required to include any exercise training which could either occur pre- or postoperatively. We applied no restrictions in length, intensity, or content of the exercise training. Co-interventions, such as psychosocial management, lifestyle, or education were allowed. The control intervention was defined as standard medical care and follow-up and was allowed to include psychosocial and/or educational interventions, but no structured exercise training. We considered all randomized clinical trials for inclusion irrespective blinding, publication status, sample size or language. We also included quasi-randomized and prospective observational comparative studies but risk of bias and results were evaluated separately.

Search strategy
The search strategy was completed by a librarian and checked by a second librarian. Searched databases included The Cochrane Library, PubMed/MEDLINE and EMBASE until 18th October 2017. We also searched references of the identified studies to identify any further relevant trials, *i.e.* backward snowballing. The detailed search strategies are listed in the supporting information files (Supplementary Material 3, Text File 2).

Study selection and data extraction
Two authors (FB and WD) independently selected randomized trials and observational studies for inclusion. Clearly irrelevant hits were excluded based on title and abstract, and remaining hits were evaluated based on full text. Differences in opinion were resolved through discussion and studies excluded based on full text were all listed with reasons for exclusion. We contacted corresponding authors for any unclear or missing information. The following data was extracted: study characteristics (lead author, publication year, study design, risks of bias, numbers of patients enrolled), participant characteristics (baseline characteristics, type of surgery), intervention characteristics (sequence, timing, modalities, and intensity) and outcomes.

Outcome measures
The primary outcome was all-cause mortality at maximum follow-up. Secondary outcomes were serious adverse events (SAEs), health-related quality of life (HRQoL), work participation, functioning, and costs/cost-effectiveness. The outcomes are defined in the review protocol (17). In addition, measures to evaluate functioning were considered from a patient perspective in terms of the ability to perform daily activities.

Risk of bias assessment

Risk of bias assessment was performed by two reviewers independently using the Cochrane's Collaboration's risk of bias tool for Randomized Clinical Trials (RCTs) (14). The following risk of bias domains were assessed for each trial: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias (academic or funding bias, low inclusion rate). Trials with one or more of the risk of bias domains scored as unclear or high risk were classified as having high overall risk of bias. Risk of bias of observational studies were assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (18). This tool can be used for quantitative non-randomized studies estimating the effectiveness of an intervention. The six domains include: confounding, participant selection, intervention classification, departure from intended interventions, missing data, measurement of outcomes, and selection of reported results (19). For each domain, an outcome of low or moderate risk of bias (summarized as low risk of bias), serious or critical risk of bias (summarized as high risk of bias) and no information for risk of bias was assessed. Observational studies were classified as having low overall risk of bias if all the domains were assessed as low risk.

Statistical analysis

We performed the meta-analyses according to The Cochrane Handbook for Systematic Reviews of Interventions (14) and The Cochrane Hepato-Biliary Group Module (20). We used the software package Review Manager v. 5.3.5 for meta-analyses (21). For Trials Sequential Analysis, the TSA program v. 0.9 beta was used (22).Dichotomous outcomes were presented in relative risks (RR) with TSA-adjusted confidence intervals (CI) and continuous outcomes in mean differences (MD) or weighted mean differences (WMD) with TSA-adjusted CI, provided there were two or more trials for an outcome. For rare events (<5% in the control group) we calculated odds ratio's (OR) and for very rare events (<2% in the control group) we used Peto's OR (14). We used a fixed-effect model (23) and a random-effects model (24) and presented both models in case of discrepancy. Considering the anticipated clinical heterogeneity (in populations, interventions and settings) we emphasized the result from the random-effects model providing the most conservative estimate of effect and/or confidence interval except in the presence of one or few large trials. Heterogeneity was explored by the chi-squared test with significance set at p-value of 0.10, and the quantity of heterogeneity was measured by I^2 (25).

The following subgroup analysis were pre-planned (1) bias risk (low risk of bias trials compared to high risk of bias trials); (2) sequence of the rehabilitation intervention (pre-surgery rehabilitation versus post-surgery rehabilitation); (3) types of patients (patients having CABG compared to other cardiac surgery patients). Funnel plots were used to explore small trial bias provided data from more than ten randomized trials were available (14).

Trial Sequential Analysis

Meta-analyses may result in type-I errors due to an increased risk of random error when few data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials (26–30). We applied TSA since it controls the risks of type I and type II errors in a cumulative meta-analysis and may provide important information on how many more patients need to be included in further trials. The idea in TSA is that if the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit or harm, a sufficient level of evidence has been reached and no further trials may be needed. If the Z-curve does not cross the boundaries for benefit, harm or futility and the required information size has not been reached, there is insufficient evidence to reach a conclusion (22,23,25).

GRADE approach

We used GRADE to assess the quality of the body of evidence associated with each of the major outcomes in our systematic review using GRADE software (31). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within study risk of bias, indirectness of evidence, heterogeneity of data, imprecision of effect estimates and risk of publication bias.

EVIDENCE SYNTHESIS

The search strategy identified 9108 hits (Figure 1). Three additional hits were identified by backward snowballing. After removal of duplicates and clearly irrelevant hits based on title and abstract 139 hits remained. A total of 99 hits were excluded based on full text evaluation. All excluded studies with reason for exclusion are listed in the supporting information (Supplementary Material 4 Table II). A total of 40 papers, reporting 33 studies (18 RCTs and 15 observational studies) were included in this systematic review. Six papers reported results of one randomized trial (32–37), two papers reported results of another randomized trial (38,39) and two referred to one observational study (40,41). The authors of three studies were contacted for missing data, of which two responded (42,43).

Characteristics of the included studies

Eighteen randomized trials (33,38,44–59) and fifteen observational studies (40,42,43,60–71) evaluated 3654 patients (Table I, II). One trial used a four-arm parallel group design (48) and three studies, one RCT (59) and two observational studies (63,69) used a three-arm parallel group design; all others had a two-arm group design. Twenty-five studies (fifteen RCT's and ten observational studies) included only CABG patients, one study included patients with type-A aortic dissection (62), three RCT's included patients with valve repair/replacement (38,49,56) and four observational studies included patients with combined procedures (43,63,65,70). All interventions included a postoperative exercise component, with intensity varying from 20-30 minutes daily to three times a

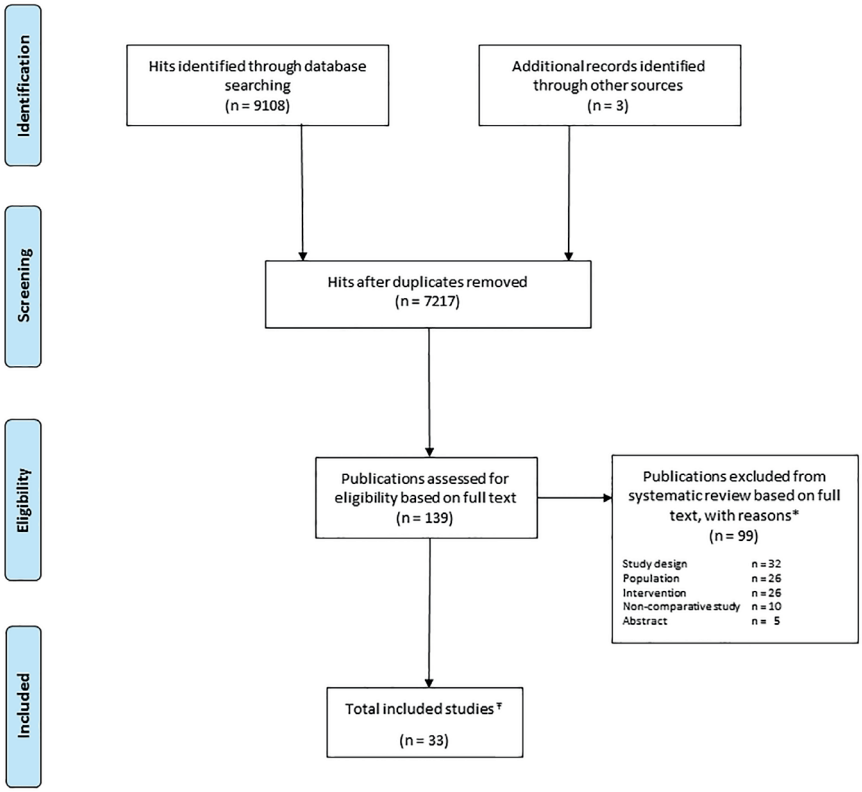


Figure 1. PRISMA flow diagram. *Study design: control group received CR with a physical exercise element. Population: combined population of cardiac and cardiac surgery patients with <80% surgical patients. Intervention: no postoperative exercise training.

week for up to six months. Five studies also used preoperative exercise training during several weeks prior to surgery (47,49,51,57,64). Occasionally, preoperative exercise training was combined with a psychological intervention for patients and relatives (49,51).

Bias risk assessment

Bias risk assessment was performed for eighteen RCT's (14). Low risk of bias was observed regarding sequence generation in eight trials (44%), allocation concealment in five trials (28%), blinding of participants and personnel in none, blinding of outcome assessors in four trials (22%), incomplete outcome data in ten trials (56%), selective reporting in 15 trials (83%), and other risk of bias in seven

Table I. Characteristics of included *randomized trials*

Trial	Year	Patients (n)	Type of surgery	Intervention/ type of CR-program	Start of intervention (weeks after surgery)	Duration (weeks)	Frequency	Max. follow-up (months)	Comparator *	Outcomes
Ågren (44)	1989	37	CABG	physical(hospital)	6	12	3h/week cycling	12	care as usual	functioning
Bilińska (45)	2013	100	CABG	physical(center)	12	6	3h/week cycling	1.5	no physical exercise	SAE, functioning
Engblom[‡] (32–37)	1992 - 1997	228	CABG	physical(center) psycho-educational	8	3	7h/week exercise. Psycho-ed: 2+2 days pre-op + at 8 months	60	standard care	mortality, HRQoL (Nottingham), work participation, functioning
Firouzabadi (46)	2014	70	CABG	physical(center)	4	16	3h/week exercise	4	standard medical care	HRQoL(SF-36)
Herdy (47)	2008	56	CABG	physical(center)	5 days pre + 5 days post (ph I)	2	several hrs daily	0.5	no physical therapy	SAE, functioning
Højskov (48)	2016	60	CABG	1) physical or 2) psycho-ed or 3) physical + psycho-ed (hospital + home)	day 1 (ph I)	4	Resp.training + aerobics twice daily (ph I). Daily walks + home-exercise psycho-ed: 4 consultations	1	standard postoperative instructions	mortality SAE HRQoL(SF-36) functioning
Lin (49)	2004	104	valve	physical psycho-educational (center + home)	pre- and post-op (ph I) + home-based CR	13	resp training (pre-op) + aerobics 30 min during 3x/week	3	routine treatment	mortality SAE functioning
Maiorana (50)	1997	31	CABG	physical(center)	≥ 12	10	3h/week circuit training	3	medical follow-up	SAE, functioning
Mutwalli (51)	2012	49	CABG	physical psycho-educational (hospital + home)	2 days pre + 1 week post (ph I) + home-based	24	30 min daily (ph I + at home). Psycho-ed: 2 h + phone contact	6	standard medical care	mortality HRQoL(SF-36) functioning
Oldenburg (52)	1995	91	CABG	physical(center) psycho-educational	4-8	6	18h/week education or exercise	12	standard care	HRQoL(GHQ) functioning
Ross (53)	2000	190	CABG	physical(hospital) psycho-educational	6	10	2h/week aerobic	4	standard medical care	HRQoL (GHQ) functioning
Salavati (54)	2015	110	CABG	physical (center +home)	≥ 8	5	4h/week + home-based	5	care as usual	HRQoL(Mac New)
Sharif (55)	2012	80	CABG	physical(center) psycho-educational	1	4	2h/week fitness 2h/week education	3	medical follow-up	functioning
Sibilitz (38) Hansen (72)	2016	147	valve	physical psycho-educational	4	12	3h/week exercise monthly (5 times)	6	no exercise program	SAE, HRQoL(SF-36) functioning
Sire (56)	1987	50	valve	physical + vocational (center + home)	8	4	3-4 h daily aerobic vocational evaluation at control	12	no intervention	SAE, functioning work participation
Stein (57)	2009	20	CABG	physical(hospital)	1 day pre + 1 week post (ph I)	6	resp training + daily exercises + walks	1	no physical intervention	mortality, SAE functioning
Tsai (58)	2005	30	CABG	physical(center)	1	12	40 min 3x/week aerobic	3	no CR	functioning
Wu (59)	2006	54	CABG	physical: 1) center or 2) home-based	1	12	1) and 2) 1-3h/week aerobic training	3	no exercise program	functioning

Physical training can be hospital-based, rehabilitation center-based or home-based. CR: cardiac rehabilitation; valve: all kinds of valve repair- or replacements; resp. training: respiratory training;, SAE: serious adverse events; HRQoL: Health Related Quality of life; ph I: phase I rehabilitation. *Comparator defined as stated by the authors. [‡]One randomized trial reported in six papers.

Table II. Characteristics of included *observational studies*

Study	Year	Patients (n)	Type of surgery	Intervention/ type of CR-program	Start of intervention (weeks after surgery)	Total duration (weeks)	Frequency	Max follow-up (months)	Comparator*	Outcomes
Ben-Ari (60)	1986	96	CABG	physical (hospital)	≥ 12	unclear	cycling twice/week	60	usual medical care	work participation functioning
Dolansky (42)	2004	65	CABG	physical (hospital)	6	12	3h/week cycling or treadmill	6	no exercise program	SAE, HRQoL(SF-36) functioning
Dubach (61)	1993	34	CABG	physical(center) psycho-educational	6	4	3h/day walks, calisthenics/fitness Education + diet	2	care as usual	functioning
Fuglsang (62)	2017	29	Type-A aortic dissection	physical (hospital) psycho-educational	6-12	12	3h/week fitness+ muscle strength education+ psycho-social support	3	no CR	HRQoL(SF-36) functioning
Goel (43)	2015	201	valve + CABG	physical+ psycho-ed (hospital)	4-6	12	1–3h/week exercise	120	care as usual	mortality SAE
Hansen (63)	2015	500	valve ± CABG	physical + psycho-educational: hospital CR or municipality CR	4-6	2-24	exercise-training twice/week	12	no CR	work participation cost-effectiveness
Hedbäck ‡ (40,41)	1990 - 2001	147	CABG	physical + psycho-ed (hospital + home)	6	12	2h/week dynamic interval training	120	no physical training program	mortality functioning
Ku (64)	2002	60	CABG	physical (hospital)	1-2 weeks pre + 1-2 weeks post (ph I)	2	walking + participating in activities daily living	1	regular medical care	functioning
Nehyba (65)	2009	72	valve ± CABG	physical(center)	4-8	8	3h/week aerobic	2	no exercise program	functioning
Shabani (66)	2010	60	CABG	physical(hospital)	≤ 8	12	3h/week endurance+ resistance training	4-5	usual care	functioning
Sieber (67)	1986	211	CABG	physical(center) psycho-educational	6	4	daily walks + aerobic/swimming regular group meetings	60	no CR	mortality work participation functioning
Simchen (68)	2001	372	CABG	physical(center) psycho-educational	1-6	12-24	unclear	12	no CR	HRQoL(SF-36) work participation
Wosornu (69)	1996	81	CABG	physical 2 types: 1) aerobic 2) strength	6	24	3x/week 12-40min aerobic or strength training	6	no exercise	functioning
Yuen Yee (70)	2000	152	valve/ CABG/ VSD	physical psycho-educational	unclear	8	2x/week exercise + education	2	no CR	functioning
Zoroufian (71)	2011	67	CABG	physical (center) + psycho-educational	unclear	8	3h/week exercise during first week	2	care as usual	functioning

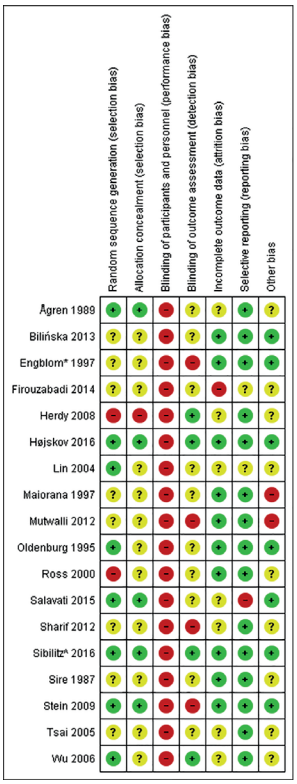
Physical training can be hospital-based, rehabilitation center-based or home-based. CR: cardiac rehabilitation; valve: all kinds of valve repair- or replacements; VSD: ventricular septal defect repair; resp. training: respiratory training; SAE: serious adverse events; HRQoL: health-related quality of life; ph I: phase I rehabilitation. * Comparator defined as stated by the author. ‡ One observational study reported in two papers.

trials (39%). All trials were considered to have high overall risk of bias (Figure 2A). Risk of bias assessment using the ROBINS-I tool was performed for fifteen non-randomized studies (19). Low risk of bias was observed regarding confounding factors in two studies (13%), selection of participants in four studies (27%), classification of interventions in twelve studies (80%), deviations from intended interventions in eleven studies (73%), missing data in seven studies (47%), measurement of outcomes in five studies (33%), and selection of reported results in eleven studies (7%). One observational study was classified as having low overall risk of bias (63) (Figure 2B).

Outcomes

Mortality

Six RCT's (37,48,49,51,56,57) and four observational studies (43,48,67,69) reported all-cause mortality with a maximum follow-up of ten years. Time-specific analyses and subgroup analyses per types of patients showed similar results



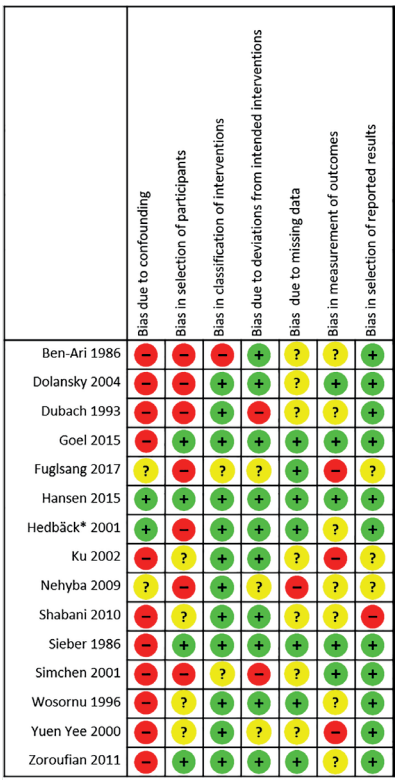


Figure 2A. Risk of bias of randomized clinical trials. *One randomized trial was reported in six papers (32-37). ^One randomized trial was reported in two papers (38, 72).

Figure 2B. Risk of bias of observational studies. *One observational study was reported in two papers (40,41).

(Supplementary Material 5, Figure 1 and 2). One trial reported three deaths but not the allocation group (52). Six randomized trials and four observational studies reported mortality data of 510 and 640 patients, respectively. TSA could not be performed due to a limited amount of data (Supplementary Material 6, Figure 3). No low risk of bias trials reported mortality as outcome. Conventional meta-analysis of high risk of bias randomized trials suggested no statistically significant difference in mortality between exercise-based CR and usual care (random-effects RR=0.93; 95% CI: 0.48 - 1.81), while conventional meta-analysis of high risk of bias observational studies suggest a statistically significant beneficial mortality effect associated with exercise-based CR compared to usual care (random-effects RR=0.49; 95% CI: 0.35 – 0.68; Figure 3). Other subgroup analyses could not be conducted due to insufficient data.

Serious adverse events

Eight randomized trials (38,45,47–50,56,57) and four observational studies (42,43,66,69) reported serious adverse events data of 566 and 407 patients, respectively. TSA could not be conducted due to insufficient data (Supplementary Material 7, Figure 4). Conventional meta-analysis of both high risk of bias randomized trials and high risk of bias observational studies suggested no

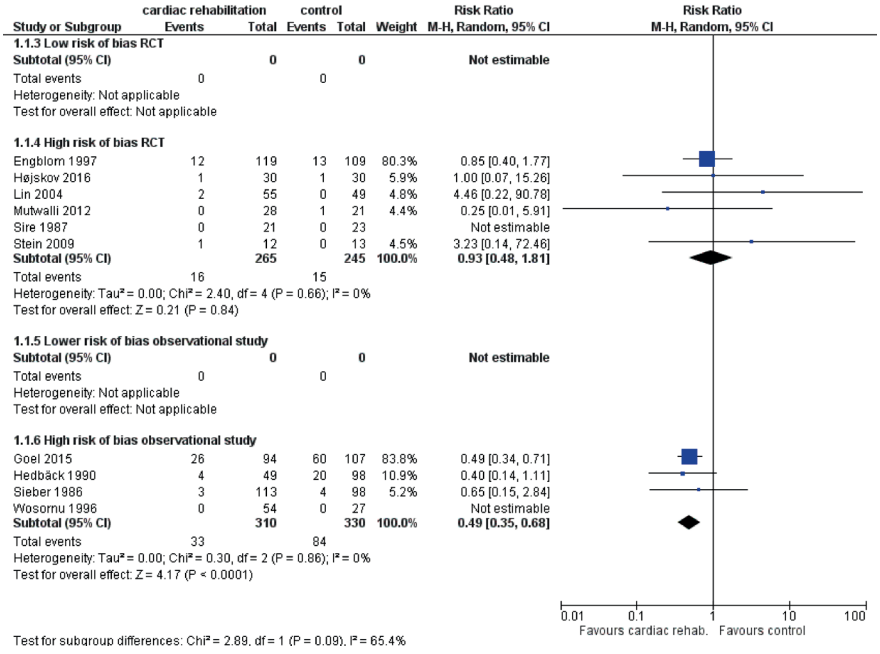


Figure 3. Forest plot of all-cause mortality at maximum follow-up. Randomized trials and observational studies: exercise based CR versus usual care. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars represent 95% confidence intervals (CI).

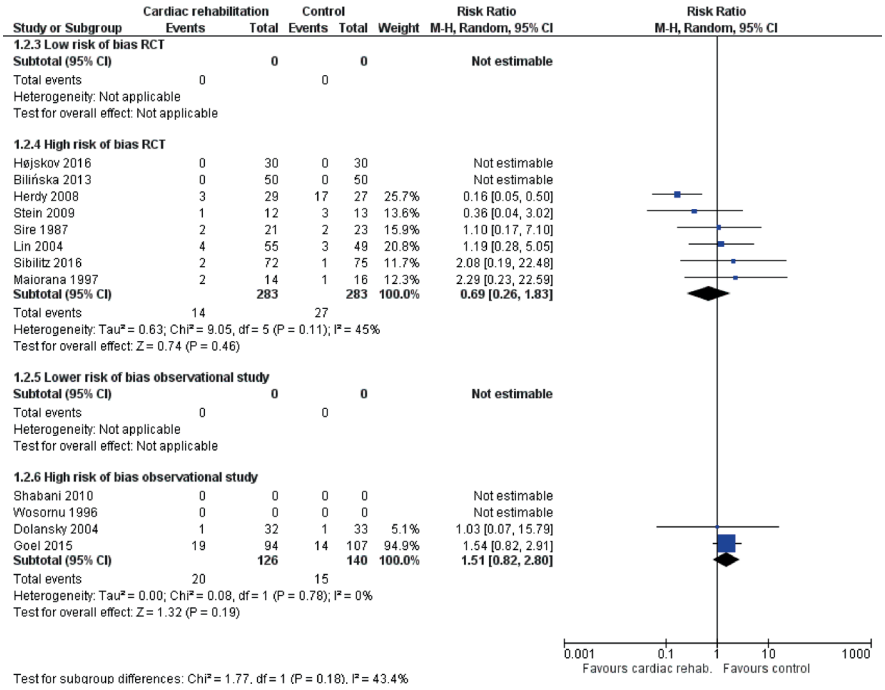


Figure 4. Forest plot of serious adverse events. Randomized trials and observational studies: exercise based CR versus usual care. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars represent 95% confidence intervals (CI).

statistically significant difference in SAEs between exercise-based CR and usual care (random-effects RR=0.69, 95% CI: 0.26 – 1.83 and RR=1.51, 95% CI: 0.82 – 2.80, respectively; Figure 4). Subgroup analyses per types of patients showed similar results (Supplementary Material 8, Figure 5), other subgroup analyses could not be performed due to the limited amount of data.

