CARDIAC REHABILITATION REVISITED

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CARDIAC REHABILITATION REVISITED

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“Alleen wie bezig blijft wil honderd worden”.

een Japans gezegde

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GENERAL INTRODUCTION

Cardiac rehabilitation: a comprehensive program

Cardiac rehabilitation (CR) is defined as a comprehensive secondary prevention program, with exercise as the cornerstone of a comprehensive intervention which includes an educational program, risk factors control and the patient's voluntarily adoption of a healthy lifestyle to be kept for lifetime (1). Secondary prevention programs in general, and CR programs in particular, are designed to minimize the negative physiological and psychological effects of cardiac illness, reduce the risk for sudden death or re-infarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of patients (2,3). Although exercise training is a core component, current practice guidelines consistently recommend that rehabilitation is offered as a "comprehensive" strategy, encompassing a variety of components to optimize cardiovascular risk reduction, foster healthy behaviors and compliance to these behaviors, reduce disability, and promote an active lifestyle (3). Furthermore, according to the latest guidelines, CR is not only indicated in patients with coronary artery disease (CAD), but also in patients with an implantable cardioverter defibrillator, heart failure, heart transplantation, congenital heart disease, atrial fibrillation and cardiac surgery (4,5).

Cardiac rehabilitation: how it evolved

When the phenomenon of angina pectoris was described in the 18th century, it was also recognized that symptoms improved by working in the woods half an hour per day (6). Further anecdotal evidence that exercise may lower the risk of CAD was revealed by Morris *et al*. in 1953, who showed that ticket sellers had a lower rate of coronary events than bus drivers in London (7). Interestingly, despite the early knowledge on the beneficial effects of exercise and movement, it was believed for centuries that patients with acute expressions of coronary disease would benefit of prolonged (bed) rest (6). In fact, early cardiac rehabilitation pioneers, including Levine and Lown, experienced very strong opposition for advocating early mobilization of patients (8).

In 1968, Saltin *et al.* published the Dallas Bed Rest and Exercise Study, which provided a strong proof of the importance of exercise and the detrimental effect of prolonged bed rest in CAD patients (9). The subsequent work of Braunwald, Hellerstein, Naughton (10,11) and many others helped establishing the physiologic basis of exercise benefits and led to the development of CR programs as a multidisciplinary approach to help cardiovascular patients recover and optimize their functional and mental status (6). Evidence that was gained by clinical trials and observational studies in the past decades, CR is undeniable associated with improved mortality and morbidity (9). Consequently CR has been recommended 'standard care that should be integrated into the overall treatment plan of patients with CAD' since the early 1990's (12).

Low participation rates

One might expect that treatment that has been proven (safe and) effective would easily finds its way in clinical practice. However, not so with regards to CR, as referral rates in potential eligible CAD patients are reported as low as 30-40% worldwide (13,14). Apparently, CR uptake varies between countries (Figure), but even the best performing countries do not reach uptake values above 50%. The reason why is not well understood.

Throughout the past decades, patients who are referred for CR constitute a heterogeneous and changing population. Still, they constitute for the main part of patients who have survived an acute coronary syndrome (ACS). We realize that major changes have been implemented in ACS treatment since the 1980s, which have highly influenced mortality and morbidity. Currently, most ACS patients undergo percutaneous coronary intervention (PCI) in the acute phase, and receive antiplatelet therapy, lipid lowering therapy and other cardioprotective medication during long-term follow-up. As a result, ACS patients usually have preserved left ventricular function and, consequently, a good survival (15). Patients are discharged as early as 3 or 4 days after ACS admission, and return to work within a few weeks. Against the background of these developments, it is possible that patients and their treating physicians no longer see the value of CR as an adjunct to medical treatment. Indeed, we cannot exclude the possibility that CR is in need of renewal.

Aims and outline of this thesis

This thesis was designed to understand the implementation of and outcomes after 12-week standard CR as currently recommended by European and Dutch guidelines (***Part 1***), and to study if standard CR can be improved by adding behavioral interventions during prolonged follow-up until 1 year (***Part 2***). We focus on ACS patients who underwent state-of-the-art medical treatment, including primary PCI and dual antiplatelet therapy.

In ***Part 1*** we studied determinants of CR participation and completion **(chapter 1)**, survival after CR **(chapter 2)**, the relationship between age and CR outcomes **(chapter 3)** changes in physical activity and sedentary behavior during cardiac rehabilitation **(chapter 4)** the participation in the society before and after CR **(chapter 5)**, and fatigue in patients during and after CR **(chapter 6)**, marital quality and loneliness as determinants of subjective health status **(chapter 7)**, the association between body mass index and health status **(chapter 8)**.

Part 2 describes the design and results of the Optimizing Cardiac Rehabilitation (OPTICARE) trial that we conducted. OPTICARE was a multicentre, open, multidisciplinary randomized controlled trial that compared two extended CR programs with standard CR. The main outcome parameter was the Systematic Coronary Risk Evaluation (SCORE), an estimate of 10- year cardiovascular risk (16). We provide a full description of the design **(chapter 9)**, the main results **(chapter 10),** results of secondary objective: the effects of extended CR on physical activity **(chapter 11)**, the relation between CR and incidence of cardiovascular events during prolonged follow-up (**chapter 12**), and, finally, the long-term benefits of CR on aerobic capacity and fatigue **(chapter 13).**