Health-related Quality of life

Eight randomized trials (37,38,46,48,51–54) and three observational studies (42,62,68) reported health-related quality of life data of 945 and 498 patients, respectively. One study (32) used a self-made questionnaire and the Nottingham Health Profile at five years follow-up (37). Other studies used validated questionnaires of HRQoL, including one disease-specific instrument, the MacNew Heart Disease questionnaire (54) and two generic HRQoL instruments, the General Health Questionnaire (52,53) and the Short-Form 36 (38,42,46,48,51,62,68). The seven studies that assessed HRQoL with the SF-36 used different scales as well as a wide range in follow-up. Meta-analysis of data was deemed inappropriate given the heterogeneity in measures and reporting (Supplementary Material 9, Table III).

Work Participation
Two randomized trials (35,56) and three observational studies (60,67,68) reported return to work of 168 and 559 patients, respectively. Individually, all studies suggest that CR improves return to work. All studies reported one-year follow-up (35,56,60,68) while one study reported 3.7 years follow-up (67). TSA could not be conducted due to insufficient data. Conventional meta-analysis of both high risk of bias trials and high risk observational studies suggested a quicker return to work associated with exercise-based CR compared to usual care (random-effects RR=0.69, 95% CI: 0.50 – 0.95 and RR=0.58, 95% CI 0.46 – 0.73, respectively; Figure 5). Subgroup analyses per types of patients showed similar results (Supplementary Material 10, Figure 6). Two observational studies (56,63) reported sick leave data both before and after surgery and observed no significant differences between CR and usual care.

Functioning
We found a wide variety of measurements which could all be interpreted as functioning (Supplementary Material 11, Table IV). All these functioning measures can be classified in three domains:

- exercise capacity, *e.g*. peak oxygen consumption (VO^2), walking distance, workload expressed in metabolic equivalents (METs) or kilojoules (kJ);
- modifiable risk factors, *e.g.* blood pressure, heart rate, rate pressure product (RPP), blood lipids, smoking behaviour and weight;
- mental well-being, *e.g.* self-esteem or anxiety and depression assessed by questionnaires such as the Hospital Anxiety and Depression Questionnaire (HADS), Beck's Depression Inventory (BDI) or the State-Trait Anxiety Inventory (STAI).

Pooling of data in all three domains was considered inappropriate given the heterogeneity in types and methods of measurements as well as follow-up.

Costs and cost-effectiveness
One RCT (72) including 147 patients reported cost-effectiveness from a societal perspective and reported that CR after heart valve surgery is likely to be cost-effective. One observational study (63) including 500 patients reported costs and cost-effectiveness and concluded that cardiac rehabilitation is cost-neutral from a healthcare perspective. Meta-analysis was not performed due to insufficient data.

GRADE approach
The quality of evidence was assessed using GRADE (31). The quality of evidence was graded either low (work participation) or very low (mortality and severe adverse events), mainly due to risks of bias, inconsistency and imprecision (Table III). HRQoL, functioning, and cost(-effectiveness) could not be graded due to insufficient data for pooling.

Limitations of the study
This review has some limitations. First, CR varied in length, dose and intensity

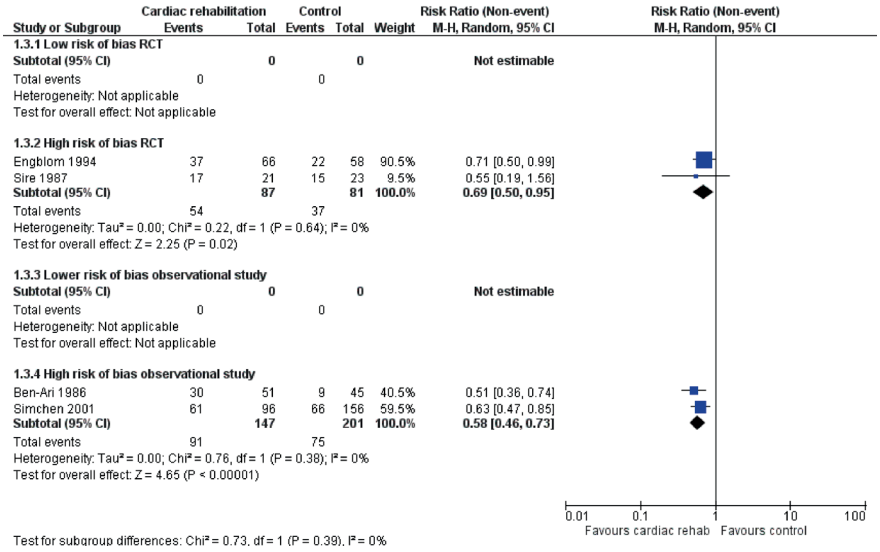


Figure 5. Forest plot of work participation. Randomized trials and observational studies: exercise based CR versus usual care. Events represent numbers of patients who return to work. Size of squares for risk ratio (RR) reflects the weight of the trial in the pooled analyses. Horizontal bars represent 95% confidence intervals (CI).

which means that we merged inpatient CR and early post-discharge programs in this review. Also, CR programs in older studies varied from the modern CR programs evaluated in more recent studies. However, systematic evaluation of an intervention requires inclusion of all possibly relevant studies. Second, like any systematic review this review is limited by the quality of the studies included, and all except one study had high risk of bias. High risk of bias is associated with overestimation of benefit and underestimation of harms (72). Randomized trials may lack external validity due to selection criteria, while observational studies suffer selection bias. For the evaluation of harms and benefits we decided to include both designs as suggested by the Cochrane handbook for systematic reviews of interventions (14). Nevertheless, even with the inclusion of both study designs our question remains unanswered.

CONCLUSIONS

We conducted a systematic review to evaluate the benefits and harms of CR for patients having cardiac surgery. Eighteen RCTs and fifteen comparative observational studies with 3654 patients have been conducted, all except one with overall high risk of bias. The results do not allow us to reach any reliable conclusions about the effectiveness, or lack thereof, of cardiac rehabilitation following cardiac surgery. The pre-planned subgroup analyses concerning bias risk

Table III. GRADEpro summary of findings table of the outcomes of interest

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cardiac rehabilitation	care as usual	Relative (95% CI)	Absolute (95% CI)		
Mortality at maximal follow-up (follow up: range 1 months to 10 years)												
6	randomized trials	serious[a]	serious[b]	not serious[c]	very serious[d]	all plausible residual confounding would reduce the demonstrated effect	16/265 (6.0%)	14/245 (5.7%)	**RR 0.98** (0.50 to 1.91)	**1 fewer per 1,000** (from 29 fewer to 52 more)	⊕◯◯◯ VERY LOW	CRITICAL
serious adverse events (follow up: range 1 weeks to 8 months)												
8	randomized trials	serious[a]	serious[b]	not serious[c]	very serious[d]	all plausible residual confounding would suggest spurious effect, while no effect was observed	15/283 (5.3%)	26/283 (9.2%)	**RR 0.79** (0.26 to 2.36)	**19 fewer per 1,000** (from 68 fewer to 125 more)	⊕◯◯◯ VERY LOW	CRITICAL
Work participation (follow up: range 1 months to 12 months)												
2	randomized trials	serious[a]	serious[b]	not serious[c]	very serious[d]	strong association all plausible residual confounding would reduce the demonstrated effect	54/87 (62.1%)[e]	37/81 (45.7%)[e]	**RR 0.69** (0.50 to 0.95)	**142 fewer per 1,000** (from 23 fewer to 228 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Health-related Quality of Life - not reported												
Functioning - not reported												
Cost-effectiveness - not reported												

CR: cardiac rehabilitation. [a]No trial with low risk of bias in all domains . [b] There was considerable clinical and statistical heterogeneity. [c] Comparator exercise-based CR versus usual care in all trials.[d] Many trials with few patients and few events; less than 5% of DARIS accrued. [e]Events here represent patients returning to work; low quality, TSA not possible.

of trials, sequence of the rehabilitation intervention and types of patients/surgical procedure could not be performed as planned due to insufficient data.
We graded the outcomes of this systematic review following GRADE recommendations. Data on outcomes considered critical for decision making were sparse. Ten studies reported mortality and twelve studies reported SAEs, but such events were often described as reasons for dropouts and withdrawals. Work participation (four studies) and cost-effectiveness (two studies) were sparsely evaluated. All outcomes were primarily studied within short term follow-up missing potential beneficial effects on the longer term. As recommended in other reviews concerning CR (9–11,13), future studies need to consider outcomes at long term follow-up, including work participation and health economic outcomes.

One major important outcome for patients after cardiac surgery is functional recovery in terms of the ability to perform daily activities. This outcome is increasingly important to address, since numbers of elderly patients having cardiac surgery are growing. Data on such outcomes are key important for consenting to surgery and for authorities when allocating resources. Validated tools for assessment of functional status are the Karnofsky Performance Scale, the Barthel Index, or the Katz Index of Independence in Activities of Daily Living. None of the included studies evaluated functional status with one of these tools before and after surgery. The findings of our review are in line with two other reviews (73,74) which concluded that functional status is insufficiently studied in cardiac surgery patients.

Most included studies in this review evaluated physical capacity and modifiable risk factors. The established beneficial effect of CR in patients with cardiovascular disease (CVD) is considered partly attributable to modified risk factors. Modification of risk factors might be less clinically relevant in patients having cardiac surgery either because these risk factors have already been modified or the effect of modification does not translate (anymore) into benefits in daily activities in the older aged. Functional status is specifically important for elderly patients to maintain their independency.

It is likely that exercise-based CR will improve outcome in terms of functioning when properly measured in patients having cardiac surgery. However, the included studies in this review measured functioning by a wide variety of instruments. The Core Outcome Measures in Effectiveness Trials (COMET) initiative (75) has been launched to agree on a standard minimum set of clearly defined outcomes for specific conditions and interventions to facilitate exchange of information. Authorities and caregivers responsible for implementation of complex interventions such as CR would benefit from such a set of outcomes and especially the outcome ‘functioning’ needs clear definitions (76–78). In this review, seven studies used the SF-36 questionnaire for evaluation of health-related quality of life. This instrument might be one of the standards.

The current body of evidence does not allow us to reach any firm conclusion on exercise-based CR in patients having cardiac surgery. Future studies need to be well designed with overall low risk of bias including a wide range of clearly defined outcomes, which need to be developed and consented upon by relevant stakeholders following COMET.

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Supplementary Material
Due to space limitations the supplementary material is not printed here. All supplementary material may be accessed at the journals website:
The Journal of Cardiovascular Surgery https://www.minervamedica.it/en/journals/cardiovascular-surgery. DOI:10.23736/S0021-9509.18.10462-9

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Chapter 3

QUALITY OF LIFE IN ELDER ADULTS ONE-YEAR AFTER CORONARY BYPASS

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ABSTRACT

Background: Survival rates in the elderly after cardiac surgery have improved over the last decades and therewith more attention is directed toward Quality of Life (QoL) as a patient reported outcome measure.

Objective: The purpose of this study was to explore QoL in patients one year after coronary artery bypass grafting, with special interest in the elderly patients (≥ 80 years).

Methods: In a quantitative, retrospective single-center study patients with isolated CABG (eg. nonvalve) surgery aged 80 years or older and operated in 2013 were included (n = 32). A control group of patients aged younger than 80 years was selected by matching based on gender and a recalculated (for age) logistic European System for Cardiac Operative Risk Evaluation (log EuroSCORE I) during the same period (n = 48). QoL assessment by the EuroQol questionnaire (EQ-5D) and additional questions were performed at one-year follow-up.

Results: QoL in elderly patients was 0.79 versus 0.90 in younger patients (P = 0.013). Overall, 54.8% of the elderly experience some or extreme problems in mobility versus 18.8% in the younger group (p=0.001). Elderly patients also experience more problems in self care (19.3 versus 4.2%, P = 0.029). Nine of the elderly (29%) valued their postoperative health status to be worse than preoperatively, versus 5 (10%) in the younger group (P = 0.028). Only patients aged 80 years or older would choose not to have surgery again (12.9%). Hospital mortality was 3.1% in the elderly group (n = 32) and 0% in the younger group (n = 48).

Conclusion: Not all elderly patients experience benefits in terms of QoL one year after cardiac surgery. Therefore, potential benefits and risks need to be considered and discussed by physicians and patients before making the decision to operate or not.

INTRODUCTION

It is estimated that the world population will count 400 million persons aged over 80 years in 2050 (1). More than 40% of these elderly have symptomatic cardiac disease and an increasing number of them may become candidates for cardiac surgery (2). Continued advances in operative techniques, myocardial protection and perioperative care have led to a steady decline in operative mortality, and nowadays, cardiac surgery can be performed safely in patients of 80 years and older (3). Approximately 8,400 patients had an isolated coronary artery bypass grafting (CABG) procedure (without valve surgery) in the Netherlands in 2010 (4).

Potential benefits and risks need to be balanced individually whenever taking the informed decision to operate or not. Good survival rates after cardiac surgery have been shown repeatedly, even for the elderly (5), although they have an increased risk for prolonged intensive care and hospital stay and postoperative morbidity such as neurologic and pulmonary complications (6,7).
Moreover, the importance of outcome measures has shifted from a physician's perspective towards the patient's perspective (8). Recent studies suggest that Quality of Life (QoL) improves after CABG even for the elderly (9,10), but there are also studies with contradictory findings (7,11) Therefore, QoL after CABG is of utmost interest, especially in elderly patients, not only as an outcome of surgery but even more as an important aspect in taking the decision to operate or not.
The aim of this study was to evaluate whether elderly patients differ in health-related quality of life one year after CABG as compared with younger patients. There is no consensus in the definition of elderly. However the latest American Heart Association guidelines define elderly as 80 years of age or older (12).

METHODS

Study design and patients

We conducted an observational single-center cohort study including all patients aged 80 years or older scheduled for isolated CABG procedures operated on in 2013. Patients aged younger than 80 years were the control group, selected by matching based on gender and a recalculated logistic European System for Cardiac Operative Risk Evaluation (log EuroSCORE I). Controls were selected by two researchers who were blinded for the outcome. Patients having any kind of combined (e.g., valve) surgery were excluded. The study was approved by the Institutional Review Board (METc.2014/208). Patients were identified by chart review and then contacted for consent for the follow-up one year after surgery. One research nurse interviewed all patients by telephone. A window of -/+ 10 days was allowed when contacting the patients.

Baseline characteristics

Baseline demographic data included age, gender, body mass index and comorbidity such as diabetes (oral therapy or insulin dependent diabetes), pulmonary disease (chronic obstructive pulmonary disease and/or history of previous lung disease), vascular disease (peripheral, abdominal vascular pathology, or operation),

neurological disease (cerebrovascular accidents and/or transient ischemic attack), renal disease (renal failure: creatinine ≥200µmoll/L, preoperative dialysis or renal transplant), myocardial infarction (history of myocardial infarction before the operation) and ventricular function (ejection fraction <30%). Baseline demographic and clinical characteristics of all patients were retrieved from the hospital information system and entered in a database anonymously.
The log EuroSCORE I is a widely used risk stratification system for adult cardiac surgery which calculates a mortality risk based on several risk factors (13). Since age is a major contributing risk factor in log EuroSCORE I the score of all patients was recalculated without age. The control group was matched based on this recalculated log EuroSCORE I so that patient groups had comparable risk profiles, except for age. Consequently, the recalculated score has no dimension and does not represent predicted mortality.

Outcome measures
The primary outcome was QoL measured by the five dimensions questionnaire (EQ-5D) at one year follow-up. The EQ-5D 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 evaluation (14).
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 and depression. The respondent is required to rate his own health on these five dimensions. Each dimension has three levels: no problems (1 point), some problems (2 points) and extreme problems (3 points). 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). The EQ-5D may be converted into one single summary index (range - 0.33 to 1.00) by using a formula that essentially attaches values to each of the levels in each dimension (14).

Secondary outcome measures were mortality and the numbers of patients with any complication and with two or more complications during admission. Postoperative complications included pulmonary infection, reoperation through thoracotomy, stroke, renal failure (or renal replacement therapy), myocardial infarction and wound complications such as sternal dehiscence and mediastinitis. Furthermore, patients were requested to value their postoperative health status when compared with their preoperative health status and whether they would again choose to undergo surgery. Other secondary outcomes were intensive care unit (ICU) stay, ventilator time, Acute Physiology and Chronic Health Evaluation IV score when admitted to the ICU and hospital stay. The Acute Physiology and Chronic Health Evaluation IV score predicts hospital mortality in critically ill adults (15), with an increased score (range 0 - 299) reflecting an increased risk of hospital death (16).

Analyses

Data were analyzed using SPSS Statistics version 22.0 (SPSS Inc., Chicago, Illinois). Characteristics of patients are presented as proportions (with percentages) for dichotomous variables and as means (with standard deviations) for continuous variables. Differences in dichotomous and continuous variables were tested using the chi-square test, Fisher's exact test, Mann-Whitney *U* test, or the student's *t*-test when appropriate. All tests were two-sided and statistical significance was assumed at $P \leq 0.05$.

RESULTS

In 2013, a total of 468 isolated CABG procedures were performed in our hospital, including 32 patients (6.8%) aged 80 years and older. Forty-eight matched controls were selected from 436 patients aged below 80 years. Hospital mortality was 3.1% in the elderly group (n = 32) and 0% in the younger group (n = 48). Mean age was 81.6 ±1.8 years in the elderly group and 68.2 ±8.7 years in the younger group (Table 1). One patient in the elderly group died in the ICU shortly after surgery. The recalculated mean log EuroSCORE I (excluding age) was 5.4 in the elderly group and 5.6 in the younger group. Baseline characteristics are presented in Table 1. No statistical significant differences were observed between both groups concerning any of the comorbidity risk factors.

Postoperative data

No statistical significant differences were found in postoperative outcomes between both groups, although the proportion of patients with one complication was slightly higher in the elderly group (16.1%) compared with the younger group (14.6%; P = 0.198). The proportion of patients with two or more postoperative complications was also not statistically significant different in both groups (12.9 vs 4.2%, P = 0.211, in elder and younger patients, respectively; Table 2).

Table 1. Baseline characteristics of elderly and younger patient groups

Characteristics	Elderly (n = 32)	Younger (n = 48)	P value
Age (mean ±SD)	81.6 ± 1.8	68.2 ± 8.7	
Sex (female)	12 (37.5)	17 (35.4)	0.849
BMI (mean ±SD)	27.0 ± 4.1	26.9 ± 3.6	0.910
Recalculated log EuroSCORE 1 (without age)	5.4 (11.1)	5.6 (5.8)	0.921
Diabetes	10 (31.3)	14 (29.2)	0.842
Pulmonary disease	6 (18.8)	9 (18.8)	1.000
Vascular disease	5 (15.6)	5 (10.4)	0.510
TIA/stroke	3 (9.4)	5 (10.4)	1.000
Renal disease	1 (3.1)	2 (4.2)	1.000
Myocardial infarction	18 (56.3)	36 (75)	0.079
Left ventricular function			1.000
Good	29 (90.6)	44 (91.7)	
Poor	3 (9.4)	4 (8.3)	

BMI= body mass index; SD= standard deviation; TIA= transient ischemic attack.
All numbers are presented n and percentage unless otherwise indicated

Table 2. Perioperative and postoperative characteristics of elderly and younger patient groups

Characteristics	Elderly (n = 32)	Younger (n = 48)	P value
Number of grafts (mean ±SD)	2 ± 0.35	2 ± 0.25	0.528
Use of at least one arterial graft	31 (96.9)	46 (95.8)	1.000
Pulmonary infection	4 (12.5)	1 (2.1)	0.151
Re-operation	2 (6.3)	5 (10.4)	0.696
TIA/stroke	1 (3.1)	0 (0.0)	0.400
Renal complications	2 (6.3)	0 (0.0)	0.157
Myocardial infarction	2 (6.3)	3 (6.3)	1.000
Wound complications	5 (15.6)	2 (4.2)	0.109
Patients with any complication	5 (16.1)	7 (14.6)	0.198
Patients with two or more complications	4 (12.9)	2 (4.2)	0.211
ICU stay(d; mean ± SD)	2.6 ±4.8	1.6 ±1.2	0.897
Ventilator time (h; mean ± SD)	20.8 ±35.4	11.6 ±14.5	0.058
APACHE IV score (mean ± SD)	53 ±10.6	49 ±13.3	0.161
Hospital stay (d; mean ± SD)	10.7 ±14.2	8.0 ±4.0	0.502

APACHE= Acute Physiology and Chronic Health Evaluation; ICU= intensive care unit.
All numbers are presented n and percentage unless otherwise indicated

Follow-up variables

The telephone calls conducted at follow-up took approximately 10-15 minutes for each patient. One to four attempts of telephone calls were needed before patients answered. After the operation all patients were living at home, except for two elderly patients who were living in a nursing home. The two patients in the nursing home regarded their operation for causing their dependency.

Table 3 shows data on the five domains of EQ-5D, the QoL-index for both groups at one-year follow-up and the patient's health status. There are differences in two of the five domains of the EQ-5D, including mobility and self care. Elderly patients indicate more problems in mobility and self care compared with younger patients. The summary EQ-5D index also showed a significant difference between both age groups (0.79 vs 0.90, P = 0.013).

There is also a significant difference in health status between the elderly and the younger patient groups (P = 0.028). Four patients (12.9%) in the elderly group would not accept surgery again if they should make this decision anew compared to none in the younger group.

DISCUSSION

We evaluated the impact of CABG on QoL one year after surgery with special interest in the elderly patients. Our study found a significant difference in QoL between elderly and younger patients one year after CABG. Three of the five dimensions assessed by the EQ-5D were not statistically significant different between both groups but elderly scored worse on the dimensions mobility and self care. Decrease in QoL in elderly may be associated with surgery or may simply be associated with increasing age. However, a recent study by Govers et al (17) showed that functional decline in elderly patients after cardiac surgery appears to be much larger than observed in other community-dwelling older persons. Furthermore, elderly patients might need more time to recover from surgery which suggests that QoL could still improve with longer follow-up. Studies with

Table 3. Outcome measures of quality of life (EQ-5D) and health status at one-year follow-up

Outcome Measures	Elderly (n=31)°	Younger (n=48)	P value
Mobility			0.001*
* No problems	14 (45.2)	39 (81.2)	
* Some problems	17 (54.8)	9 (18.8)	
* Extreme problems	0 (0.0)	0 (0.0)	
Self care			0.029*
* No problems	25 (80.6)	46 (95.8)	
* Some problems	5 (16.1)	2 (4.2)	
* Extreme problems	1 (3.2)	0 (0.0)	
Usual activities			0.257
* No problems	21 (67.7)	38 (79.2)	
* Some problems	10 (32.3)	10 (20.8)	
* Extreme problems	0 (0.0)	0 (0.0)	
Pain & discomfort			0.075
* No problems	26 (83.9)	46 (95.8)	
* Some problems	4 (12.9)	1 (2.1)	
* Extreme problems	1 (3.2)	1 (2.1)	
Anxiety & depression			0.086
* No problems	20 (64.5)	39 (81.3)	
* Some problems	10 (32.3)	9 (18.8)	
* Extreme problems	1 (3.2)	0 (0.0)	
VAS (mean ± SD)	7.0 ±1.45	7.4 ±0.86	0.134
Quality of Life index (mean ± SD)	0.79 ±0.25	0.90 ±0.14	0.013*
Health status compared to preoperative state			0.028*
* Better	12 (38.7)	29 (60.4)	
* No changes	10 (32.3)	14 (29.2)	
* Worse	9 (29.0)	5 (10.4)	

VAS= visual analogue scale. All numbers are presented n and percentage unless otherwise indicated
°n= 31 for elderly group, 1 patient died after surgery. *significant P values

follow-up up to 8 years claim that QoL-scores of elderly after CABG were similar to the general population (18,19), although selection of the fittest could have played a role.

We found that 29% of the elderly and 10% of the younger group valued their postoperative health status worse when compared with preoperative health status. At one-year follow-up most patients responded that they would again consent to surgery. Some elderly patients stated that they would now refuse surgery. These outcomes suggest that elderly patients need more counselling before they consent to cardiac surgery. The use of a frailty screening list in elderly patients might help in the process of decision-making. Lee et al (20) reported frailty to be a risk for postoperative complications and an independent predictor of in-hospital mortality, institutional discharge, and reduced mid-term survival.
As in our study, several other studies also reported low benefits in terms of QoL in older patients after CABG (7,11), while contradictory findings have also been reported (5,9,10).

Disagreements in findings on QoL after cardiac surgery may be explained by methodological weaknesses relating to design issues and length of follow-up (21). Noyez et al proposed five minimal requirements to increase validity of

postoperative QoL studies (21). These requirements include information on the total number of patients that could have been included; the number of patients actually included; information about preoperative QoL; information on how missing data were handled; and information about demographics, comorbidity, and the cardiac risk of all patients including the ones that dropped out. Maybe a sixth requirement should be to have at least one year follow-up. Our study complies with the five requirements suggested by Noyez et al except for having data on QoL at baseline. There were no missing data in our study.

When interpreting the results of QoL studies we should be aware of other confounding factors, both measured and unmeasured, associated with age, health and QoL. Kurlansky et al (22) found that diabetes mellitus, previous myocardial infarction and reoperation are predictors of impaired QoL in elderly patients after CABG. The results of our study confirm these findings.

Study Limitations

Our single-center observational cohort study has some important limitations. Our patient selection might differ from other nonacademic environments which may limit generalizability. A second limitation is the use of the EuroQol questionnaire for assessing QoL. The internationally most frequently used questionnaire is the short form 36 (SF36). However, there is no gold standard and the simplicity of the EQ-5D made this list most suitable for follow-up by telephone. Another limitation is the small number of patients so that the present study has insufficient power to reach strong conclusions. However, the percentage of elderly patients with isolated CABG and operated in 2013 in our hospital (6.8%) is comparable with the general population of people over 80 in the Dutch society in 2013 (4.2%) (23). Additional limitations include the lack of QoL data at baseline and the limited follow-up (one year).

CONCLUSION

The outcomes of our study show that a proportion of elderly patients did not achieve similar improvements in health-related quality of life compared to younger patients and may even have poor outcomes. Also, some elderly patients stated that they would now refuse surgery, which might suggest that elderly patients need more counseling before they consent to cardiac surgery. Further studies with QoL-data at baseline, longer follow-up and larger sample sizes are necessary to confirm our findings. We should realize that treatments for patients must be justified by benefits. Outcome measures such as mortality, morbidity and especially QoL are critical for decision-making from a patients perspective.

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Chapter 4

QUALITY OF LIFE AFTER CORONARY BYPASS – A MULTICENTRE STUDY OF ROUTINELY-COLLECTED HEALTH DATA IN THE NETHERLANDS

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ABSTRACT

Objectives: in this study, our aim was to explore how coronary artery bypass grafting affects quality of life, and how this varies with age, particularly with patients at risk of deterioration.

Methods: in a retrospective, multicentre cohort study, patients with isolated coronary artery bypass grafting and electively operated between January 2011 and January 2015 with pre- and postoperative quality- of-life data were included. Patients were classified into three age groups: <65, 65-79 and ≥80 years. Quality of life was measured up to 1-year follow-up using the Short Form-12 or Short Form-36 health survey. A multivariable, linear regression analysis, with an adjustment for confounders, was used to evaluate the association between age and quality of life.

Results: a total of 2606 patients were included in this study. Upon one-year of follow-up, the mean physical health of patients increased from 54 at baseline to 68, and mental health increased from 60 to 67. We observed decreased mental health in 20% of patients aged <65 years, 20% of patients aged 65-79 years, and 29% of patients aged ≥80 years (P = 0.039). In this study, age was not associated with a lower physical or mental component score (P = 0.054 and P = 0.13, respectively). Independent risk factors for a decrease in quality of life consist of a better physical and mental score at baseline (P <0.001) and a reduced left ventricular function (P <0.001).

Conclusions: most patients experience a relevant increase in physical and mental quality of life, but a proportion of patients aged ≥80 years undergo significant deterioration in mental health.

INTRODUCTION

During the past decades, in Western countries, increasing life expectancy has resulted in a greater number of elderly people. Between 2011 and 2040 the Dutch population of 75 years and older is expected to double from 1.2 million to 2.6 million (1,2). As a result, during the next 30 years the number of patients with heart disease will increase by approximately 55% (2), as will the number of older patients who might benefit from cardiac surgery. Meanwhile, continued advances in operative techniques, myocardial protection and perioperative care have led to a steady decline in operative mortality (3), thus further augmenting the numbers of elderly with a history of cardiac surgery.

Before making an informed decision as to whether to operate, one must weigh the potential advantages and disadvantages for each individual patient. The main reason to offer cardiac surgery is to improve survival and quality of life (QoL) (4). The assessment of outcome measures has shifted from a physician's perspective towards the patient's perspective, and QoL is of critical importance for decision making (5). So far, findings on benefits in terms of QoL have been contradictory. Some studies report improvements in QoL (6,7) whereas other studies allude to deterioration (8,9). Two review articles (9,10) on QoL after coronary artery bypass grafting (CABG) have argued the need for more well-designed studies with a large numbers of patients, including preoperative and long-term postoperative quality-of-life data and information on patients lost to follow-up, to establish the generalizability of the results.

In this multicentre study, we evaluate in a large cohort of patients the influence of CABG on 1-year QoL and its variation with age. We also explore whether it is possible to identify characteristics of subgroups marked by deterioration in QoL.

MATERIALS AND METHODS

We conducted an observational, retrospective multicentre cohort study. The study was approved by the institutional review board of the Catharina Hospital Eindhoven (no. 2014-20), and conducted in agreement with the principles of the Helsinki declaration. The study is reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines (11) (Supplementary material Section S1 checklist).

Eligibility criteria

We included all adult patients who had undergone elective CABG and were operated between 1 January 2011 and 1 January 2015, and for whom preoperative and 1-year follow-up QoL data were available. Patients were operated in one of the 3 participating centres in the Netherlands: Isala Zwolle, Catharina Hospital Eindhoven, or St. Antonius Hospital, Nieuwegein. We classified patients into three age groups: younger than 65 years, between 65 and 79 years, and 80 years or older. We retrieved baseline demographic and clinical characteristics from the

Netherlands Heart Registry (formerly Meetbaar Beter), a nationwide initiative of cardiac surgeons and cardiologists to improve the quality and transparency of care for patients with heart disease. All participating centres systematically collected patient-oriented and clinically relevant outcome measures (12). We obtained mortality data from the regional municipal administration registration.

Baseline characteristics

Baseline demographic data included age, sex, body mass index (BMI), logistic European System for Cardiac Operative Risk Evaluation (log EuroSCORE I) and perioperative data, including the use of cardiopulmonary bypass and the number of grafts. We also collected data on previous cardiac surgery and comorbidities such as diabetes mellitus (oral therapy or insulin-dependent diabetes (13), pulmonary disease (prolonged use of steroids or other lung medication) (14), arterial vascular disease (peripheral or abdominal vascular pathology or operation due to arterial vascular disease) (14), renal disease (a reduced renal function prior to surgery with an estimated glomerular filtration rate <60 ml/min/1.73 m^2) (15), and ventricular function (left ventricular ejection fraction: good >50%, moderate 30–50% or poor <30%) (16). The log EuroSCORE I is a widely used risk stratification system which estimates mortality risk for individual adult cardiac surgery patients (17).

Outcome measures

The primary outcome was QoL, which was assessed using the Short Form Health Survey-36 (SF-36; version 2) or the Short Form Health Survey-12 (SF-12; version 2). The SF-36 is a validated and widely used questionnaire for the assessment of quality of life. The questionnaire consists of 8 domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health (18). The SF-12 is a shortened version of the SF-36 questionnaire, developed to limit the survey length (19). Two summarized scores can be calculated from both instruments: a physical component summary (PCS) and a mental component summary (MCS). A higher score indicates a better QoL; a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability (18). The Isala and Catharina Hospitals used the SF-36 questionnaire, and the St. Antonius Hospital used the SF-12 questionnaire. Because the same domain and summary scores are calculated with a standard syntax file, and because in patients with coronary disease the sensitivity and responsiveness to change measured by both questionnaires seem similar (19), all data were merged into 1 database.

We assessed QoL at baseline (up to 2 months before surgery) and 10-14 months after surgery. For inclusion, at least 50% of the questions of each domain had to be filled in when using the SF-36 and 100% when using the SF-12. For each patient we calculated an increase, decrease or no change in QoL at 1 year after surgery compared to baseline. The minimal clinically important difference (MCID) was set at 5 points: an increased QoL was defined by an increase in the component

score >5 points, a decrease was defined by a decrease in score >5 points, and no change in QoL was defined by a ≤5 point decrease or increase in score (20). We defined as responders patients who completed both the preoperative and follow-up questionnaires. Non-responders were patients who completed only the preoperative questionnaire. We compared demographics, comorbidity, surgical data and preoperative QoL between the responders and non-responders to evaluate the generalizability.

Secondary outcomes were postoperative complications including surgical re-exploration (13), deep sternal wound infection (21), renal failure within 30 days after surgery (14) and stroke within 72 h after surgery (22). Coronary re-intervention and myocardial infarction were measured up to one year after surgery (13). Definitions of complications are included in the Supplementary Material Section S2.

Analyses

Characteristics of patients are presented as proportions (with percentages) for dichotomous variables. Differences in dichotomous variables between the age groups were tested using the χ^2 test or Fisher's exact test. The analysis of variance was used, with multiple comparison (Bonferroni correction) for analyses of age groups. Differences between summary scores at baseline and at 1-year follow-up were tested using a paired t-test. On the basis of a recent study concerning MCID in SF-36 scores, sensitivity analyses were conducted using a MCID of 4 points (23). The linear regression analysis was used to evaluate the impact of age (independent variable) on the difference in QoL (dependent variable). Univariable analyses were used to identify possible deteriorating subgroups based on comorbidities at baseline; age was always included as the independent variable in the model, because this was our variable of interest. All variables with P <0.1 in the univariable analyses were included in the multivariable model. All analyses were tested 2-sided, and variables with P-values of < 0.05 were considered statistically significant. All data were analysed using SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY).

RESULTS

A total of 8643 patients underwent an elective CABG procedure in the 3 participating centres. Of them, both the preoperative and the postoperative quality-of-life assessments were completed (responders) in 2606 patients (30%).

Characteristics of the patients

Table 1 presents all baseline, operative and postoperative characteristics of the study population. The proportion of women increases with age (P < 0.001). A greater proportion of patients aged 65-79 years suffered from diabetes, pulmonary, and/or arterial vascular disease. Patients aged ≥80 years more frequently had reduced left ventricular function (P = 0.010) and renal disease prior to surgery (P <

Table 1. Baseline, operative and postoperative characteristics of patients with CABG

		<65 years (n = 1073)	65-79 years (n =1380)	≥80 years (n =153)	P value
Baseline characteristics:					
Sex (female)		136 (13)	283 (21)	56 (37)	<0.001
BMI[a] (kg/m^2)	< 25	158 (23)	252 (27)	33 (34)	
	25-30	353 (51)	454 (49)	48 (50)	0.035
	> 30	180 (26)	214 (23)	15 (16)	
Log EuroSCORE[b] I (%)	< 10	1065 (99)	1299 (94)	121 (79)	
	10-20	4 (0.4)	68 (4.9)	25 (16)	<0.001
	> 20	0 (0.0)	13 (0.9)	7 (4.6)	
Diabetes mellitus		202 (19)	340 (25)	35 (23)	0.003
Pulmonary disease		70 (6.5)	138 (10)	12 (7.8)	0.009
Arterial vascular disease		74 (6.9)	183 (13)	17 (11)	<0.001
Renal disease (ml/min/1.73 m^2)					
	eGFR ≥ 60	985 (92)	1081 (78)	84 (55)	<0.001
	eGFR 30-59	84 (7.8)	283 (21)	67 (44)	
	eGFR < 30	4 (0.4)	16 (1.2)	2 (1.3)	
LVEF[c] (%)	> 50	871 (81)	1058 (77)	110 (72)	
	30-50	173 (16)	263 (19)	39 (26)	0.010
	< 30	29 (2.7)	55 (4.0)	4 (2.6)	
Previous cardiac surgery		16 (1.5)	28 (2.0)	2 (1.3)	0.55
Operative characteristics:					
Use of one arterial graft		438 (41)	861 (62)	109 (71)	<0.001
Use of two or more arterial grafts		594 (55)	469 (34)	41 (27)	
Use of ECC[a]		653 (94)	860 (93)	93 (97)	0.24
Postoperative characteristics:					
Deep sternal wound infection		5 (0.5)	7 (0.5)	2 (1.3)	0.33
Stroke		0 (0.0)	7 (0.5)	0 (0.0)	0.040
Renal failure		2 (0.2)	2 (0.1)	0 (0.0)	1.00
Surgical re-exploration		24 (2.2)	45 (3.3)	3 (2.0)	0.25
Myocardial infarction[d]		26 (2.5)	22 (1.6)	3 (2.0)	0.34
Coronary reintervention[e]		31 (2.9)	45 (3.3)	2 (1.4)	0.41

Values are presented as n(%). [a]BMI is unknown for 899 patients and the use of ECC is unknown for 884 patients; data are available from two of the participating hospitals. [b]Log EuroSCORE I, data missing for 4 patients. [c]LVEF, data missing for 4 patients. [d]Myocardial infarction, data missing for 34 patients. [e]Coronary reintervention, data missing for 29 patients. BMI: body mass index; CABG: coronary artery bypass grafting; ECC: extracorporeal circulation; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction.

0.001). During hospitalization the incidence of stroke was higher in patients aged 65-79 years (P = 0.040). We observed no significant differences between the 3 age groups concerning any of the other postoperative complications.

Quality of life

Mean MCS and PCS scores at baseline and at 1-year follow-up are presented in bar charts per age group (Fig. 1). All subscale scores are provided in the Supplementary Material, Section S3. Differences in QoL between baseline and 1 year after surgery are presented in Fig. 2A and B. We observed a decrease in physical health 1 year after CABG (>5 points) in 15% of patients younger than 65 years, in 15% of patients between 65 and 79 years, and in 16% of patients ≥80 years (P = 0.92; Fig. 2A). We registered a decrease in mental health 1 year after CABG (>5 points) in 20% of patients aged <65 years, in 20% of patients aged 65-79 years, and in 29% of patients aged ≥80 years (P = 0.039) (Fig. 2B). Sensitivity analyses (using an MCID of 4 points) of differences in QoL revealed similar proportions of decreased physical and mental health components (Supplementary Material, Section S4A and B).

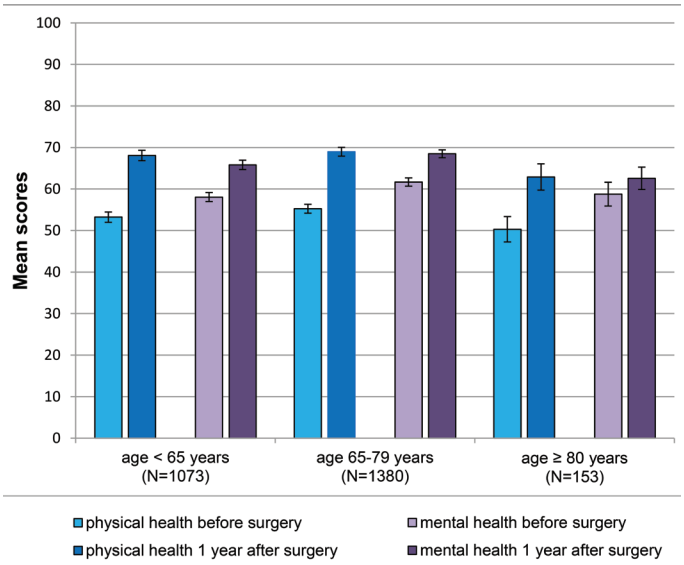

Figure 1. Quality-of-life data of patients with coronary artery bypass grafting according to age categories. Mean scores of the physical and the mental health component scores (with 95% confidence intervals) of patients with coronary artery bypass grafting before and 1 year after surgery for each age category

Association between age and QoL

Table 2 shows the results of the regression analysis. Higher age was not significantly associated with a difference in QoL after 1-year follow-up (PCS P = 0.054 and MCS P = 0.13; respectively). Differences in QoL between men and women were also not significant. The multivariable regression analysis identified baseline PCS (P < 0.001), pulmonary disease (P < 0.001), a reduced left ventricular function (P < 0.001 for 30-50%), and renal disease (P < 0.001) as independent risk factors of a decreased physical QoL one year after surgery. The baseline MCS (P < 0.001) and a reduced left ventricular function (P < 0.001 for 30-50% ejection fraction) were identified as independent risk factors for decreased mental QoL 1 year after surgery. R^2 is 0.25 for the multivariable PCS model and 0.24 for the multivariable MCS model, meaning that ~25% variation in the dependent variable, i.e., change in QoL, can be explained by the independent variables included in the multivariable models.

Responders & non-responders

Non-responders (n=1644) provided baseline data on QoL but no follow-up data. Baseline characteristics, operative characteristics and postoperative complications of responders and non-responders are listed in table 3.

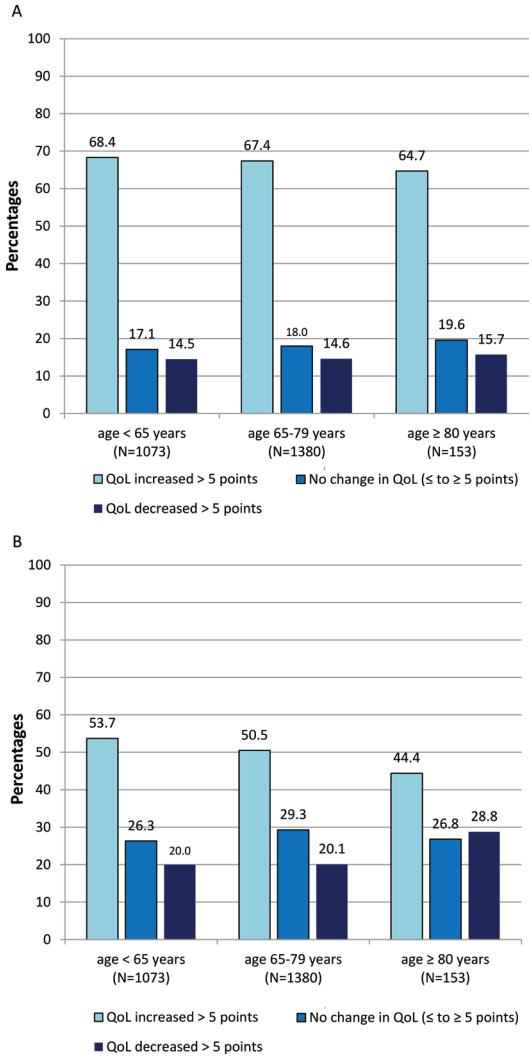

Figure 2. (A) Difference in QoL of patients with coronary artery bypass grafting: physical component score. Differences between baseline and 1-year follow-up per age group, in the quality of life physical component score; cut-off value 5 points. (B) Difference in QoL of patients with coronary artery bypass grafting mental component score. Differences between baseline and 1-year follow-up per age group, in the quality of life mental component score; cut-off value 5 points.

In the non-responder group 37 patients (2.3%) died within <120 days, and a total of 75 patients (4.6%) died during the first year. Significant differences between the groups were BMI (P = 0.042), diabetes (P < 0.001), arterial vascular disease (P = 0.003), and renal disease (P < 0.001). Also, the incidence of postoperative complications, such as stroke (P = 0.008) and renal failure (P = 0.006) was higher

Table 2. Association between age and difference in quality of life in patients with CABG

	Univariable analysis (single component age adjusted)			Multivariable analysis (adjusted for all variables listed)		
	physical component score			physical component score		
	Beta	95% CI	P value	Beta	95% CI	P value
Age (years)	-0.82	-0.16 to 0.00	0.054	-0.04	-0.11 to 0.03	0.28
Baseline PCS	-0.46	-0.49 to -0.42	<0.001	-0.47	-0.51 to -0.44	<0.001
Pulmonary disease	-4.04	-6.75 to -1.32	0.004	-7.27	-9.65 to -4.89	<0.001
LVEF						
EF 30 - 50%	-2.80	-4.77 to -0.83	0.005	-3.23	-4.94 to -1.51	<0.001
EF < 30%	-0.63	-4.82 to 3.57	0.77	-1.44	-5.10 to 2.22	0.44
Renal disease	-0.03	-0.04 to -0.01	0.002	-0.03	-0.04 to -0.01	<0.001
Previous cardiac surgery	9.89	4.16 to 15.61	0.001	0.99	-4.04 to 6.03	0.69
	mental component score			mental component score		
	Beta	95% CI	P value	Beta	95% CI	P value
Age (years)	-0.06	-0.13 to 0.02	0.13	0.01	-0.05 to 0.08	0.67
Baseline MCS	-0.45	-0.49 to -0.42	<0.001	-0.46	-0.49 to -0.43	<0.001
Sex	3.09	1.33 to 4.84	0.001	-1.17	-2.72 to 0.38	0.14
LVEF						
EF 30 – 50%	-3.54	-5.27 to -1.80	<0.001	-3.70	-5.22 to -2.19	<0.001
EF < 30%	-1.49	-5.20 to 2.22	0.43	-2.18	-5.38 to 1.02	0.18
Previous cardiac surgery	5.08	-0.00 to 10.17	0.050	-0.02	-4.43 to 4.38	0.99

Adjusted univariable and multivariable association between age and difference in the physical or mental component score.
Beta: unstandardized regression coefficient; CABG: coronary artery bypass grafting; CI: confidence interval; LVEF: left ventricular ejection fraction; MCS: mental component summary; PCS: physical component summary.

among the non-responders. Between both groups baseline PCS measurements were similar (P = 0.42), but we found statistically significant differences in baseline MCS (P = 0.001).

DISCUSSION

One-year after CABG the quality of life of patients usually increases rather than decreases. The potential beneficial effects of CABG hold true especially for the physical component score of QoL. We observed less favourable effects of CABG on the mental component score. Age as a continuous variable was not significantly associated with a difference in QoL after one year of follow-up. Nevertheless, one out of three patients aged ≥80 years reported a decline in mental QoL.

Several factors might explain why some patients report a decline in QoL. The results of this study show that baseline MCS and baseline PCS are both independent risk factors for a decreased QoL after CABG; in other words, patients with a higher QoL before surgery are more at risk of experiencing a decreased QoL after surgery. This finding, in statistics known as regression to the mean, is also observed in other studies (7,24,25), resulting in convincing evidence that a QoL assessment should be part of the preoperative examination, and expectations regarding QoL should also be discussed with the patient preoperatively. Another factor behind the decline in QoL in some patients could be side-effects of surgery, like a new co-morbidity or reduced independence. Post-operative cognitive decline after CABG is reported with incidence rates varying between 30-60%, depending on cognitive tests, time of assessment, and patient population (26,27). Cognitive performance, QoL as well as the ability to perform daily activities, reflect on patient-centred domains that are crucial to the patient's retention of independence (26). Furthermore,

Table 3. Baseline, operative and postoperative characteristics of responding and non-responding patients with CABG

		Responders (n = 2606)	Non-responders (n = 1644)	P value
Baseline characteristics:				
Sex (female)		475 (18)	374 (23)	<0.001
Age, mean (SD)		66 (9.0)	65.7 (10.2)	0.34
BMI[a] (kg/m^2)	< 25	443 (26)	214 (25)	0.042
	25-30	855 (50)	410 (47)	
	> 30	409 (24)	249 (29)	
Log EuroSCORE[b] I (%)	< 10	2485(96)	1538 (94)	0.024
	10-20	97 (3.7)	80 (4.9)	
	> 20	20 (0.8)	23 (1.4)	
Diabetes mellitus[c]		577 (22)	455 (28)	<0.001
Pulmonary disease[c]		220 (8.4)	164 (10)	0.089
Arterial vascular disease[c]		274 (11)	222 (14)	0.003
Renal disease[c] (ml/min/1.73 m^2)				<0.001
	eGFR ≥ 60	2150 (83)	1257 (77)	
	eGFR 30-59	434 (17)	359 (22)	
	eGFR < 30	22 (0.8)	27 (1.6)	
LVEF[d] (%)	> 50	2039 (78)	1261 (77)	0.31
	30-50	475 (18)	310 (19)	
	< 30	88 (3.4)	69 (4.2)	
Previous cardiac surgery		46 (1.8)	37 (2.3)	0.27
QoL score baseline PCS, mean (SD)		54.1 (20.4)	53.6 (21.9)	0.42
QoL score baseline MCS, mean (SD)		60.0 (18.6)	57.8 (20.6)	0.001
Operative characteristics				<0.001
Use of 1 arterial graft		1408 (54)	981 (60)	
Use of 2 or more arterial grafts		1104 (42)	593 (36)	
Use of ECC[a]		1606 (93)	803 (90)	0.005
Postoperative characteristics:				0.58
Deep sternal wound infection		14 (0.5)	11 (0.7)	
Stroke		7 (0.3)	14 (0.9)	0.008
Renal failure		4 (0.2)	11 (0.7)	0.006
Surgical re-exploration		72 (2.8)	63 (3.8)	0.053
Myocardial infarction[e]		51 (2.0)	25 (1.7)	0.49
Coronary reintervention[f]		78 (3.0)	53 (3.6)	0.35

All numbers are presented with percentages, unless otherwise indicated. [a]BMI and the use of ECC data available from two of the participating hospitals. [b]Log EuroSCORE 1 for 13 patients is unknown. [c]Diabetes mellitus, pulmonary disease, arterial vascular disease and renal disease is unknown for 2 patients. [d]LVEF for 22 patients is unknown. [e]Myocardial infarction for 458 patients is unknown. [f]Coronary reintervention for 451 patients is unknown. BMI: body mass index; CABG: coronary artery bypass grafting; ECC: extracorporeal circulation; LVEF: left ventricular ejection fraction; MCS: mental component summary; PCS: physical component summary; QoL: quality of life; SD: standard deviation.

factors influencing QoL, like other health problems or loss of relatives, might have been experienced in these patients irrespective of cardiac surgery, and not at all been caused by the intervention.

In our study population we found significant differences in baseline characteristics; more patients aged 65-79 years suffered from diabetes, pulmonary disease and/ or arterial vascular disease. Also, the incidence of postoperative stroke was significantly higher in this age group. These findings however, do not account for the lower postoperative physical or mental QoL observed in our patients aged ≥80 years; this suggests that QoL relates to much more than just the presence of symptoms of disease, comorbidities and complications of surgery. The Constitution of the World Health Organisation (WHO) defined QoL as 'individuals' perception of their position in life in the context of the culture and value systems

in which they live and in relation to their goals, expectations, standards and concerns'(28); in other words, QoL is influenced by various physical, mental, social and environmental factors. This probably explains why independent 'medical' variables account for only 25% of the variance of QoL in both of our regression models. Future studies to compare the QoL of patients after surgery with patients after less invasive treatments (e.g. medication or percutaneous interventions) would provide valuable knowledge about the real harms and benefits of surgery on elderly patients and the impact on their QoL.

To assess the generalizability of our results we compared data from the responding and non-responding CABG-patients, as recommended by Noyez (10). We included information on demographics, comorbidity and cardiac risk of all patients who could possibly have been included and on the patients actually included. Compared to the responding patients the non-responders had a higher prevalence of several comorbidity risk factors. A recent study suggested that the so-called non-responders in studies evaluating QoL after cardiac surgery may be older, be at higher operative risk and have a lower preoperative QoL; these factors may result in a positive overestimation of change in QoL for the total population (29). This also seems to apply to our study meaning that in the total population of CABG-patients the number of patients with decreased mental well-being might be higher. However, compared to the QoL data from an age-matched control group of Dutch inhabitants, data from our patients resulted in remarkably high PCS and MCS scores (mean PCS 54.1 vs. 50.4 and mean MCS 60.0 vs. 52.5 for responders vs. the general population) (30).

Our multicentre study also has important limitations. First, the number of patients with total available QoL-data is low (30%), and reasons for the lack of pre- and/or postoperative data remain unclear. All data were collected by e-mail or a written survey, which might have led to reporting bias. A more personal approach (e.g. follow-up by telephone or at the outpatient clinic) might have led to higher response rates. For the non-responders we chose to include only patients with complete preoperative QoL information, because these are the only patients from whom we could expect one-year QoL data. Second, we lack information on preoperative mental health, discharge destination, participation in a rehabilitation programme, and other events influencing QoL upon one-year follow-up (e.g. other health problems, dependency or loss of relatives). Third, we lack information on survival and QoL from patients who were not accepted for surgery.

The outcomes of our study show that although most patients experience an improved physical and mental quality of life, a relevant proportion of patients deteriorate in mental health. Because in vulnerable elderly patients a small decline can have important consequences for their daily lives, such as loss of independence, it is imperative to discuss this issue during preoperative counselling.

Conflict of Interest

M.M. has received grants from Atricure Inc, Edwards Lifesciences and Abbot Inc and has given training for Livanova and Getinge. The other authors have nothing to declare.

Supplementary Material

Only supplement S2 is printed here due to space limitations. All supplementary material may be accessed at the journals website:

https://academic.oup.com/ejcts/article/56/3/526/5382121?searchresult=1
DOI: 10.1093/ejcts/ezz051

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Supplement S2. Definitions postoperative complications

Surgical re-exploration: thoracotomy due to bleeding, cardiac tamponade, graft- or valve failure within 30 days after surgery (13).

Deep wound infection (within 30 days after surgery): when deeper tissues are affected (muscle, sternum and mediastinum) and one or more of the following three criteria are met:
1) surgical drainage/refixation
2) an organism is isolated from culture of mediastina tissue or fluid
3) antibiotic treatment because of a sternal wound (21).

Renal failure (within 30 days after surgery) one or more of the following criteria are met:
renal replacement therapy (dialysis or CVVH) which was not present preoperatively highest postoperative creatinine level > 177 µmol/L and a doubling of the preoperative value (the preoperative creatinine value is the value on which the EuroSCORE is calculated) (14).

Cerebral vascular accident/stroke: an acute neurological event within 72 hours after surgery with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnoses of stroke requires confirmation by a neurologist (22).

Coronary re-intervention: a percutaneous re-intervention like CAG or PCI after surgery (13).

Myocardial infarction: myocardial infarction (MI) in the postoperative period. Myocardial infarction associated with CABG (within 48 hours after CABG) is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile upper reference limit (URL) in patients with normal baseline cardiac troponin values. In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. After 48 hours, the standard definition of myocardial infarction is appropriate. The following criteria meets the diagnosis for MI: detection of a rise and/or fall of cardiac biomarker values, preferably cardiac troponin, with at least one value above the 99th percentile URL and in addition, either (i) symptoms of ischaemia, or (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), or (iii) development of pathological Q waves in the ECG, or (iiii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy (13).

4

Chapter 5

THE IMPACT OF SURGICAL AORTIC VALVE REPLACEMENT ON QUALITY OF LIFE – A MULTICENTER STUDY

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ABSTRACT

Objectives: To explore the effect of surgical aortic valve replacement on quality of life and the variance with age, particularly in patients at risk of deterioration.

Methods: In an observational, multicenter cohort study of routinely collected health data, patients undergoing and electively operated between January 2011 and January 2015 with pre- and postoperative quality of life data were included. Patients were classified into 3 age groups: <65, 65-79 and ≥80 years. Quality of life was measured at baseline and at 1-year follow-up using the Short-Form Health Survey-12 or SF-36. We defined a >5-point difference as a minimal clinically important difference. Multivariable linear regression analysis, with adjustment for confounders, was used to evaluate the association between age and quality of life.

Results: In 899 patients mean physical health increased from 55 to 66, and mental health from 60 to 66. A minimal clinically important decreased physical health was observed in 12% of patients aged <65 years, 16% of patients aged 65-79 years, and 22% of patients aged ≥80 years (P = 0.023). A decreased mental health was observed in 15% of patients aged <65 years, 22% of patients aged 65-79 years, and 24% aged ≥80 years (P = 0.030). Older age and a higher physical and mental score at baseline were associated with a decreased physical and mental quality of life (P < 0.001).

Conclusions: Patients surviving surgical aortic valve replacement on average improve in physical and mental quality of life; nonetheless, with increasing age patients are at higher risk of experiencing a deterioration.

INTRODUCTION

In western countries, aortic valve stenosis (AS) is the most common acquired native valve disease (1,2). The prevalence of AS increases with age due to age-related calcific degeneration. Current incidences of AS are 0.2% at age 50 to 59, 1.3% at age 60 to 69, 3.9% at age 70 to 79 and 9.8% at age 80 to 89 years (3). Consequently, aortic valve replacement is increasingly performed in elderly patients (1,2).

With increasing severity of valve disease, patients often experience chest pain, increasing fatigue, syncope and heart failure. These symptoms lead to decreasing quality of life (QoL) due to an inability to participate in daily activities. Patients who eventually become symptomatic face a prognosis of up to 50% mortality within 2 years, if left untreated (4). QoL is a major important outcome after surgical aortic valve replacement (SAVR) alongside symptom relief and increased survival (5). Two systematic reviews on QoL after SAVR revealed that methodological differences limit interpretation and more well-designed QoL studies are required including the use of validated QoL tools, conducted with only elective patients, and preferably set up as multicenter studies to minimize bias and increase patient numbers (6,7). Since QoL is an important outcome after cardiac surgery, studies on QoL are valuable for both patients and surgeons because they may inform in the process of shared-decision making (8).

In this multicenter study, we evaluated the influence of SAVR on 1-year QoL and its variation with age in a large cohort of patients. In addition, we explored whether we could identify subgroups of patients who deteriorate in QoL and hypothesized that, compared to younger patients, elderly patients would more often experience a deterioration in QoL.

METHODS

We conducted an observational, multicenter cohort study. The study was approved by the institutional review board of the Catharina Hospital Eindhoven (no. 2014-20; April 24, 2014) and conducted in agreement with the principles of the Helsinki declaration. For this study we used methods similar to a previous cohort study on QoL after coronary artery bypass grafting (CABG) (9). The study is reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines (10) (Table E1).

Eligibility criteria

We included adult patients who had undergone elective SAVR either with or without concomitant revascularization, operated between January 1, 2011 and January 1, 2015 and for whom preoperative and 1-year follow-up QoL data were available. Patients were operated in 1 of the 3 participating centers in the Netherlands: Isala Zwolle, Catharina Hospital Eindhoven, or St. Antonius Hospital Nieuwegein. Patients were classified into 3 groups: younger than 65 years, between 65 and 79 years, and 80 years or older.

Baseline characteristics

We retrieved data from the Netherlands Heart Registry (formerly Meetbaar Beter) (11) and obtained mortality data from the regional municipal administration registration. Baseline demographic data included age, sex, body mass index, logistic European System for Cardiac Operative Risk Evaluation 1 (log EuroSCORE I) and perioperative data, including valve type and concomitant revascularization. We also collected data on previous cardiac surgery and comorbidities such as diabetes (12), pulmonary disease (13), arterial vascular disease (13), renal disease (14), and ventricular function (15). Definitions of comorbidities are included in Appendix E1.

Outcome measures

The primary outcome was QoL assessed using the Short Form Health Survey-36 (version 2) (16) or the Short Form Health Survey-12 (version 2). QoL-data were collected at baseline (up to 2 months before surgery) and 10 to 14 months after surgery by e-mail or a written survey. Two summarized scores ranging from 0-100 were calculated; a Physical Component Summary (PCS) and a Mental Component Summary (MCS) (16). All data were merged into one database since both questionnaires calculate the same scores with a standard syntaxfile and the sensitivity and responsiveness to change measured by both questionnaires seem similar (17).

Based on a minimal clinically important difference (MCID) of 5 points we calculated for each patient an increase (≥5), decrease (≤-5), or no change in QoL (18). To evaluate generalizability, we compared data between responders (patients who completed preoperative and follow-up questionnaires) and nonresponders (patients who only completed the preoperative questionnaire).

Secondary outcomes were postoperative complications including surgical re-exploration (12), deep wound infection (19), renal failure (12), the implantation of a permanent pacemaker, all within 30 days after surgery (12) and stroke within 72 hours after surgery (20). A surgical re-intervention due to valve problems or coronary reintervention in case of concomitant revascularization was measured within 1 year after surgery (12). Definitions of complications are included in Appendix E1.

Analyses

Characteristics of patients are presented as proportions (with percentages) for categorical variables or as means (with standard deviations) for continuous variables when normally distributed. Differences in dichotomous variables were tested using chi-square or the Fisher's exact test. Analysis of variance was used with multiple comparison (Bonferroni correction) for analyses of baseline variables among age groups. Differences between the QoL scores at baseline and at 1 year were tested using a paired t test. Sensitivity analyses were conducted using a MCID of 4 points (21). Linear regression analysis was conducted to evaluate the impact of age (independent variable) on difference in QoL (dependent variable). Bivariable analyses (since age was always included in all models), were used to

identify possible deteriorating subgroups exploring the previously mentioned baseline characteristics. All variables in the bivariable analysis with P < 0.1 were included in the multivariable model and R-square was calculated. All analyses were tested 2-sided and variables with *P* values ≤0.05 were considered statistically significant. All data were analyzed using SPSS, version 23.0 (Released 2015, IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY).

RESULTS

A total of 2958 patients underwent a SAVR with or without bypass grafting. Preoperative and postoperative QoL assessments were completed by n=899 patients (30.4%; responders) (Figure E1).

Characteristics of the patients

Table 1 presents baseline, perioperative and postoperative characteristics of the study population. The proportion of women, compared with men, increased with age (P < 0.001) as well as the proportion of patients with renal disease (P < 0.001). A larger proportion of patients aged 65 to 79 years suffered from diabetes and arterial vascular disease. The incidence of implantation of a permanent pacemaker

Table 1. Baseline, operative and postoperative characteristics of patients undergoing SAVR

	<65 yrs (n = 232)	65-79 yrs (n = 554)	≥80 yrs (n = 113)	P value
Baseline characteristics: Sex (female)	70 (30)	183 (33)	63 (56)	< 0.001
BMI[1] (kg/m^2)				0.49
< 25	36 (21)	111 (27)	22 (27)	
25-30	80 (47)	195 (47)	39 (47)	
> 30	54 (32)	105 (26)	22 (27)	
Log EuroSCORE I				< 0.001
10%	226 (97)	474 (86)	50 (44)	
10-20%	5 (2.2)	65 (12)	47 (42)	
> 20%	1 (0.4)	15 (2.7)	16 (14)	
Diabetes mellitus	31 (13)	135 (24)	25 (22)	0.003
Pulmonary disease	17 (7.3)	66 (12)	13 (12)	0.16
Arterial vascular disease	13 (5.6)	72 (13)	6 (5.3)	0.001
eGFR (ml/min/1.73 m^2)				< 0.001
≥ 60	205 (88)	402 (73)	63 (56)	
30-59	26 (11)	145 (26)	48 (43)	
< 30	1 (0.4)	7 (1.3)	2 (1.8)	
LVEF[2]				0.19
> 50%	200 (86)	471 (85)	91 (81)	
30-50%	30 (13)	64 (12)	19 (17)	
< 30%	2 (0.9)	18 (3.3)	3 (2.7)	
Previous cardiac surgery[3]	15 (8.7)	15 (4.9)	4 (6.5)	0.26
Operative characteristics: Bio-prosthesis	122 (53)	527 (95)	110 (97)	< 0.001
Concomitant CABG	59 (25)	248 (45)	51 (45)	< 0.001
Postoperative characteristics: Deep sternal wound infection	0 (0.0)	4 (0.7)	1 (0.9)	0.41
Stroke	1 (0.4)	5 (0.9)	0 (0.0)	0.72
Renal failure	2 (0.9)	2 (0.4)	0 (0.0)	0.76
Surgical reintervention[4]	2 (0.9)	3 (0.5)	1 (0.9)	< 0.001
Implantation permanent pacemaker[5]	1 (0.6)	6 (2.0)	3 (4.8)	< 0.001

All numbers are presented with percentages. *BMI* , Body mass index; *log EuroSCORE 1*, logistic European System for Cardiac Operative Risk Evaluation 1; *eGFR*, estimated Glomerular Filtration Rate; *LVEF*, left ventricular ejection fraction; *CABG*, coronary artery bypass grafting. [1]BMI data missing for 235 patients. [2]LVEF data missing for one patient. [3]Previous cardiac surgery data missing for 358 patients; [4]Valve reintervention data missing for 359 patients; [5]Implantation permanent pacemaker data missing for 359 patients.

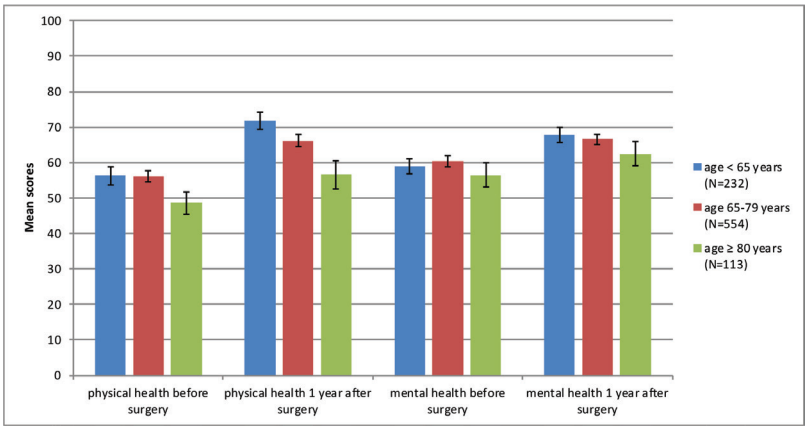

Figure 1. Quality of life data of patients with surgical aortic valve replacement according to age categories. Mean scores of the Physical and Mental Component Summary scores (with 95% confidence intervals) of patients with surgical aortic valve replacement before and 1 year after surgery for each age category.

and surgical reintervention was greater in patients aged ≥80 years (P < 0.001). Differences between the 3 age groups concerning any of the other postoperative complications were not significant.

Quality of Life

Mean MCS and PCS scores at baseline and at 1-year follow-up are presented in bar charts per age group (Figure 1). Physical health on average increased from 55 at baseline to 66 at 1-year follow-up, and mental health on average increased from 60 to 66. All subscale scores are provided in Table E2. Differences in QoL between baseline and 1 year after surgery are presented in Figure 2, A and B. We observed a minimal clinically important decrease in physical health in 12% of patients aged younger than 65 years, in 16% aged 65 to 79 years, and in 22% aged ≥80 years (P = 0.023; Figure 2, A). We observed a minimal clinically important decrease in mental health in 15% of patients aged <65 years, in 22% aged 65 to 79 years and in 24% aged ≥80 years (P = 0.030; Figure 2, B). Sensitivity analyses (using an MCID of 4 points) revealed a smaller group of patients without change in QoL and more patients with an increased and decreased physical and mental health (Figures E2 and E3). Subgroup analyses comparing results between patients undergoing solitary SAVR or SAVR with concomitant revascularization shows that there is no significant difference between both subgroups in difference in QoL (Table E3 and Figure E4).

Association between age and QoL

Table 2 shows the results of the linear regression analysis. Older age was associated with a significant decrease in QoL after 1-year follow-up (both PCS and MCS P < 0.001). Differences in QoL between men and women were not statistically

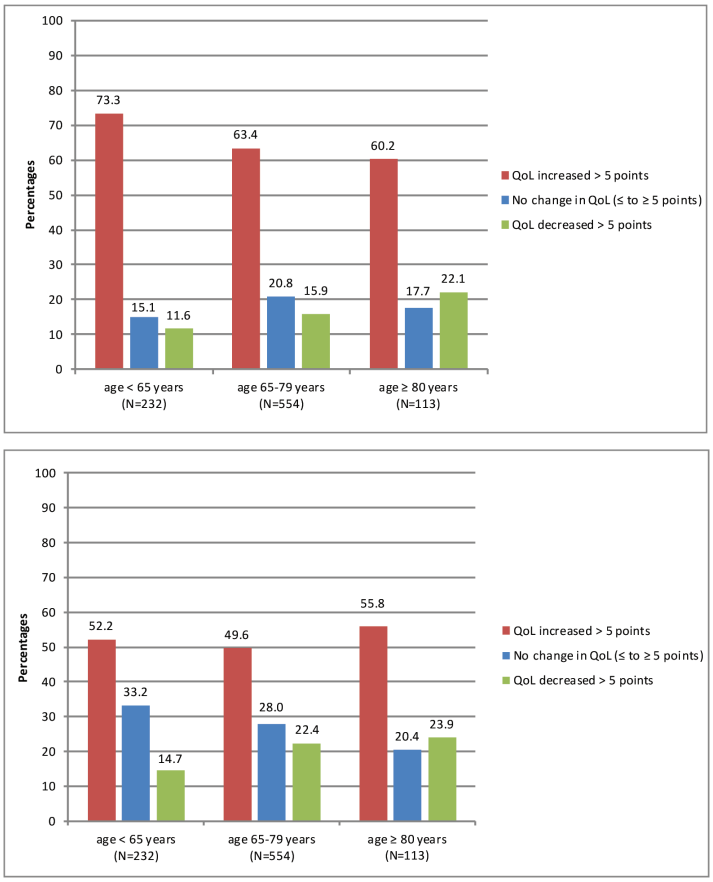

Figure 2. A. Difference in quality of life of patients with surgical aortic valve replacement: Physical Component Score. Differences between baseline and 1-year follow-up per age group in the quality of life physical component score; cut-off value 5 points. B. Difference in quality of life of patients with surgical aortic valve replacement: Mental Component Score. Differences between baseline and 1-year follow-up per age group, in the quality of life mental component score; cut-off value 5 points. QoL, Quality of life.

significant. Multivariable regression analysis identified older age ($P < 0.001$) and greater baseline PCS ($P < 0.001$) as independent risk factors for a decreased physical QoL. Independent risk factors for a decreased mental QoL were older age ($P < 0.013$) and greater baseline MCS ($P < 0.001$). R-squares suggest that approximately 21% and 28% of the variation in change in physical and mental QoL respectively, can be explained by the independent variables included in the multivariable models.

Responders and nonresponders

Baseline characteristics, operative characteristics and postoperative complications of the responders and nonresponders (n = 371) are listed in Table 3. Among the

Table 2. Association between age and difference in quality of life in 899 patients undergoing SAVR

	Bivariable analysis (single component age adjusted)			Multivariable analysis (adjusted for all variables listed)		
physical component score				physical component score		
	Beta	95% CI	P value	Beta	95% CI	P value
Age	-0.33	-0.46 to -0.20	< 0.001	-0.42	-0.53 to -0.29	< 0.001
Baseline PCS	-0.41	-0.47 to -0.36	< 0.001	-0.41	-0.46 to -0.35	< 0.001
LVEF						
EF 30-50%	2.17	-1.38 to 5.72	0.23	0.07	-3.15 to 3.29	0.96
EF < 30%	9.73	2.26 – 17.19	0.011	5.82	-0.94 to 12.5	0.092
mental component score				mental component score		
	Beta	95% CI	p value	Beta	95% CI	p value
Age	-0.20	-0.33 to -0.08	0.001	-0.15	-0.27 to -0.32	0.013
Baseline MCS	-0.49	-0.55 to -0.44	< 0.001	-0.49	-0.56 to -0.42	< 0.001
Sex	2.30	-0.09 to 4.69	0.059	-0.61	-2.95 to 1.72	0.61
BMI (kg/m^2)	0.33	0.04 – 0.61	0.028	0.11	-0.15 to 0.37	0.40
Diabetes	3.25	0.48 – 6.02	0.022	0.07	-2.70 to 2.84	0.96
LVEF						
EF 30-50%	1.80	-1.62 –to 5.22	0.30	-0.77	-4.03 to 2.48	0.64
EF < 30%	8.89	1.71 – 16.08	0.015	2.83	-3.63 to 9.30	0.39

Adjusted bivariable and multivariable-adjusted association between age and difference in physical or mental component score is shown. *Beta*, Unstandardized regression coefficient; *CI*, confidence interval; *LVEF*, left ventricular ejection fraction; *EF*, ejection fraction; *BMI,* body mass index.

nonresponders 32 patients (8.6%) died within 120 days, and 49 patients (13.2%) died within 1 year. The nonresponders were older (P < 0.001), had a greater EuroSCORE I (P < 0.001), a lower baseline PCS (P < 0.001) and more postoperative complications.

DISCUSSION

The results of this study show that 1-year QoL after SAVR has on average increased from baseline in the majority of patients. A mean beneficial effect of SAVR on postoperative QoL was observed in all age groups; nonetheless, with increasing age, patients are at greater risk of experiencing a deterioration in QoL. QoL is often argued to be the most relevant outcome (over survival or complication rates), especially in elderly patients. For both patient and health care professionals, expected QoL benefit may be crucial for optimal patient selection and shared-decision making, and for society in allocating health care resources (22-24) (Figure 3).

As the prognosis of untreated symptomatic AS is poor with an expected deterioration in QoL and a mortality rate more than 50% within 2 years, less-invasive treatments such as transcatheter aortic valve replacement (TAVR) has been proven a suitable alternative for SAVR. Both TAVR and SAVR result in important mortality reductions and symptom improvements (4). With the PARTNER 1, 2 and 3 trials, efforts are made to optimize treatment options at various levels of surgical risk (25–27). In future studies, it will be challenging to highlight patient-related outcomes such as QoL when deciding between TAVR and SAVR, due to variability in patients' individual values and preferences (23).

Table 3. Baseline, operative and postoperative characteristics of responding and non-responding patients with CABG

		Responders (n = 2606)	Non-responders (n = 1644)	P value
Baseline characteristics:				
Sex (female)		475 (18)	374 (23)	<0.001
Age, mean (SD)		66 (9.0)	65.7 (10.2)	0.34
BMI[a] (kg/m^2)	< 25	443 (26)	214 (25)	0.042
	25-30	855 (50)	410 (47)	
	> 30	409 (24)	249 (29)	
Log EuroSCORE[b] I (%)	< 10	2485(96)	1538 (94)	0.024
	10-20	97 (3.7)	80 (4.9)	
	> 20	20 (0.8)	23 (1.4)	
Diabetes mellitus[c]		577 (22)	455 (28)	<0.001
Pulmonary disease[c]		220 (8.4)	164 (10)	0.089
Arterial vascular disease[c]		274 (11)	222 (14)	0.003
Renal disease[c] (ml/min/1.73 m^2)				<0.001
	eGFR ≥ 60	2150 (83)	1257 (77)	
	eGFR 30-59	434 (17)	359 (22)	
	eGFR < 30	22 (0.8)	27 (1.6)	
LVEF[d] (%)	> 50	2039 (78)	1261 (77)	0.31
	30-50	475 (18)	310 (19)	
	< 30	88 (3.4)	69 (4.2)	
Previous cardiac surgery		46 (1.8)	37 (2.3)	0.27
QoL score baseline PCS, mean (SD)		54.1 (20.4)	53.6 (21.9)	0.42
QoL score baseline MCS, mean (SD)		60.0 (18.6)	57.8 (20.6)	0.001
Operative characteristics				<0.001
Use of 1 arterial graft		1408 (54)	981 (60)	
Use of 2 or more arterial grafts		1104 (42)	593 (36)	
Use of ECC[a]		1606 (93)	803 (90)	0.005
Postoperative characteristics:				0.58
Deep sternal wound infection		14 (0.5)	11 (0.7)	
Stroke		7 (0.3)	14 (0.9)	0.008
Renal failure		4 (0.2)	11 (0.7)	0.006
Surgical re-exploration		72 (2.8)	63 (3.8)	0.053
Myocardial infarction[e]		51 (2.0)	25 (1.7)	0.49
Coronary reintervention[f]		78 (3.0)	53 (3.6)	0.35

All numbers are presented with percentages, unless otherwise indicated. [a]BMI and the use of ECC data available from two of the participating hospitals. [b]Log EuroSCORE 1 for 13 patients is unknown. [c]Diabetes mellitus, pulmonary disease, arterial vascular disease and renal disease is unknown for 2 patients. [d]LVEF for 22 patients is unknown. [e]Myocardial infarction for 458 patients is unknown. [f]Coronary reintervention for 451 patients is unknown. BMI: body mass index; CABG: coronary artery bypass grafting; ECC: extracorporeal circulation; LVEF: left ventricular ejection fraction; MCS: mental component summary; PCS: physical component summary; QoL: quality of life; SD: standard deviation.

A factor that might explain why elderly patients report a decline in QoL is that in our study, as well as in another recent study (21), age is associated with a lower QoL after cardiac surgery. In other words, patients undergoing SAVR at an elderly age are at greater risk of experiencing a worse QoL compared with younger patients. In our multivariable model, the other independent risk factor (besides age) for a decreased QoL is a greater baseline QoL score, suggesting that patients with greater preoperative QoL scores are more likely to experience decreased QoL after surgery. We interpreted this finding as regression to the mean, which has been confirmed in other studies on QoL after cardiac surgery (9,21,28). To correct for this finding, we included baseline QoL scores in the multivariable regression analyses. Other explanations might be residual confounding due to differences in baseline characteristics. In our study renal disease and female sex were not

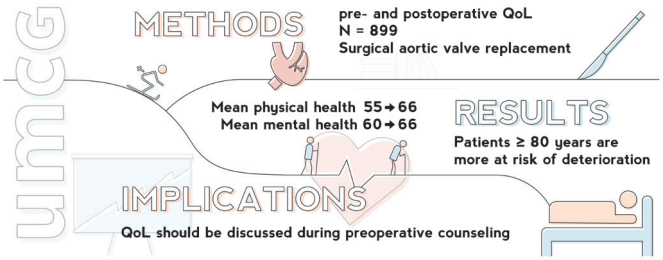

Figure 3. Visual summary of the paper on quality of life (QoL) after surgical aortic valve replacement.

associated with an impaired QoL, whereas other studies did suggest these factors as predictors for impaired QoL after SAVR (21,29). We included patients undergoing SAVR with or without concomitant revascularization to increase groups. Subgroup analyses show that although patients with solitary SAVR on average experience a greater physical and mental QoL, change in QoL was not significantly different between both groups.

Other explanations for the decline in QoL could be side-effects of surgery (ie, new comorbidities or reduced independence) or factors not caused by or related to the intervention. Such unmeasured confounders might have been present irrespective of surgery and may explain why only 21% and 28% of the variance of QoL in our regression models is associated with the included variables.

We used a MCID set at 5 points to classify the change in QoL (18). Two recent studies (21,30) on QoL after SAVR also reported change in QoL and used lower MCID thresholds (2.5 and 3.5). The thresholds for MCID used in our study were stricter: if we had used lower MCID thresholds for deterioration, the numbers of patients with a decreased QoL would have been greater (Figures E2 and E3).

To interpret the generalizability of our results we compared data from responders and nonresponders following recommendations by van Laar and colleagues (31). Compared with the responding patients the nonresponders had more comorbidity, lower preoperative QoL scores and more postoperative complications, which suggests that QoL data are not missing at random. When comparing our results with the QoL scores of the general Dutch population, the scores of our study population are greater (mean PCS 55.1 vs 50.4 and mean MCS 59.5 vs 52.5 for responders vs the general population) (32). Overall, this suggests that the responders are healthier, possibly due to selection bias, potentially leading to a positive overestimation of change in QoL for the total group, as suggested in other studies (31,33). This implies that the numbers of patients with decreased postoperative QoL in the total population are expected to be even greater.

Our multicenter study has important limitations. First, the numbers of patients with total available QoL data are rather low (30%). Data were collected by e-mail or a written survey, which might have led to reporting bias. Second, we have a significant amount of missing data in some of the postoperative outcomes. With a more complete dataset, we might have arrived at slightly different conclusions in subsets of patients. Finally, we lack information on length of hospital stay, discharge destination, and other events influencing QoL (ie, cerebral vascular disease, marital status).

In conclusion, our study suggests that although most patients experience an improved QoL after SAVR, patients with increasing age are more at risk of deterioration in both physical and mental QoL. Well-being and QoL are likely to be valued more important than quantity of life in the elderly patients. Therefore, patients' individual preferences and expectations on postoperative QoL should be discussed prior to surgery in order to optimize shared-decision making (Video 1).

Conflict of interest

Dr Mariani has received grants from AtriCure Inc, Edwards Life Sciences and Abbot Inc, and has provided training for Livanova. All other authors have nothing to disclose with regard to commercial support.

Supplementary Material

Only appendix E1 is printed here due to space limitations. All supplementary material may be accessed at the journals website:

https://doi.org/10.1016/j.jtcvs.2019.09.184

Video 1. The importance and relevance of our study for patient care.

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Appendix E1. Definitions of comorbidities & postoperative complications

COMORBIDITIES
Diabetes: oral therapy or insulin dependent diabetes (12).
Pulmonary disease: prolonged use of steroids or other medication for pulmonary disease (13).

Arterial vascular disease: peripheral or abdominal vascular pathology or operation due to arterial vascular disease (13).

Renal disease: a reduced renal function prior to surgery with an estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73 m^2 (14).
Ventricular function: ejection fraction: good >50%, moderate 30–50% or poor <30% (15).

POSTOPERATIVE COMPLICATIONS
Surgical re-exploration: thoracotomy due to bleeding, cardiac tamponade, graft- or valve failure within 30 days after surgery (12).
Deep wound infection (within 30 days after surgery): when deeper tissues are affected (muscle, sternum and mediastinum) and one or more of the following three criteria are met:
1) surgical drainage/refixation
2) an organism is isolated from culture of mediastina tissue or fluid
3) antibiotic treatment because of a sternal wound (19).

Renal failure (within 30 days after surgery) one or more of the following criteria are met:
renal replacement therapy (dialysis) which was not present preoperatively
highest postoperative creatinine level > 177 µmol/L and a doubling of the preoperative value (the preoperative creatinine value is the value on which the EuroSCORE is calculated) (12).

Cerebral vascular accident/stroke: an acute neurological event within 72 hours after surgery with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnoses of stroke requires confirmation by a neurologist (20).

Re-intervention: a percutaneous re-intervention (coronary angiography or percutaneous coronary intervention) or a surgical procedure (valve repair or re-replacement of the same valve as the primary procedure) within one year after surgery (12).

Implantation of a permanent pacemaker: implantation of a new permanent implantable cardiac defibrillator (ICD) or pacemaker within 30 days after surgery (12).

5

Chapter 6

BARRIERS THAT OBSTRUCT RETURN TO WORK AFTER CORONARY BYPASS SURGERY – A QUALITATIVE STUDY

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Submitted

ABSTRACT

Purpose: Coronary artery bypass grafting is the most frequently performed cardiac surgical procedure. Despite its benefits on survival and quality of life, it is associated with a considerable financial burden on society including sick leave. Our study aimed to explore the barriers that obstruct return to work after coronary artery bypass grafting.

Methods: We performed a qualitative study with in-depth interviewing of patients six months after their surgery. We included ten working patients and interviewed them and their spouses at home. The interviews were transcribed and two investigators independently searched the transcriptions for barriers that had obstructed return to work.

Results: Based on the interviews we were able to distinguish four main groups of barriers: 'personal', 'healthcare', 'work' and 'law & regulation.' The personal barriers were subgrouped in affective, physical, cognitive, social and individually determined factors.

Conclusions: In a qualitative study we showed that personal barriers as well as barriers regarding healthcare, work and law & regulation, were perceived by patients as important factors obstructing return to work after coronary artery bypass grafting. To overcome the identified barriers, the process of return to work could preferably be initiated during the hospital phase, started during cardiac rehabilitation, and coordinated by a case-managing professional.

INTRODUCTION

In the Netherlands, over 15,000 cardiac surgeries are performed every year (1). The main reasons to offer cardiac surgery, including coronary artery bypass grafting (CABG) are to improve survival and quality of life (2). A relevant number of patients are at working age when undergoing coronary bypass and return to work (RTW) is an important goal during recovery (3,4). Because ischemic heart disease, including coronary artery disease, can be life-threatening, anxiety and uncertainty have been suggested as barriers for RTW, not only for the patient but also for the occupational physician (3,4). Guidelines of the Dutch society of occupational physicians describe how to guide employees with ischemic heart disease during the process of resuming their work (4). These guidelines are based on internationally conducted studies and recommend to resume work during cardiac rehabilitation (CR) to overcome possible barriers of fear and anxiety (4). The guidelines suggest partial or fully RTW within approximately six weeks for patients with coronary artery disease, including patients after CABG, provided that postoperative recovery was uncomplicated (4).

Only a few studies on return to work after CABG have been conducted. RTW is observed between 8 and 13 weeks after surgery in two studies with CABG patients not participating in cardiac rehabilitation-programs (5,6) while another study reported 64% of patients fully resuming work within six months after cardiac rehabilitation (7). There seems to be a notable discrepancy between guidelines recommendations on RTW after CABG and literature reports, although evidence is scarce. Younger age (6,8,9), higher job satisfaction (5), positive occupational expectations (7,10) and absence of diabetes and myocardial damage (6,8,11) have been suggested to facilitate quicker RTW but may not be considered comprehensive, because they are all personal factors. In RTW models, such as the case-management ecological model, work-related and other factors influencing the disability process are also present (12). While this model was developed for the case management of disability due to low back pain and has been applied in other medical conditions, it has not been used in patients after CABG.

In-depth interviewing of patients after CABG and their spouses may enrich our knowledge on the process of RTW after CABG from the patient perspective including the facilitators and barriers influencing this process. The aim of our study was to identify barriers that obstruct return to work of patients after CABG.

METHODS

Study design

The study is reported according to the Standards for Reporting Qualitative Research (SRQR) (13). A qualitative study design was applied to evaluate barriers that obstruct return to work in patients after CABG. Through in-depth interviewing of patients and their partners we explored personal experiences (14). An essential characteristic of the data collection by in-depth interviewing is that critical issues identified in one interview are used to refine questions and topics in the next

interview. This design of inductive inference provides the opportunity to elaborate each issue with each subsequent interview (14).

Participants

Participants were selected based on distinct inclusion criteria: all patients underwent elective, isolated CABG, were living with a spouse and had paid work before surgery. To ensure that other severe comorbidities or a complicated recovery did not affect the process of RTW, we excluded patients with the following preoperative comorbidities: ejection fraction <30%, stroke, psychiatric illnesses, chronic obstructive pulmonary disease (COPD) GOLD III-IV or renal disease (a reduced renal function prior to surgery with an estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73 m^2 (15). We also excluded patients who participated in the Heart-ROCQ study, a randomized trial on an extended CR-program before and after cardiac surgery (16).

Sample and setting

All interviews were held at the participants' homes between six and seven months after their CABG surgery in line with an expected full recovery. Based on current literature, we defined that data saturation would be reached when in three subsequent interviews, no new additional themes emerged (17).

Data collection

The interviews were semi-structured, using an interview guide which was divided into different topics based on recent literature (13,17)(Appendix 1). The interviewer can use an interview guide as a list of topics and open-ended questions; the guide was not used as a questionnaire but rather as a memory aide during the interview (14). To start, some baseline questions were asked to identify narratives of people's lives (i.e. type of work, education level, working hours). All interviews were conducted by one of the researchers (FB) who works at the university hospital as a nurse practitioner and PhD-student at the department of cardiothoracic surgery. All interviews were audiotaped with permission from the participants.

Data analysis

After verbatim transcriptions, two researchers (FB and MO) independently performed data analyses following the thematic content approach, which focuses on identifying, analyzing and interpreting patterns of meaning within qualitative data (18). All transcriptions were examined to create one large preliminary list of barriers obstructing return to work as derived from the in-depth interviews (19). Both researchers independently created items and after inductive and axial coding using consensus techniques, more collectively shared underlying concepts were analysed leading to a codebook utilized by the qualitative analysis software package ATLAS.ti. (version 8, ATLAS.ti Scientific Software Development, Berlin) (20). Finally, higher-level grouping was guided by the case-management ecological model (12). The frequency of the individual barriers was assessed using

quantitative techniques by determining how frequent each item was mentioned. The frequency of all mentioned barriers was only used in a semi-quantitative approach to guide emphasis in the description of the results section.

Ethical considerations

The institution's ethical committee approved the protocol (reference number 2019/075) and waived the need for formal evaluation according to the Dutch Law on Scientific Medical Research with Humans. All participants were approached by telephone for their participation in this study and formal written informed consent was obtained prior to the interview. To ensure anonymity, all data that may plausibly identify any of the participants were eliminated from the transcripts.

RESULTS

All interviews were held between March and June 2019. Data saturation was reached after ten interviews. Baseline characteristics of the participants are listed in Table 1. Five participants had fully returned to work; two after two months and three within 4-6 months. The other five participants were still in the process of returning to work guided by an occupational physician. Two participants were self-employed. One participant reported that during hospital admittance, a nurse practitioner in the hospital had discussed the expectations regarding RTW with the participant. All patients had participated in a multidisciplinary CR-program after CABG, either a phase I program (inpatient CR-program) (n=2) or a phase II program (an early post-discharge outpatient CR-program (n=8). Nine participants reported that the process of RTW had started after having finished

Table 1. Characteristics of participants

Participant	Age (years)	Gender	Education-level	Occupation (collar)	Employment	Contract hours
1	57	male	high	white	employed	32
2	49	male	high	white	employed	40
3	62	male	low	blue	employed	40
4	61	male	medium	white	employed	40
5	56	male	high	white	employed	36
6	53	male	high	white	self-employed	> 40
7	56	male	medium	pink (service industry)	employed	40
8	63	male	medium	white	self-employed	> 40
9	59	female	high	white	employed	40
10	54	male	low	blue	employed	40

the rehabilitation program, and seven participants reported their impression that there was no communication between the physicians involved.

After verbatim transcription and analyses of the data, four main groups of barriers were defined: 'personal', 'healthcare' 'work' and 'law and regulation'. The personal barriers were divided into five subgroups: 'affective', 'physical', individually determined', 'social' and 'cognitive'. All barriers and associated items are listed in table 2.

Within the personal barrier, the subgroup concerning affective factors was mentioned most frequent, i.e. loss of self-confidence, anxiety, bad feeling due to physical complaints & limitations, and being unable to handle a lot of fuss.

Table 2. Barriers that obstruct return to work in patients after CABG

Personal	**132 (55%)**
Affective	*57*
Loss of self-confidence	12
Anxiety	10
Feeling bad due to physical limitations	9
Not being able to handle a lot of fuss	9
Feeling of being out of balance	5
Fear of becoming physically active again	4
Post-traumatic stress	3
Awareness of suddenly being a heart patient	3
Grief/very emotional	2
Physical	*43*
Fatigue	17
Physical complaints due to other health issues	16
Loss of condition	8
Chest pain	2
Individually determined	*13*
Feeling obliged to resume work	5
No attention for others (focusing on yourself)	3
Change in personality due to illness	2
Feeling superfluous at work during reintegration	2
Not being able to let go of work during reintegration	1
Social	*12*
Family experiencing stress	7
Social environment advising to take it easy	5
Cognitive	*7*
Memory loss	4
Concentration disorder	3

Healthcare	**63 (26%)**
No advice concerning RTW	24
No guidance/follow-up after cardiac rehabilitation	15
Discouraging RTW	14
Employment consultant available but not involved	3
Physicians conflicting opinions concerning RTW	3
Pressure by occupational physician to RTW	3
Leaflet concerning RTW not applicable	1
Work	**38 (16%)**
Factors causing work stress	18
Communication with supervisor	13
High costs to hire a replacement	3
Interaction with colleagues	3
Sole employee in the own company	1
Law & regulation	**6 (3%)**
Limited insurance when ill (self-employed)	3
Temporary contract: job loss due to illness	2
Uncertainty about income	1

Participants for example mentioned: "… the fear that you visit the cardiologist in the morning and are put in a wheelchair immediately and admitted because you are a ticking time bomb although you felt great, that realization of being a heart patient all of a sudden was very emotional …"[P (participant) 1]. "…The fact that you simply could not have made it and luckily that is not the case but well, the thought was there because it is your heart…" [R (relative) 5]. One of the partners described the uncertainty as being out of balance: "…because being healthy is a balance and if you are physically out of balance, then this also impacts mentally and right now, the balance is lost in everything…" [R.5]. Among the physical barriers fatigue was often mentioned. Physical complaints due to other health issues and loss of condition were relevant as well. One participant mentioned: "…then I arrive at work and I am very busy, thousand things to do and when I go home I am exhausted while there is still plenty to do at home but I am not capable of doing anything after work…"[P.4].

Among the barriers concerning healthcare, patients mentioned the lack of advice concerning RTW, professionals discouraging RTW, and no follow-up after cardiac rehabilitation, as the most critical barriers in the process of RTW. Participants for example mentioned: "… when I asked my cardiologist about RTW he said to me that work did not interest him, my health was his priority, not work…" [P.3]. "… the occupational physician advised me to take it easy, but I did not know exactly what to do with this advice…" [P.4]. "… during cardiac rehabilitation there was an informative meeting in the hospital for cardiac patients, and we saw a short movie of a man who wanted to RTW after surgery, but that he did not succeed at all. That was not an uplifting video because my wife and I thought I would go back to work pretty soon…" [P.2]. Another participant: "… because actually after the rehabilitation then suddenly there is nothing left. Yes, then there is your job - you have to pick up all vocational and social activities again but there is no guidance or whatsoever…" [P.2].

In the work-related barrier, factors causing work stress (i.e. excessive workload, busy workplace, understaffed) and the communication with the supervisor (i.e. difficult relationship) were mentioned most frequently.

DISCUSSION

This qualitative research showed that personal as well as healthcare-, work- and law & regulation-related factors, are all barriers in returning to work after CABG. Personal barriers concerning affective or physical complaints were most frequently mentioned during the interviews. Remarkably, many participants were dealing with feelings of anxiety, loss of self-confidence and fatigue during RTW, although their CABG was uncomplicated from a medical perspective.

Other recent studies also revealed that affective factors play an essential role in RTW after a cardiac event and suggest to identify this as soon as possible

to allow for targeted psychosocial care (7,10,11). We did not identify other studies confirming our findings on physical barriers such as fatigue that impedes resumption of work after CABG. Previous studies though, focused on patients with coronary artery disease, including also patients after less invasive procedures such as percutaneous coronary interventions or patients treated by medication only. These patients deviate severely from patients after coronary bypass as CABG is a major invasive procedure with impact on the entire body both physically (i.e. a sternal wound, postoperative anemia) as well as mentally, likely leading to prolonged recovery. The invasiveness of the treatment likely explains the long-term complaints of fatigue and feelings of anxiety. Because CR-participants after CABG deviate from other CR-participants in general, further research may possibly lead to adapted guidelines for patients after cardiac surgery. The previously mentioned guidelines suggest RTW within six weeks but based on recent studies (5–7) and based on the findings in our study, this may not be feasible for patients after coronary bypass.

Another finding of our study are the healthcare-related barriers on RTW after CABG. Remarkably, there is either complete absence or contradictory advice and guidance from the healthcare professionals. Many participants mentioned that surgeons, cardiologists, general practitioners, or occupational physicians did either not advise them concerning RTW, or alternatively, the given advice was discouraging or unclear (e.g. the advice to 'take it easy'). This pattern of contradictory, or lack of advice was previously recognized for patients after cholecystectomy (21). No or unclear advice may negatively interact with the mentioned feelings of anxiety and uncertainty among patients and their spouses. Also, participants indicated that there appeared to be no communication between the physicians involved. All participants joined a CR-program following international guidelines for patients with CAD, including patients after coronary bypass (22–24). An essential goal of CR is to optimize participation in society regarding different aspects of daily life, such as domestic, occupational, and recreational activities (23,25). While participants were positive about their CR-program, participants also mentioned that the lack of follow-up after CR induced feelings of uncertainty about their activities at home and in resuming work. These feelings of uncertainty became even stronger because participants were advised to start the process of RTW only *after* completing CR, which is in contrast with guideline recommendations. Returning to work during CR requires coordination between the occupational physician and the cardiac rehabilitation team. Our findings are in line with the suggestions for improvement mentioned in the Dutch rehabilitation guidelines (3). A case-managing professional as a central contact is insufficiently imbedded in current practice resulting in inadequately aligned treatment- and RTW-plans (3). Surprisingly, the only participants returning to work during CR and within two months after surgery were the participants who were self-employed.

After the interviews many participants reported that they felt the importance to improve the process of RTW after CABG, which was their incentive to participate

in this study. We fully agree with the participants as there is a lot to improve. RTW itself can improve quality of life and economic security from both the individual (26) and the societal perspective; a quicker RTW can lead to reductions in sick-leave and substantial savings in indirect costs. Two recent reviews on RTW for workers with musculoskeletal pain-related conditions and on workers with coronary heart disease revealed that there is evidence suggesting that long term absence is significantly reduced by multi-domain interventions (i.e., health-focused, service coordination and work modification interventions) (27,28). This model of care may also be of added value in RTW after CABG. Feelings of anxiety and uncertainty can possibly be reduced or overcome by an earlier start of the process of RTW causing positive feedback (self-efficacy) or by proper counseling by healthcare professionals.

This study has several limitations. We focused on individual aspects using a qualitative design and results should, therefore, be considered in an explorative perspective. Further quantitative studies are necessary on RTW after coronary bypass to demonstrate the quantitative importance of the identified barriers. We included patients with paid work and without severe comorbidities limiting generalisability. Also, we excluded patients with complicated recovery. Although we did not use member checking or participant feedback to see whether the participants recognized the results, it is reassuring that most factors reflect the items from the case-management ecological model and another Dutch study on barriers influencing RTW after surgery (21,29). The results may be different in countries without a social security system, so that factors influencing RTW differ as well in these countries. This study focused on perspectives of patients and their spouses. Future studies should also focus on perspectives of supervisors and coworkers, as well as healthcare professionals.

CONCLUSION

Several barriers play a role in the process of return to work after coronary bypass. Affective and physical barriers and the absence or contradictory guidance from the healthcare professionals involved were mentioned most often. As guidelines suggest, the process of RTW could preferably be initiated during the hospital phase, started during CR, and coordinated by a case-managing professional to overcome the barriers of RTW after CABG.

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Conflicts of interest
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Chapter 7

THE INFLUENCE OF CORONARY BYPASS ON COGNITIVE FUNCTION AND QUALITY OF LIFE

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Submitted

ABSTRACT

Objectives: This study aimed to explore the influence of coronary artery bypass grafting on both postoperative cognitive dysfunction and quality of life and the association between both patient-related outcomes.

Methods: In a prospective, observational cohort study, patients with elective, isolated coronary artery bypass grafting were included. Cognitive function was assessed using the Cogstate computerised cognitive test battery preoperatively, 3 days and 6 months after surgery. Quality of life was measured preoperatively and at 6 months using the RAND-36 questionnaire divided in a physical and mental component score. Regression analysis, with adjustment for confounders, was used to evaluate the association between postoperative cognitive dysfunction and quality of life.

Results: A total of 142 patients were included in the study. Evidence of persistent cognitive dysfunction was observed in 33% of patients after six months. At six months the physical component score was improved in 59% and decreased in 21% of patients, and the mental component score increased in 49% and decreased in 29%. Postoperative cognitive changes were not associated with quality of life scores.

Conclusions: Postoperative cognitive dysfunction and decreased quality of life are common six months after surgery, although cognitive function and quality of life were found to have improved in many patients at six months follow-up. Impaired cognitive function is not associated with impaired quality of life at six months.

INTRODUCTION

During the past few decades improvements in operative techniques and perioperative care have led to a steady decline in mortality after cardiac surgery. Although survival rates have improved, elderly patients are at increased risk of postoperative complications such as neurological and pulmonary problems (1,2). Neurological complications after cardiac surgery have been classified by The American College of Cardiology and the American Heart Association into two categories (3). Type-I deficits result from well-defined local or regional insults resulting in transient ischaemic attack, stroke, coma and fatal brain injury. Type-II deficits result from more diffuse and poorly understood insults, and include delirium and postoperative cognitive dysfunction (POCD). Delirium is an acute and short-lasting disorder of fluctuating changes in attention, mental status and level of consciousness, which is clearly defined in the Diagnostic and Statistical Manual for Mental Disorders-V (4). In contrast, the definition and operationalization of POCD is less clear, it is mostly described as a deficit of concentration, attention, memory and motor speed that lasts for several weeks or months (3). Recently, an expert working group produced a set of recommendations for diagnosis and nomenclature for post-operative neurocognitive disorders to align the terminology used with that of the DSM-V (5). They have recommended that the term POCD be used for mild or major neurocognitive disorders found to be present between 1 and 12 months after a surgical operation. Studies of patients who have undergone coronary artery bypass grafting (CABG) describe an incidence of POCD of 30-60% depending on the timing, type and interpretation of cognitive tests used, and the patient-population involved (6,7). Despite this high incidence, and the fact that in vulnerable elderly patients even a small decline may have important consequences such as loss of independence (8,9), data on the impact of POCD on quality of life (QoL) are scarce. The primary aim of this study was to explore the influence of CABG on cognitive function and QoL, and to investigate the association between POCD and QoL in adult patients after CABG. Our secondary aim was to explore identifiable risk factors for POCD.

METHODS

We conducted a prospective single-center observational cohort study. The study protocol is registered at ClinicalTrials.gov (NCT03774342). The study was waived by the institutional review board (reference number 2018/226) and conducted in agreement with the principles of the Helsinki declaration. The study results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (10) (Supplementary Material Section S1 checklist).

Eligibility criteria

We included adult patients admitted for elective on-pump CABG in the University Medical Center Groningen, the Netherlands. Exclusion criteria were previous cardiac surgery and combined (i.e. valve) surgery due to the increased risk of

complications, pre-existing neurological deficits (i.e. dementia, stroke, epilepsy) and psychiatric illness limiting reliability of screening tests. If patients were likely to experience difficulty completing cognitive testing due to impaired eyesight or hearing, or problems understanding the Dutch language, they were also excluded from the study.

Procedures

On the day of admission, usually the day before surgery, patients were identified and contacted for informed consent by the attending doctor or nurse practitioner. After informed consent patients were included and baseline preoperative measurements were obtained. Postoperative assessment of cognitive function was performed in the hospital three days after surgery (short-term) and at the patients' homes six months after surgery (long-term).

Demographic and medical characteristics

Baseline demographic data were retrieved from the electronic patient medical records and included age, sex, body mass index, education level, log EuroSCORE I and the presence of comorbidity such as diabetes (11), pulmonary disease (12), arterial vascular disease (12), renal disease (13) and impaired ventricular function (14). Definitions of comorbidities are included in the Supplementary Material Section S2. The log EuroSCORE I is a widely used risk stratification system for adult cardiac surgery patients from which an individual patient mortality risk can be calculated (15). Perioperative data included duration of surgery, time on cardiopulmonary bypass (CPB) both in minutes and the number of (arterial) grafts.

Outcome measures

Cognitive function was assessed using the Cogstate brief computerised cognitive test battery (Cogstate Ltd, Melbourne, Vic., Australia). The test battery we used consisted of 4 tasks: the detection task (DET), the identification task (IDN), the one card learning task (OCL) and the one back task (ONB), assessing psychomotor speed, selective attention, visual learning and working memory, respectively (16). The Cogstate tests have been used in several other studies indicating a good sensitivity for detecting subtle changes in cognitive performance and strong test-retest reliability (16,17). On the day before surgery, the battery of tests were performed twice. The first was to minimise practice effects and the second was used as baseline test. Before starting, each task was introduced by the researcher using standardized written instruction. Each set of 4 tests required approximately 20 minutes to complete. All cognitive function scores were standardised according to normative data from age-matched controls, provided by the software vendor (18). A standardized score higher than 100 indicated a better than average score compared with the age-matched population (19). To perform a within-subject analysis a standardized reliable change Z-score for each postoperative cognitive test was calculated, based on the difference between the postoperative and baseline score, and normalized using test-retest variability data provided by the software vendor (20). The standardized change Z-scores of all four individual

tasks were summed to generate a composite Z-score (7). POCD was operationally defined as a Z-score <-2 in two or more individual tasks or a composite Z-score of <-2 (20). The threshold of <-2 was chosen to provide consistency with the suggestion of the expert working party of defining POCD as equivalent to major neurocognitive disorder if the decline in test scores is >2 standard deviations (5).

QoL was measured using the RAND-36 version-2 questionnaire. The questionnaire is a widely used and validated instrument containing eight health domains: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, mental health, vitality, pain, and general health perception (21). Each dimension is scored on a scale between 0 and 100, where a higher score is equivalent to better health. Two summarized scores were calculated: a physical component score (PCS) and a mental component score (MCS). We considered a minimal clinically important difference (MCID) to be five points, and calculated the change in QoL for each patient. QoL was judged as being improved (>5 points), worse (<5 points), or unchanged (≤5 points decrease or increase in score) (22).
Secondary outcomes were postoperative complications including delirium (23), atrial fibrillation (24), myocardial infarction (25), surgical re-exploration (11), deep sternal wound infection (26), and renal failure (12) within 30 days after surgery and stroke within 72 hours after surgery (27). Definitions of complications are included in the Supplementary Material Section S2. Additional outcomes were duration of stay at the Intensive Care Unit and discharge destination.

Analyses
The sample size calculation was based on the hypothetical association between POCD and QoL. POCD was assumed to be the independent variable and QoL as the dependent variable. A previous study on patients with POCD after CABG reported an SD of 8.5 (19) and a study on QoL after cardiac events reported an SD of 11 (28). A sample size of 123 patients was required for a two-tailed test at a minimal detectable difference of 0.33, an α of 0.05 and power of 80% to detect an association between POCD and QoL. To account for missing data, we included 142 patients.

Characteristics of patients are presented as numbers (with percentages) for dichotomous variables and as means (with standard deviations) or medians (with interquartile ranges) for continuous variables depending on distribution. Differences between baseline and six months follow-up of cognitive function and QoL were tested using paired t-tests. Differences between the patients with and without POCD were tested using the chi-square or Fisher's exact test. Linear regression analysis was used to evaluate the impact of POCD on the difference in QoL (dependent variable) and possible risk factors for POCD based on literature, as well as age and baseline PCS/MCS, were included in the multivariable model. All analyses were tested 2-sided and variables with P-values of <0.05 were considered statistically significant. All data were analysed using SPSS version 25.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 25.0, Armonk NY).

RESULTS

A total of 142 patients undergoing elective CABG were enrolled (CONSORT chart in Figure 1). Table 1 presents all baseline, operative and postoperative characteristics. Based on the standardized composite Z-score at baseline, two patients already had mild cognitive impairment preoperatively. Short term postoperative cognitive tests were performed after a median of three days [range 3-7] after surgery. Three patients refused further participation and 5 patients were unable to complete the early postoperative test due to pain or dizziness during testing (3 patients), a prolonged stay in the ICU (1 patient) and transfer to another hospital on day 3 (1 patient). Among the remaining 134 patients, 80 patients (60%) fulfilled the criteria for early cognitive dysfunction based on delayed neurocognitive recovery in the terminology suggested by Evered (5). Two patients died during follow-up, one patient moved abroad, and 5 patients refused further participation. Long-term cognitive tests were performed in 131 patients after a median of 192 days [range 177–219] after surgery. Forty-three patients (33%) had persistent cognitive dysfunction at long-term follow-up, whereas 29 patients (22%) showed improved cognitive function with a >2 increase in their composite cognitive function scores. Mean cognitive test scores are presented in Table 2.

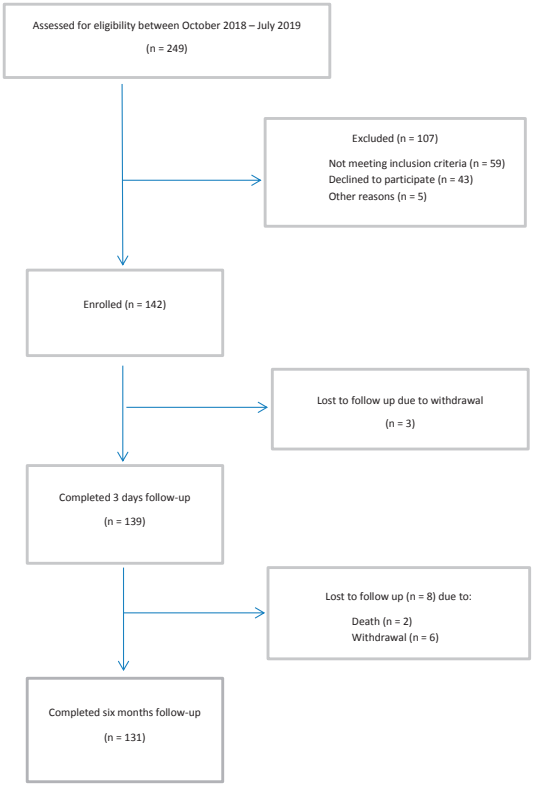

Figure 1. CONSORT study flowchart

Table 1. Baseline, operative and postoperative characteristics of patients with CABG

	n = 142
Baseline characteristics	
Sex (female)	18 (13)
Age (years),mean (SD)	64.3 (9.4)
BMI (kg/m^2)	
< 25	34 (24)
25-30	71 (50)
> 30	37 (26)
Log EuroSCORE I	
< 10%	133 (94)
10-20%	9 (6.3)
> 20%	0 (0.0)
Diabetes mellitus	31 (22)
Pulmonary disease	15 (11)
Arterial vascular disease	7 (4.9)
Renal disease	14 (9.9)
LVEF	
> 50%	96 (68)
30-50%	45 (32)
< 30%	1 (0.7)
Education level[1]	
Low	40 (28)
Moderate	55 (39)
High	46 (33)
Operative characteristics	
Number of grafts	
One graft	1 (0.7)
Two grafts	139 (98)
Three grafts	2 (1.4)
Number of arterial grafts	
Use of 1 arterial graft	100 (70)
Use of 2 or more arterial grafts	39 (27)
No arterial grafts	3 (2.1)
Surgical time[2], mean (SD)	254 (41)
CPB-time[2],median (IQR)	64 (48–78)
Postoperative characteristics	
Delirium	7 (4.9)
Atrial fibrillation	14 (9.9)
Myocardial infarction	2 (1.4)
Surgical re-exploration	3 (2.1)
Deep sternal wound infection	3 (2.1)
Stroke	0 (0.0)
Renal failure	0 (0.0)
ICU stay[3],median (IQR)	21 (18-25)
Discharge destination	
Home	99 (71)
Other hospital	21 (15)
Rehabilitation centre	18 (13)
Nursing home	1 (0.7)

Values are presented as n (%) unless otherwise indicated. [1]Education level for one patient unknown. [2] surgical time and CPB-time in minutes. [3]ICU-stay in hours. BMI:body mass index; CPB:cardiopulmonary bypass; ICU:intensive care unit; IQR:interquartile range; LVEF:left ventricular ejection fraction.

Table 2. Standardised cognitive test-scores of patients before and after CABG

Test	Preoperative (n = 142)	3 days[1] (n = 134)	6 months (n = 131)	P value[2]
DET; speed	101.8 ± 6.2	98.1 ± 8.4	100.5 ± 8.3	0.07
IDN; speed	100.6 ± 4.8	98.2 ± 6.3	100.8 ± 5.5	0.26
OCL; accuracy	103.6 ± 8.7	100 ± 9.0	104.5 ± 9.4	0.58
ONB; speed	98.3 ± 5.6	95.6 ± 6.2	97.5 ± 5.8	0.08

[1]Five patients did not complete the test. [2] paired T-test only from patients with complete dataset; P-value based on preoperative and 6 months scores. DET:detection task; IDN:identification task, OCL:one card learning task; ONB:one back task. All numbers are presented as mean with standard deviation.

Quality of life

Mean MCS, PCS and subscale scores are presented in table 3. At six months follow-up, PCS was increased (>5 points) in 59% of the patients and decreased (>5 points) in 21%. MCS was increased in 49% of the patients and decreased in 29%.

Association between postoperative cognitive dysfunction and quality of life

Table 4 shows the results of the linear regression analysis. Associations between POCD and difference in QoL six months after surgery were non-significant (PCS P=0.66 and MCS P=0.91; respectively). In the multivariable analysis baseline PCS and education level were statistically significantly correlated with difference in PCS at six months follow-up. Baseline MCS was associated with the difference in MCS six months after CABG.

Table 3. Quality of life of patients before and after CABG –subscale scores

Scores	Preoperative (n = 140)	6 months (n = 131)	P value
Physical component score	63.4 ±19.9	73.0 ±17.4	<0.001
General health	64.0 ±17.4	65.7 ±17.3	0.24
Physical functioning	64.9 ±27.1	79.4 ±20.2	<0.001
Role physical	57.4 ±30.2	64.3 ±29.0	0.009
Bodily pain	70.5 ±25.1	83.1 ±20.5	<0.001
Mental component score	70.6 ±20.4	74.6 ±18.7	0.018
Mental health	74.7 ±19.2	78.3 ±18.1	0.012
Vitality	61.6 ±23.9	63.6 ±19.9	0.29
Social functioning	74.3 ±26.7	81.6 ±21.2	0.001
Role emotional	74.6 ±25.7	75.5 ±26.9	0.68

All numbers are presented as mean with standard deviation.
For a few patients not all scores on all subscales are known.

Table 4. Univariable - and multivariable linear regression model of the effect of pre- and postoperative factors on the difference in quality of life 6 months after coronary artery bypass grafting

	Univariable analysis			Multivariable analysis		
Physical component score				Physical component score		(R^2 = 0.42)
	Beta	95% CI	P value	Beta	95% CI	P value
6 months POCD Z-score	0.20	-0.68 to 1.07	0.66	0.18	-0.53 to 0.88	0.62
Age	-0.35	-0.71 to 0.02	0.06	-0.23	-0.52 to 0.07	0.13
Baseline PCS	-0.59	-0.73 to -0.45	<0.001	-0.59	-0.73 to -0.45	<0.001
Baseline cognitive functioning	7.83	-19.8 to 35.1	0.57	6.99	-15.3 to 29.3	0.54
Education level	4.50	0.17 to 8.84	0.04	5.00	1.52 to 8.48	0.05
Delirium	3.72	-12.3 to 19.8	0.65	-4.06	-17.5 to 9.45	0.55
Mental component score				Mental component score		(R^2 = 0.28)
	Beta	95% CI	P value	Beta	95% CI	P value
6 months POCD Z-score	0.03	-0.71 to 0.76	0.94	-0.18	-0.85 to 0.50	0.61
Age	-0.10	-0.41 to 0.21	0.52	0.06	-0.23 to 0.34	0.69
Baseline MCS	-0.41	-0.53 to -0.29	<0.001	-0.43	-0.56 to -0.30	<0.001
Baseline cognitive functioning	-0.99	-32.1 to 14.1	0.44	-1.99	-23.4 to 19.4	0.86
Education level	0.16	-3.52 to 3.84	0.93	0.60	-2.69 to 3.89	0.72
Delirium	3.78	-9.78 to 17.3	0.58	-5.00	-18.0 to 7.97	0.45

Patients with and without POCD at six months follow-up

Of 80 patients with POCD at short-term follow-up, 37 (46%) had recovery of their POCD, and 43 (54%) were classified as having POCD at long-term follow-up. Baseline characteristics, operative characteristics and postoperative complications of patients with and without POCD at six months after surgery, are presented in Table 5. Age (P = 0.040), education level (P = 0.046) and postoperative delirium (P = 0.015) were different between the groups, all other variables were not. Differences in PCS and MCS between the groups were not significantly different (Figure 2).

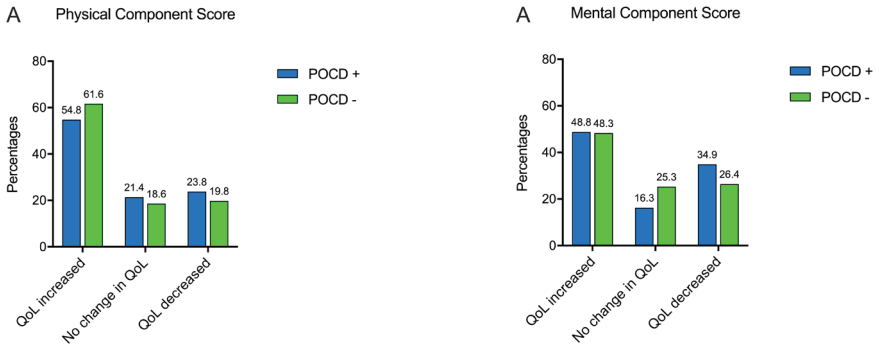

Figure 2. Difference in QoL of CABG-patients with and without POCD: physical and mental component score.

Table 5. Characteristics of patients with or without POCD six months after CABG

	No POCD (n = 88)	POCD (n = 43)	P value
Baseline characteristics			
Sex (female)	10 (11)	5 (12)	>0.99
Age (years),mean(SD)	63 (9.2)	67 (9.0)	0.040
BMI (kg/m^2)			0.29
< 25	18 (20)	13 (30)	
25-30	49 (56)	18 (42)	
> 30	21 (24)	12 (28)	
Log EuroSCORE I			0.72
< 10%	83 (94)	40 (93)	
10-20%	5 (6.0)	3 (7.0)	
Diabetes mellitus	20 (2.3)	9 (20.9)	0.79
Pulmonary disease	7 (8.0)	7 (16.3)	0.23
Arterial vascular disease	4 (4.5)	3 (7.0)	0.68
Renal disease	8 (9.1)	5 (11.6)	0.76
LVEF			0.54
> 50%	58 (66)	33 (36)	
30-50%	29 (33)	10 (23)	
< 30%	1 (1.1)	0 (0.0)	
Education level			0.046
Low	27 (31)	9 (21)	
Moderate	39 (44)	14 (33)	
High	22 (25)	20 (46)	
Baseline PCS, mean (SD)	65 (20)	63 (19)	0.46
Baseline MCS, mean (SD)	71 (20)	73 (21)	0.51
Cognitive test results, mean (SD)			
DET	101 (6.7)	103 (5.3)	0.24
IDN	100 (4.9)	101 (4.9)	0.69
OCL	104 (8.7)	104 (8.4)	0.71
ONB	98 (5.6)	98 (6.1)	0.49
Operative characteristics			
Surgical time[1],mean (SD)	257 (46)	249 (33)	0.24
CPB-time[1],median (IQR)	69 (26)	64 (26)	0.23
Postop. characteristics			
Delirium	1 (1.1)	5 (12)	0.015
Atrial fibrillation	9 (10)	5 (12)	>0.99
Myocardial infarction	1 (1.1)	0 (0.0)	>0.99
Surgical re-exploration	2 (2.3)	0 (0.0)	>0.99
Deep sternal wound infection	2 (2.3)	0 (0.0)	>0.99
ICU stay[2],median (IQR)	21 (18-25)	21 (17-23)	0.247
Discharge destination			0.99
Home	63 (72)	31 (72)	
Other hospital	12 (14)	6 (14)	
Rehabilitation center	12 (14)	6 (14)	
Nursing home	0 (0.0)	0 (0.0)	

Values are presented as n (%) unless otherwise indicated. [1] surgical time and CPB-time in minutes. [2] ICU-stay in hours. BMI:body mass index; CPB:cardiopulmonary bypass; DET:detection task; ICU:intensive care unit; IDN:identification task; IQR:interquartile range; LVEF: left ventricular ejection fraction; OCL:one card learning task; ONB:one back task.

DISCUSSION

In this prospective study we observed that many patients showed a postoperative improvement in cognitive function, and in the physical and mental component of QoL. Persistent POCD was however present in 33% of patients, and there was either no change or a decline in QoL in approximately half of all patients. Contrary to expectations, no association between POCD and difference in QoL six months after coronary bypass was found. A possible explanation for not finding an association could be that people with impaired cognitive function can still experience a high QoL or that patients adjust their intended level of QoL (glad to be alive), so that the difference between the new and the intended level is normalized after surgery.

Many studies have been performed on POCD after CABG, mostly addressing the incidence and etiology of POCD (6,19,29). Conflicting results often appear in studies on POCD, which can be explained by the fact that there are no universally accepted definition and operationalization, statistical methods or gold standards for measuring POCD (6,9). As in other POCD studies, we used the reliable change index that relates the change scores to the normal test-retest variation in an age-matched control group (7,19,20,29). Other commonly used statistical methods are an absolute decline (usually >1 SD calculated from baseline scores) or a percentage change from baseline (usually a decline >20%) however, these methods do not relate to data from age-matched controls and therefore do not account for normal variability among a population (30). Efforts should be made to establish a well-defined definition and a standard to measure POCD as the incidence of POCD appears high and its impact on patients' lives remain unclear. The Cogstate batterytest may be suitable as standard instrument, because data are comparable to data from age-matched controls, and several studies indicate this instrument to be sensitive and reliable (16–18).

The high numbers of patients not improving after CABG in our study, indicate that CABG may have a high impact on patient's QoL as suggested by other studies (31,32). The incidence of POCD at long-term in our study is also rather high, which is in line with other studies (6,7). It will be interesting to monitor improvements in QoL in future studies, as well as POCD at longer follow-up (>1 year). This is relevant because Kok et al. have reported that POCD three months after CABG is an important risk factor for POCD at 15 months after surgery (19) suggesting that the found incidences of POCD at six months in our study, may not further improve over time. Other explanations for the long-term decline in QoL and the high incidence of long-term POCD could be side-effects of surgery (i.e. new comorbidities or reduced independence) or other confounding factors unrelated to the intervention. Perhaps future studies should also assess functional status and work resumption alongside QoL, to learn more about the real impact of subtle changes in cognitive functioning on patients' daily lives.

Although not the primary outcome of our study, we found several significant differences between the groups with and without POCD at long-term. Age, education level and postoperative delirium differed significantly between both groups and have all previously been identified as risk factors for POCD after CABG in other studies (6,19). Risk factors for a decreased QoL after CABG identified in this study, are high baseline PCS and MCS, suggesting that patients with a good QoL before surgery are more likely to experience a decreased QoL after surgery also confirmed by other studies (32,33). Information on risk factors for POCD and a decreased QoL after CABG, can be useful to identify patients at risk during the process of shared decision making between patients and their healthcare professionals.

Our study has some important limitations. First, our patient selection might differ from other hospitals which may limit generalizability although we included only elective patients in our study population and mortality risk was low with a mean EuroSCORE of 3.8 (SD ±3). Second, it is likely that the early postoperative cognitive tests performed at three days after surgery, were influenced by factors like sleep disturbance and opioids. We specifically chose day three for assessment of short-term POCD due to logistic reasons: many of our patients are transferred back to other hospitals four days after surgery. Third, this is an observational study without a control group: further studies are needed to evaluate specifically the effect of alternative interventions (i.e. CABG vs. percutaneous coronary intervention) on POCD and QoL, as patients are not only subjected to surgery.

The outcomes of our study show high incidences of persistent POCD and a decreased QoL six months after CABG which may not recover in time and may negatively influence patients' daily lives. QoL and POCD are important for patients, relatives and thus for doctors taking decisions to operate or not. Studies addressing these topics can provide valuable information regarding shared decision making.

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Supplementary Material
Only supplement S2 is printed here due to space limitations.

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Supplementary Material S2. Definitions of comorbidities & complications

COMORBIDITIES
Diabetes: oral therapy or insulin dependent diabetes (11).
Pulmonary disease: prolonged use of steroids or other lung medication (12).
Arterial vascular disease: peripheral or abdominal vascular pathology or operation due to arterial vascular disease (12).
Renal disease: a reduced renal function prior to surgery with an estimated Glomerular Filtration rate (eGFR) <60 ml/min/1.73 m^2 (13).
Impaired ventricular function: left ventricular ejection fraction good >50%, moderate 30-50% or poor <30% (14).

POSTOPERATIVE COMPLICATIONS
Delirium during hospital admittance defined as:
1. A DOS score ≥ 3 at hospital ward and/or
2. A positive CAM-ICU score at the ICU and/or
3. Diagnosis confirmed by a psychiatrist or geriatrist according to the DSM-IV criteria (23).

Atrial fibrillation defined as new onset atrial fibrillation or atrial flutter requiring medical treatment or cardioversion within 30 days after surgery (24).

Myocardial infarction (MI) in the postoperative period. Myocardial infarction associated with CABG (within 48 hours after CABG) is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile upper reference limit (URL) in patients with normal baseline cardiac troponin values. In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (25). After 48 hours, the standard definition of myocardial infarction is appropriate. The following criteria meets the diagnosis for MI: detection of a rise and/or fall of cardiac biomarker values, preferably cardiac troponin, with at least one value above the 99th percentile URL and in addition, either (i) symptoms of ischaemia, or (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), or (iii) development of pathological Q waves in the ECG, or (iiii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy (25).

Surgical re-exploration within 30 days after surgery: thoracotomy due to bleeding, cardiac tamponade or graft failure (11).

Deep wound infection within 30 days after surgery: when deeper tissues are affected (muscle, sternum and mediastinum) and one or more of the following three criteria are met:

1. surgical drainage or refixation
2. an organism is isolated from culture of mediastina tissue or fluid
3. antibiotic treatment because of a sternal wound (26).

Stroke: an acute neurological event within 72 hours after surgery with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnoses of stroke requires confirmation by a neurologist (27).

Renal failure within 30 days after surgery when one or more of the following criteria are met:
1. renal replacement therapy (dialysis or CVVH) which was not present preoperatively
2. highest postoperative creatinine level > 177 µmol/L and a doubling of the preoperative value (the preoperative creatinine value is the value on which the EuroSCORE is calculated) (12).

7

Chapter

8

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 END-POINT (PROBE) TRIAL

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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 pre- 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 3 weeks), a post-operative inpatient phase (3 weeks) and an outpatient CR phase (two times per week, 4 weeks). Patients receive multidisciplinary treatment (e.g. physical therapy, dietary advice, psychological sessions, and smoking cessation). Standard care consists of 6 weeks of postsurgery 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 end-point 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 3, 7, and 12 months postsurgery.

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 UMCG (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.
Trial registration number NCT02984449.

INTRODUCTION

The leading cause of death in Western countries is ischemic heart disease (1). One of the treatments for severe ischemic 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 occur (2–4). These complications are associated with prolonged hospitalisation, increased adverse events (i.e. readmission, stroke, myocardial infarction, and mortality), reduced health-related quality of life (HRQoL), and higher health care costs (5–10). 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 surgery (8,11–19).

Over the last decades risk factors such as age, obesity, diabetes, hypertension and dyslipidaemia have steadily increased in patients undergoing cardiac surgery (20,21). 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 status (22,23). 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 position (24,25). In-hospital physical inactivity is a predictor of a longer hospital stay and rehospitalisation (24,26,27). It causes a decrease in muscle strength and aerobic capacity, both fundamental in the performance of activities of daily living (28,29). 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 reduced (30).

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). Post-operative 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 3-6 weeks after cardiac surgery (32,33). Benefits of postoperative CR are reported for a variety of cardiac patients (34); however the evidence in patients undergoing cardiac surgery is still lacking with regard to patient-relevant outcomes and mortality (35). In addition to postoperative CR, small trials suggested that preoperative CR is effective in reducing postoperative pulmonary complications, duration of hospital stay, improving HRQoL and physical fitness and increasing the compliance to postoperative CR (23,36,37). 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 (Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life) 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 with a regular Dutch postoperative outpatient CR programme (the standard care CR programme) (32). In addition, the effect of the Heart-ROCQ programme on physical and psychological functioning, including HRQoL, 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 organization

This investigator-initiated prospective randomised open, blinded endpoint trial is executed in a single center (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) (32). Figure 1 provides an overview of the study design.

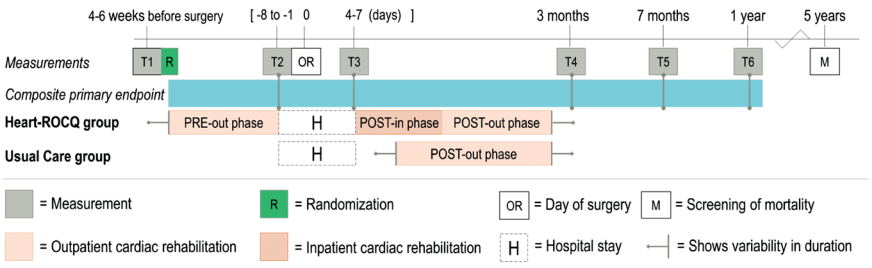

Figure 1. Research design of the Heart-ROCQ prospective, randomised, open, blinded endpoint trial. The phases of both cardiac rehabilitation programmes and the measurements are shown relative to the moment of surgery. Heart-ROCQ: Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life.

Ethical considerations and dissemination
This study has been registered at ClinicalTrials.gov. If applicable, substantial amendments will be notified to the Medical Ethical Review Board (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 limits exercise capacity, chronic obstructive pulmonary disease with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria classification 3 or 4 (38), addiction to alcohol or drugs, a serious psychiatric illness (ie, 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, or planned chemotherapy and so on); playing a sport at the (inter)national level; being unable to read, write, or understand Dutch.

Study enrolment, randomization and registry
Figure 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. Randomization (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. 7.3.2), 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

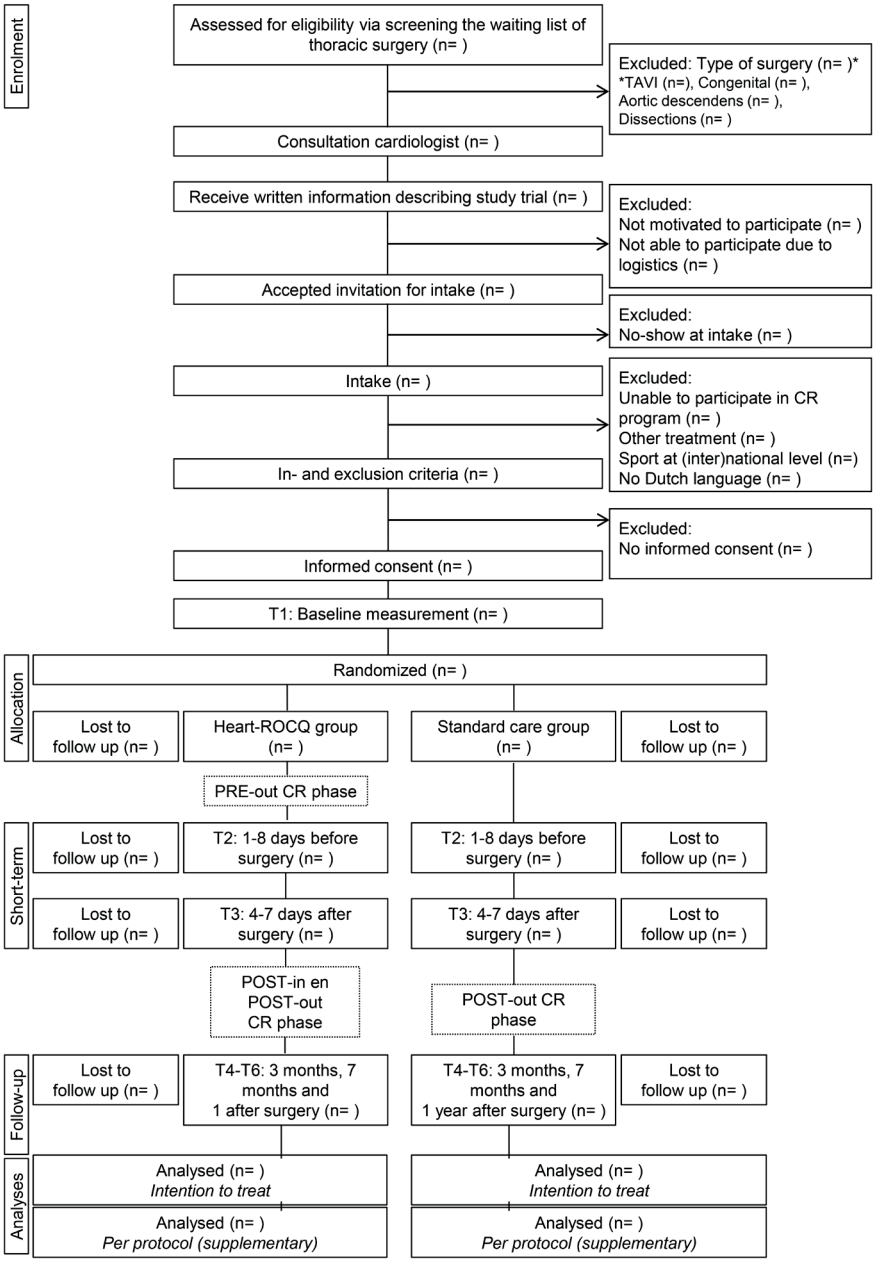

Figure 2. Flow chart of the Heart-ROCQ study. CR: cardiac rehabilitation; Heart ROCQ: Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life; TAVI: transcatheter aortic valve implantation.

using data that are collected during routine care. The data are collected in the Heart-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 insight 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 6 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 3 weeks). The second phase is a postoperative inpatient CR phase (3 weeks, weekdays only) followed by the third phase, an outpatient CR phase (two times per week, for 4 weeks). During each phase, all participants receive physical therapy including group sessions of inspiratory muscle training (39), strength training, aerobic cycling, breathing, coughing and relaxation. In addition, patients have an assessment with a dietician 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 (32,33). In general, this CR programme starts 3-6 weeks after discharge from the hospital and lasts for 6 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 dietician when needed. The content of this CR programme is based on the Dutch CR guidelines (40).

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 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 (eg, when a percutaneous coronary intervention (score 1) is complicated by a stroke (score 2), the score will be 2 and not 3 (1 + 2)).

Table 1. Definitions and score of the components of the composite primary endpoint

Functional status	**Score**
Worsening in physical functioning (domain score of health related quality of life, RAND-36 V.2)†	1
No change or improvement in physical functioning†	0
Worsening in physical problem (domain score of health related quality of life, RAND-36 V.2)†	1
No change or improvement in physical problem†	0
A clinically relevant worsening is classified as minimal change according to Wyrwich et al [43]	
(Serious) Adverse Events	
No serious adverse event	0
Prolonged mechanical ventilation Mechanical ventilation longer than 24 hours	1
Lung infection 1) A new lung radiographic infiltrate and 2) two signs that the infiltrate is of infectious origin - that is, (a) fever: body temperature >38°C or <36°C; (b) leucocytosis - white blood cells >$10x10^9$/L or $4x10^9$/L; (c) positive sputum culture and/or (d) decline in oxygenation	1
Delirium 1) A DOS score ≥ 3 at hospital ward [45] and/or 2) diagnosis confirmed by a psychiatrist, geriatrist, or supervising specialist according to the DSM-|V criteria resulting in treatment with medication	1
Readmissions to intensive care unit Unrelated to a secondary endpoint	1
Deep wound infection Deeper tissues are affected (muscle, sternum and mediastinum) and must include (1) surgical drainage/re-fixation or (2) an organism is isolated from culture of mediastina tissue or fluid, or 3) antibiotic treatment, because of sternum wound	2
Readmissions to hospital 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)	1
Any cardiothoracic surgical interventions Graft- or valve failure, CABG, valve, aortic, or other cardiac surgery‡	2
Any percutaneous interventions PCI, TAVI, and so on.	1
Myocardial infarction According to the third universal definition of myocardial infarction [44]	2
Cerebral vascular accident / stroke 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, MRI, or pathological confirmation.	2
Sudden death survivor The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.	2
Death All-cause mortality	3
Total score = sum of physical status and SAEs at 3 months and 1 year (worst score of each event)	

In grey: post-operative complications can be scored once. †Compared with baseline.
‡According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland.
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-General Health Survey; SAE: serious adverse event; TAVI: transcatheter aortic valve implantation .

The concept of the composite weighted score is adapted from the African-American Heart Failure Trial (41). Functional status is assessed through two health domains of the Medical Outcomes Study 36-item General Health Survey (RAND-36 V.2) (42): physical functioning and physical health problems. The primary endpoint is evaluated at 3 months (T4) and 1 year (T6) after surgery (Figure 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 2).

Table 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 (ie, going independently to the toilet)

Hospital admissions are checked between baseline and 1 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 3 summarises the definitions of the secondary complications and events, including at the time of screening.

Table 3. Definitions of the secondary complications and events

Definitions	Time of measure
Atrial fibrillation New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion	Surgery to T3
Prolonged ICU stay When the number of calendar days is two or more from ICU admission to discharge	Initial stay
Readmissions to hospital The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (ie, clinical signs and symptoms or change of treatment) a. Directly related to a cardiac cause b. Not directly related to a cardiac cause	Baseline to T6[§]
Hospitalisation days Total number of days of hospitalisation a. Directly related to a cardiac cause b. Not directly related to a cardiac cause	Baseline to T6[§]
Cardiovascular death 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 (eg, PCI, CABG), including those related to concomitant treatment[†]	Baseline to 5 years after surgery
Non-cardiovascular death Any death not covered by above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma	Baseline to 5 years after surgery
Concerning safety	
Surgical re-exploration for bleeding/ tamponade Surgical incision into the sternum as a result of a bleeding or tamponade a. Acute: presented within 24 hours after surgery b. Late: presented after 24 hours after surgery	Surgery to T4
Surgical re-exploration dehiscence Aseptic wound dehiscence	Surgery to T4

[§]Not measured between the day of admission before surgery and 30 days after surgery, because of POST-in phase of Heart-ROCQ programme. [†]Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (eg, cancer, infection) will be classified as cardiac death. CABG: coronary artery bypass grafting; Heart-ROCQ: Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life; ICU: intensive care unit; PCI: percutaneous coronary intervention; T4: follow-up at 3 months after surgery; T6: follow-up at 12 months after surgery.

Table 4. Time of measure, physical tests, and questionnaires of the secondary outcomes

Secondary outcomes	Measure	Time of measure
Physical health		
Cardiorespiratory fitness	6MWT[46]	T1-T4, T6
Muscle strength	STS-10, grip & leg strength[47,48]	T1-T4, T6
Independence in ADL	KATZ[49,50]	T1, T4, T6
Psychological health		
General anxiety	GAD-7[51]	T1,T2, T4, T6
Feelings of depression	PHQ-9[52,53]	T1,T2, T4, T6
Health related quality of Life	RAND-36 V.2[42]	T1, T4, T6
Life style risk factors		
Physical activity	iPAQ & Actigraph†[54,55]	T1, T4, T6
Obesity indices	BMI, waist to hip ratio	T1, T4, T6
Smoking behaviour	Number of cigarettes per day	T1, T4, T6
Economic evaluation		
Healthcare use & related medical costs	iMCQ[56]	T1, T4-T6
Work participation‡	iPCQ[57]	T1, T4-T6
QALYs	EQ-5D-5L[58]	T1, T4-T6
Potential mediators		
Cardiac self-efficacy	CSE[59]	T1, T2, T4, T6
Illness representations	IPQ-R[60]	T1, T2, T4, T6

†Patients are asked to wear the Actigraph during waking hours for one consecutive week.
‡Health-related productivity losses of paid work and unpaid work.
ADL: Activities of Daily Living; BMI: Body Mass Index; CSE: Cardiac self-efficacy; EQ-5D-5L: EuroQol Five-Dimensional Questionnaire; GAD-7: Generalised Anxiety Disorder 7-item scale; iMCQ: iMTA Medical Cost Questionnaire; iPAQ: International Physical Activity Questionnaire; iPCQ: iMTA Productivity Cost Questionnaire; IPQ-R: Illness Perception Questionnaire, Revised; KATZ: Katz Index of Independence in Activities of Daily Living; 6MWT: 6 minutes walking test; PHQ-9: Patient Health Questionnaire 9-item scale; QALY: quality-adjusted life years; RAND-36 V.2: Medical Outcome Study 36-item General Health Survey; STS-10: 10 times sit to stand test; T1: begin of waiting time; T2: 1-8 days before surgery; T3: moment that patients meet the University Medical Center Groningen discharge criteria; T4-T6: follow-up at 3, 7, and 12 months after surgery.

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 cardiothoracic surgeons) who are not employed in the UMCG and are blinded to group allocation.

Questionnaires and physical tests

Table 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 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 2). The follow-up measurements (T4, T5 and T6) are at 3, 7, 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.

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 form 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 (ie, for bicycle training: external workload, heart rate response, rate of perceived exertion using the Borg scale, and for strength training: sets, repetitions, and intensity) for both the Heart-ROCQ group and the Standard Care group.

Potential mediators
Illness perceptions (ie, 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 (60). These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress (61). The Cardiac Self-Efficacy (CSE) Scale (59) is used to measure CSE (ie, 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 at 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 database (62), and data reported in the literature (6,63–65). A decrease of 0.3 is expected in the Heart-ROCQ group, based on previous studies comparing CR with standard care (36,64,66) (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 used (67). To compare the costs with quality-adjusted life years (QALYs), QALYs are estimated with the 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 tariff (68). Results from the analysis are reported as an incremental cost effectiveness ratio, dividing the difference in effect by the difference in costs. Bootstrap resampling 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 the 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 (eg, 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 a 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 combined primary endpoint and the weighting of the individual components were derived from other studies (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 (70). In the current study, the weighted score of HRQoL 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 an adverse event cancel each other out (e.g. when a patient experiences an improvement in quality of 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 showed by Tong and colleagues (70). A disadvantage of composite endpoints is that the effect may be driven by complications that occur with the greatest frequency (71). Therefore, postoperative complications which occur frequently, such as atrial fibrillation, are evaluated separately as secondary endpoint. The primary endpoint is evaluated by an endpoint committee, which is blinded to group allocation and consists of four independent cardiologists and cardiothoracic 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 (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 (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 indepth 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 (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 (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 (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 treatment 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 postsurgery 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.

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Declaration of interest
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CHAPTER 9

GENERAL DISCUSSION

For a long time, interventions of cardiac surgery have been evaluated based on outcomes such as mortality, complications and recurrence of symptoms. Other outcomes, important from the patients' perspective, were less considered but, along with rapidly improving surgical techniques and low post surgery mortality, the focus of general healthcare and cardiac surgery as well, is now shifting towards quality of life (QoL) and other patient-reported outcomes. However, studies on postoperative patient-reported outcome measures after cardiac surgery are still low in volume, lack external validation and have been conducted in highly selected patient categories (1–3). The aim of this thesis was to evaluate the impact of cardiac surgery on patient's daily lives including patient-reported outcomes.

Data on patient-reported outcomes reflect 'patient's suffering' caused by morbidity and provide information supplementary to clinical outcomes such as mortality and complications. QoL is by far the most frequently studied patient-reported outcome in healthcare. Other patient-reported items are symptoms and satisfaction with care of which the latter is rather comprehensive (4). Satisfaction with care can be interpreted as satisfaction with care during hospitalization, but alternatively, potentially also as satisfaction with care after discharge, i.e. care in terms of cardiac rehabilitation (CR) or the follow-up at the outpatient clinic.

MAIN FINDINGS

Quality of life

Improvement in QoL, symptom relief and survival are the main incentives to conduct cardiac surgery (5,6). Reports on QoL after cardiac surgery are contradictory and several systematic reviews emphasize the lack of well-designed sufficiently powered multicenter studies, including both pre- and postoperative QoL data and information on the patients lost to follow-up (7–9). In **chapter 3, 4, 5 and 7** QoL is thoroughly studied and discussed in patients after coronary artery bypass grafting (CABG) or aortic valve replacement.

Quality of life and age

Chapters 4 and 5 of this thesis describe a multicenter study of 2606 patients after CABG (chapter 4) and 899 patients after surgical aortic valve replacement (SAVR; chapter 5) including preoperative (baseline) and postoperative data on QoL one year after surgery. We evaluated the impact of cardiac surgery on one-year QoL and its variation with age by categorizing the patients into three age groups: younger than 65 years, between 65 and 79 years and 80 years or older. We observed that most patients experienced a beneficial effect in terms of QoL, while elderly patients are more frequently at risk for a deterioration in their physical and/or mental QoL compared to younger patients. These data correspond with the findings of our single-center study described in **chapter 3**, although baseline QoL-data was lacking. Several risk factors for a reduced QoL were observed in both our multicenter studies, such as a good QoL at baseline (CABG and SAVR), a reduced left ventricular function (CABG) and higher age (SAVR). The outcomes of

our studies suggest that people of increasing age are more at risk for deterioration in QoL after surgery and these findings are in line with other studies (10,11). Though, the cut-off values for defining elderly patients remain arbitrary and these values for elderly patients range between 70 and 80 years (12–14). In all our studies we defined elderly patients by 80 years of age or older, following the 2011 American Heart Association guidelines (12).

Quality of life: definition and measurement

Although the World Health Organization has provided a uniform definition of quality of life, there is still an ongoing debate about the meaning of QoL and what should be measured (15). In research, the terms quality of life, health-related quality of life (HRQoL) and health status are used interchangeably and confusion remains about the concepts of these terms (16,17). The World Health Organization defines QoL as: 'an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns' (15). Widely validated questionnaires such as the SF-36 and EQ-5D are described as measures of QoL, HRQoL and health status. HRQoL is directly related to QoL, as reflected in the following definition: 'quality of life is an all-inclusive concept incorporating all factors that impact upon an individual's life. Health-related quality of life includes only those factors that are part of an individual's health' (18). An alternative definition of HRQoL is: 'how well a person functions in their life and his or her perceived wellbeing in physical, mental and social domains of health' (19). There seems to be an overlap between the definitions on QoL and HRQoL, resulting in a difficult practical question concerning QoL research: to what extent are people capable of separating their QoL from their HRQoL? We have addressed this question in chapters **3, 4, 5 and 7** were we have implicitly accepted that QoL is influenced by other factors unrelated to the cardiac surgery intervention, meaning that QoL may also be influenced by other aspects in life, hereby referring to the definition of the World Health Organization on QoL.

Similar to research, the terminology of QoL and HRQoL has also been used interchangeably in the reports of our studies. Because we have mostly used SF-36, an instrument that is also used to measure HRQoL, we cannot be certain that we have measured QoL or HRQoL until there are clearly distinct and consented constructs and definitions, as well as validated instruments that measure these constructs. Irrespective the confusions concerning the terminology, the aim of this thesis was to evaluate the patient-reported outcomes after cardiac surgery, including quality of life.

Missing data

One of the widely acknowledged difficulties in QoL-research is the large amount of missing-data referring to both missing items in scales and to missed assessments (20). Missing data can be classified as data missing at random (e.g., data missing due to a missed appointment or the patient moving abroad) and data missing not

at random, which is generally the case when data is missing e.g., due to disease progression or lack of symptom relief. The patients from whom data is missing not at random are typically elderly patients, with more comorbidities and therefore a higher preoperative risk and likely, loss to follow-up is associated with a reduced QoL (21,22). If such patients are dropping out of the study, then patients with a likely poorer quality of life are lost, possibly leading to an overestimation of QoL in the study. This also applies to the prospective study described in **chapter 7** where 6.3% of the patients were lost to follow-up due to physical or emotional problems. Loss to follow-up is also addressed in the discussions of our multicenter studies (**chapter 4 and 5**) where we compared the characteristics of the responders (completed preoperative and follow-up questionnaires) and non-responders (only completed preoperative questionnaires). The comparisons showed that in both studies the non-responding patients were older, had more comorbidities and had a higher preoperative risk for mortality. This implies that in our studies selection bias may have led to an overestimation of increase in QoL, and in addition, the numbers of patients with a decreased QoL after cardiac surgery are thought to be much higher in the total population.

QoL and cost-effectiveness

With the increasing number of elderly patients undergoing cardiac surgery and the expanding costs in healthcare, QoL is a highly relevant outcome not only for the patient, but also for cost-effectiveness evaluations. In this thesis we did not address cost-effectiveness, but an economic evaluation was planned as part of the Heart-ROCQ study (**chapter 9**). This economic evaluation will be performed to compare the costs between a preoperative and postoperative CR-program and a standard care postoperative outpatient CR-program, by estimating quality adjusted life years (QALYs) using the EQ-5D-5L (23). Utility values for the EQ-5D-5L will be calculated based on the healthcare reimbursements and the results will be reported as an Incremental Cost Effectiveness Ratio (ICER), were the difference in effect is divided by the difference in costs (24). A societal perspective was chosen for this economic evaluation, which means that not only the costs for healthcare are taken into account but also patient- and productivity-related costs and benefits.

Functional status

Chapter 2 of this thesis is a systematic review on the benefits and harms of exercise-based CR after cardiac surgery on several outcomes which are important from the patient's perspective (i.e. mortality, serious adverse events, quality of life, functioning, return to work and in addition costs/cost-effectiveness). The results of this review did not allow us to reach any firm conclusions on exercise-based CR in patients having cardiac surgery. It is likely that exercise-based CR will improve outcome after cardiac surgery, but the results of our review highlight that patient-centered outcomes are frequently not well defined and insufficiently studied (7,25–29). In the protocol for this review, we deliberately chose not to describe the outcome 'functioning'. It turned out that most studies included in our review evaluated functioning in terms of physical capacity and/or modifiable risk factors.

For younger patients such modifiable risk factors are important, but for elderly patients (increasingly having cardiac surgery), the ability to perform daily activities and maintain independency is at least as important. Tools for assessment of this functional status could be the Karnofsky Performance Scale or the Katz Index of Independence in Activities of Daily Living (30–32). The assessment of functional status is also one of the secondary outcomes in the Heart-ROCQ study (**chapter 9**).

Return to work

Return to work after cardiac surgery was only described in four studies included in the systematic review (**chapter 2**) and is insufficiently evaluated in patients after cardiac surgery. Return to work is highly important for working age patients undergoing cardiac surgery, which is why we conducted a qualitative study on return to work after CABG by interviewing patients and their spouses approximately at six months after their surgery (**chapter 6**). The Dutch guidelines for occupational physicians (33) suggest return to work six weeks after a cardiac event, including CABG, but this appeared to be far too early for the vast majority of patients due to the impact of major invasive surgery. Patients experience many physical and mental complaints, even long after surgery and after cardiac rehabilitation. In addition, many patients reported that there was none or insufficient advice about returning to work. A case-managing professional seemed to be missing, which is also recognized by the Dutch Rehabilitation Committee (34).

Cognitive function

Cognitive function and the impact of postoperative cognitive dysfunction (POCD) on QoL was addressed in **chapter 7** of this thesis. Like functional status, this is an important outcome for young and old, but in particular for the elderly patients, since cognitive and physical impairment are reported to often co-occur in older people (35,36). The association between cognitive and physical impairment has been confirmed by several studies, including patients undergoing cardiac surgery (37–39). We observed an incidence of postoperative cognitive dysfunction of 33% at long-term follow-up (6 months), which is in line with other studies (40,41). Although we observed no association between POCD and QoL, we were able to identify several risk factors for POCD as well as risk factors for a decreased QoL. The relationship between POCD, physical impairment in terms of sarcopenia, and QoL will be studied in the near future as we have collected data on sarcopenia in addition to the cognitive tests described in **chapter 7**. Sarcopenia is defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, leading to an increased risk of adverse outcomes, including physical disability, poor quality of life and death (42).

SHARED DECISION MAKING

As discussed in the introduction of this thesis, studies on patient-reported outcomes are needed to provide doctors and other allied healthcare professionals with reliable data to evaluate all benefits and harms of cardiac surgery. Patients can subsequently be adequately informed on the potential benefits and harms

of an intervention during preoperative counseling, and how these benefits and harms may apply to their personal situation. Sharing decisions, as opposed to clinicians making decisions on behalf of patients, is gradually becoming the norm across Western societies as the preferred model for making patient-centered healthcare decisions (43,44). In shared decision making (SDM) decisions are influenced by 'what matters most' to patients as individuals. SDM is important for several reasons, all closely related to the basic principles of ethics in healthcare:

1. Respecting autonomy: enabling individuals to make reasoned informed choices
2. Beneficence: balancing on benefits of treatment against the risks and costs
3. Non-maleficence: avoiding harm (44,45).

During the last years many SDM models have been developed, some generic and others specific to a healthcare setting. There is no consensus in the field on the best SDM-model, only on certain components (46). One proposed model on SDM in clinical practice is presented in Figure 1 (47).

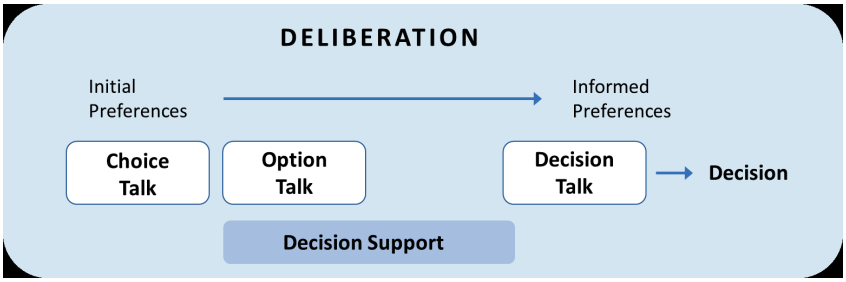

Figure 1. A shared decision making model (adapted from Elwyn et al. (2012).

As shown in figure 1 the model is based on the deliberation process, the process where the patient becomes aware of choice, in which three key steps are important:

- Choice talk: to realize that a choice exists, can be initiated by a patient or clinician
- Option talk: patients are informed by treatment options in more detail
- Decision talk: patients are supported to explore 'what matters most to them' (47).

When applying this model in clinical practice, the question arises whether shared decision making is feasible within the set time for consultation at the outpatient clinic. A practical solution could be to perform the decision talk by telephone/ video-call which gives the patient the opportunity to involve others, e.g., family members, in their decision. A written evidence-based patient information document, possibly with decision aids can be provided at the outpatient clinic,

as suggested in the current guidelines on myocardial revascularization (48). The integration of SDM into evidence based medicine may help clinicians to communicate about evidence and ask patients for their preference (44). The outcomes of our studies including several risk factors for impaired postoperative QoL and POCD are valuable for clinicians as well as patients in the process of SDM before cardiac surgery.

VALUE BASED HEALTHCARE

As in shared-decision making, patients are also placed at the center of healthcare in the theory of value based healthcare. Value based healthcare (VBHC) was introduced by Porter in 2006 and the idea of this methodology is the assumption that care can be improved by concentrating on maximizing the 'value' for patients, defined as the outcomes of care and QoL in relation to the costs of care (49). VBHC is implemented in several health organizations all over the world and in the Netherlands an example is found in the Netherlands Heart Registry (NHR) formerly known as Meetbaar Beter. The NHR is a nationwide initiative of cardiac surgeons and cardiologists to improve the quality and transparency of care for patients with heart disease. All participating centres systematically collect patient-oriented and clinically relevant outcome measures such as mortality, comorbidities, quality of life and postoperative complications (50). Outcome analysis of patients with similar medical conditions can be performed based on this registry. The studies described in **chapter 4 and 5** are based on this database. Recently, a comprehensive set of patient-relevant outcome measures for coronary artery disease has been developed and implemented. The variations between the results of the hospitals using this set may further improve cardiac care in the near future (51).

FUTURE PERSPECTIVES

Implications for clinical practice

This thesis expands our knowledge on patient-reported outcomes after cardiac surgery, with particular emphasis on the outcome quality of life. Based on our findings we would like to suggest the following implications for clinical practice.

Based on the findings of our studies on QoL, a preoperative QoL assessment should be part of the general preoperative examination of all patients, as a good QoL at baseline is a risk factor for a decreased QoL after cardiac surgery and patients should be aware of what they can expect after surgery. For elderly patients we suggest an extensive preoperative screening including assessment of QoL, functional status, cognitive performance and frailty because elderly, vulnerable patients are more at risk of a deterioration in their postoperative QoL. Several hospitals in the Netherlands already provide a preoperative screening-carousel including the consultation of a geriatrician for patients ≥ 70 years who are candidate for cardiac surgery. Screening of patients during the preoperative phase may very well be performed by dedicated allied health professionals (i.e.

nurse practitioners or physician assistants) working in the field of cardiothoracic surgery.

Patient's preferences and expectations on postoperative recovery including QoL, and a surgeon or cardiologist's personalized risk-assessment of patient-reported outcomes should be thoroughly discussed in the preoperative phase. This may eventually lead to improved quality of care from the patient's perspective. Shared-decision making may be a valuable tool during this process.

Although identified in a small qualitative study, the process of return to work for patients after cardiac surgery should preferably start early after surgery possibly by a coordinating case-managing professional. Because little research has been done in this area, further research is required.

Implications for future research

Although current recommendations in the ESC/EACTS guidelines on myocardial revascularization are mostly based on the ability of treatments to reduce adverse events including mortality, interest in patient-reported outcome measures is growing (48). Currently, patient-reported outcomes are not routinely evaluated as key outcomes in major cardiovascular trials. However, the focus on patient-reported outcomes should be encouraged because of an increased focus on improving well-being and the increasing role of cost-effectiveness assessment.

From the patient' perspective further research is needed on the harms and benefits of elderly patients undergoing cardiac surgery. Finding the best interventions for the vulnerably elderly patients is still a challenge and needs careful evaluation. Outcomes as QoL, functional status, frailty and cognitive function should be addressed and evaluated in any randomized trial when searching for the optimal intervention, including the comparison with no intervention as a control group.

Finally, studies on patient-reported outcomes in cardiac surgery and cardiac rehabilitation in general, would benefit from a set of clearly defined outcomes as suggested by the COMET (Core Outcome Measures in Effectiveness Trials) initiative and the CONSORT PRO Extension that aim to promote the transparent reporting of patient-reported outcomes in trials (52,53). The set of patient-relevant outcome measures for coronary artery disease developed by the NHR is a good example of a clearly defined set of outcomes and hopefully more will follow in the near future.

CONCLUDING REMARKS

The aim of this thesis was to contribute to the knowledge on patient-reported outcomes after cardiac surgery. Several patient-reported outcomes were addressed in this thesis to learn more about 'what really matters to patients' and to answer the three questions pointed out in the introduction.

What is the influence of cardiac surgery on patient-reported outcomes such as quality of life and return to work?
While most patients benefit in terms of QoL, approximately 30 - 50% do not benefit in terms of an increased QoL six to twelve months after surgery. Patients still at working age experience affective and physical complaints when returning to work and need on average more time to return to work than suggested in current guidelines. The results of our studies show that cardiac surgery is a major event in patients' lives and may have a substantial impact on patient-reported outcomes.

Do patients undergoing cardiac surgery, benefit from cardiac rehabilitation in terms of patient-reported outcomes?
The results of our systematic review did not allow us to reach any reliable conclusions about the effectiveness of cardiac rehabilitation following cardiac surgery on patient-reported outcomes. There was a large diversity in unclearly defined outcomes and a high risk of bias and random error.

Are elderly patients more at risk of a decreased quality of life after surgery?
Elderly patients are at higher risk of experiencing a deterioration in their QoL compared to younger patients. The decision to operate or not should, however, not solely be based on age but on the totality of individual preferences and expectations of the patient, as well-being and QoL are likely to be valued much more important than quantity of life by many, but especially by the elderly, vulnerable patients.

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9

Chapter
10

ENGLISH SUMMARY
NEDERLANDSE SAMENVATTING
CURRICULUM VITAE
DANKWOORD

ENGLISH SUMMARY

Undergoing cardiac surgery generally has a major impact on patients and their family members. This thesis was conducted to gain more insight into patient-relevant outcomes after cardiac surgery such as quality of life.

A systematic review of cardiac rehabilitation after cardiac surgery shows poor quality of the data collected with a wide variety of outcome measures, so that no reliable conclusions can be reached about the effectiveness of cardiac rehabilitation after cardiac surgery.

An observational study on quality of life in elderly patients (≥ 80 years) one year after coronary artery bypass surgery (CABG) demonstrated a lower quality of life and perceived health status compared to younger patients (<80 years). Many patients aged 80 years or older indicated that in retrospect they would not opt for surgery again. In a large multicentre cohort of patients, the effect of cardiac surgery on quality of life and its variation with age was further studied to identify potential subgroups with a higher risk of deterioration in quality of life. On average, there was an improvement in physical and mental quality of life 1 year after surgery, but a relevant proportion of older patients (≥ 80 years) deteriorated. A high quality of life preoperatively and a reduced left ventricular function were found to be independent risk factors for a reduced quality of life after CABG. In patients after surgical aortic valve replacement, older age and a high preoperative quality of life were identified as independent risk factors for a reduced quality of life after aortic valve replacement.

In a qualitative study six months after CABG, ten in-depth interviews were conducted with patients and their partners to identify potential barriers to return to work. Only half of them had fully returned to work six months after surgery, the other five were still in the process of returning to work. Physical and affective complaints were most frequently mentioned, as was the lack off, or conflicting advice given by the involved healthcare professionals.

The influence of CABG on postoperative cognitive dysfunction (POCD) and quality of life and the association between these two patient-related outcomes were also studied. Three days and six months after surgery, respectively 60% and 33% of patients experienced cognitive impairment. In about half of all patients, there was no change or a decrease in quality of life six months after surgery compared to the quality of life before cardiac surgery. An association between cognitive functioning and quality of life could not be demonstrated.

An intensive cardiac rehabilitation program may improve patient-reported outcomes. The study ‘Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life’ (Heart-ROCQ), includes a randomized trial evaluating the effect of a multidisciplinary pre- and

postoperative cardiac rehabilitation program including comprehensive quality of life aspects. This randomized trial started in May 2017.

Patient-reported outcomes after cardiac surgery have been understudied and deserve more attention. A clearly defined set of outcomes is needed for uniformity in research. Often patients do not improve in terms of quality of life after cardiac surgery, and elderly patients in particular are more at risk of deterioration in their postoperative quality of life. The postoperative expectations must be discussed with the patient in order to achieve shared-decision making.

NEDERLANDSE SAMENVATTING

Het ondergaan van een hartchirurgische ingreep heeft over het algemeen een grote impact op patiënten en diens familieleden. Dit proefschrift werd uitgevoerd om meer inzicht te verkrijgen in voor de patiënt relevante uitkomstmaten na hartchirurgie zoals kwaliteit van leven.

Een systematische review naar hartrevalidatie na hartchirurgie toont een matige kwaliteit van de verzamelde data met een grote variatie aan uitkomstmaten waardoor er geen betrouwbare conclusies kunnen worden getrokken over de effectiviteit van hartrevalidatie na een hartoperatie.

In een observationeel onderzoek naar de kwaliteit van leven bij oudere patiënten (≥ 80 jaar) één jaar na een coronaire bypassoperatie (CABG) werd bij deze ouderen een mindere kwaliteit van leven en ervaren gezondheidstoestand aangetoond ten opzichte van jongere patiënten (< 80 jaar). Veel patiënten van 80 jaar of ouder gaven aan dat ze achteraf gezien niet opnieuw zouden kiezen voor een operatie. In een groot multicenter cohort van patiënten werd het effect van hartchirurgie op de kwaliteit van leven en de variatie hierin met leeftijd verder onderzocht om mogelijke subgroepen te identificeren met een hoger risico op een verslechtering in kwaliteit van leven. Gemiddeld was er sprake van een verbetering van de fysieke en mentale kwaliteit van leven 1 jaar na de operatie, maar bij een relevant deel van de oudere patiënten (≥ 80 jaar) trad een verslechtering op. Een hoge kwaliteit van leven preoperatief en een verminderde linkerventrikelfunctie bleken onafhankelijke risicofactoren voor een verminderde kwaliteit van leven na een CABG. Bij patiënten na een aortaklepvervanging werden oudere leeftijd en een hoge kwaliteit van leven preoperatief geïdentificeerd als onafhankelijke risicofactoren voor een verminderde kwaliteit van leven na de aortaklepvervanging.

In een kwalitatief onderzoek zes maanden na CABG werden tien diepte-interviews gehouden met patiënten en hun partners om mogelijke barrières te identificeren die de terugkeer naar het werk belemmeren. Slechts de helft was zes maanden na de operatie weer volledig aan het werk, de overige vijf waren nog aan het re-integreren. Fysieke en emotionele klachten werden het vaakst genoemd, evenals het ontbreken van, of het geven van tegenstrijdige adviezen door de betrokken zorgverleners.

Ook de invloed van een CABG op postoperatieve cognitieve dysfunctie (POCD) en kwaliteit van leven en de associatie tussen deze beide patiënt-gerelateerde uitkomsten zijn onderzocht. Drie dagen en zes maanden na de operatie, was er bij respectievelijk 60% en 33% van de patiënten sprake van cognitieve stoornissen. Bij ongeveer de helft van alle patiënten was er zes maanden na de operatie geen verandering of een afname van de kwaliteit van leven in vergelijking met voor de hartoperatie. Een associatie tussen cognitief functioneren en kwaliteit van leven kon niet worden aangetoond.

Wellicht kan een intensief hartrevalidatieprogramma de patiënt-gerapporteerde uitkomsten verbeteren. De studie 'Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life' (Heart-ROCQ) omvat een gerandomiseerde trial waarin het effect van een multidisciplinair pre- en postoperatief hartrevalidatieprogramma wordt geëvalueerd inclusief uitgebreide kwaliteit van leven aspecten. Deze gerandomiseerde studie is in mei 2017 van start gegaan.

Patiënt-gerapporteerde uitkomsten na hartchirurgie zijn te weinig bestudeerd en verdienen meer aandacht. Een duidelijk gedefinieerde set van uitkomsten is nodig ten behoeve van uniformiteit in onderzoek. Vaak verbeteren patiënten niet na een hartoperatie op het gebied van kwaliteit van leven en vooral oudere patiënten lopen meer risico op een verslechtering van hun postoperatieve kwaliteit van leven. De postoperatieve verwachtingen moeten met de patiënt besproken worden om tot een gedegen gezamenlijke besluitvorming te komen.

DANKWOORD

Zo, en nu is het dus (al) af! De afgelopen jaren heb ik met hart en ziel gewerkt aan mijn proefschrift. Dit had ik niet gekund zonder de samenwerking met, en hulp van, een groot aantal mensen. Ik wil iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift en een aantal mensen in het bijzonder.

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CURRICULUM VITAE

Fredrike Blokzijl werd geboren op 1 februari 1979 te Hoogeveen. Na het behalen van haar VWO-diploma aan het Menso Alting College in Hoogeveen, begon zij in 1997 met de HBO-opleiding Verpleegkunde aan de Christelijke Hogeschool Windesheim in Zwolle. In 2001 behaalde Fredrike haar bachelor diploma Verpleegkunde waarna zij een baan kreeg op de afdeling Cardiologie van het Martini Ziekenhuis in Groningen. Na enige jaren werkervaring, startte Fredrike in 2003 met de opleiding Cardiac Care aan de Academie voor de Gezondheidszorg, welke zij in 2004 succesvol afrondde. Naast haar werk als CCU-verpleegkundige gaf zij Basic Life Support en Advanced Life Support training aan de medewerkers van het Martini Ziekenhuis en maakte zij deel uit van de Verpleegkundige Advies Raad. In 2006 stak Fredrike over naar het Universitair Medisch Centrum in Groningen waar zij startte met de Intensive Care opleiding aan het Wenckebach Instituut van het UMCG. Deze opleiding werd met goed gevolg afgerond in 2007. In de daaropvolgende jaren was Fredrike naast haar werk als IC-verpleegkundige op de Thorax Intensive Care, betrokken bij het opzetten van de Mobiele Intensive Care Unit (MICU) waarbij haar takenpakket met name bestond uit het ontwikkelen en opzetten van de verpleegkundige functie binnen deze nieuwe tak van de Intensive Care organisatie. In september 2009 werd Fredrike benoemd tot regieverpleegkundige bedrijfsvoering op de Intensive Care en hield zij zich naast haar taken als IC-verpleegkundige en bedrijfsvoerende, onder andere bezig met coaching, het verzorgen van Advanced Life Support trainingen en het opzetten van de werkgroep Moreel Beraad. In 2011 volgde zij de Basisopleiding Operationeel Leidinggeven aan het Wenckebach Instituut. In de zomer van 2013 maakte Fredrike de overstap naar de afdeling Cardiothoracale Chirurgie om in opleiding te gaan tot verpleegkundig specialist. Van september 2013 tot september 2015 volgde zij de Master Advanced Nursing Practice aan de Hanzehogeschool in Groningen welke zij cum laude wist af te ronden. Tijdens deze opleiding beleefde Fredrike veel plezier aan het verrichten van onderzoek en schreef zij haar eerste wetenschappelijke artikel wat resulteerde in hoofdstuk 3 van dit proefschrift. Dit stuk werd eind 2015 genomineerd voor de landelijke prijs ‘Beste Masterthese’ en gepresenteerd tijdens het jaarcongres van de V&VN verpleegkundig specialisten. In februari 2016 startte Fredrike met haar PhD-traject aan de Graduate School of Medical Sciences van de Rijksuniversiteit Groningen en bleef zij werkzaam als verpleegkundig specialist in de kliniek. Tijdens haar PhD-traject begeleidde Fredrike studenten van de HBO-V en de opleiding Verplegingswetenschappen en presenteerde zij haar onderzoeksresultaten op diverse (inter)nationale congressen. In oktober 2018 ontving zij de prijs voor beste presentatie tijdens het jaarcongres van the European Association for Cardio-Thoracic Surgery in Milaan, Italië. Fredrike is getrouwd met Peter Zwiers en samen hebben zij twee kinderen, Lauren (11 jaar) en Jesse (8 jaar).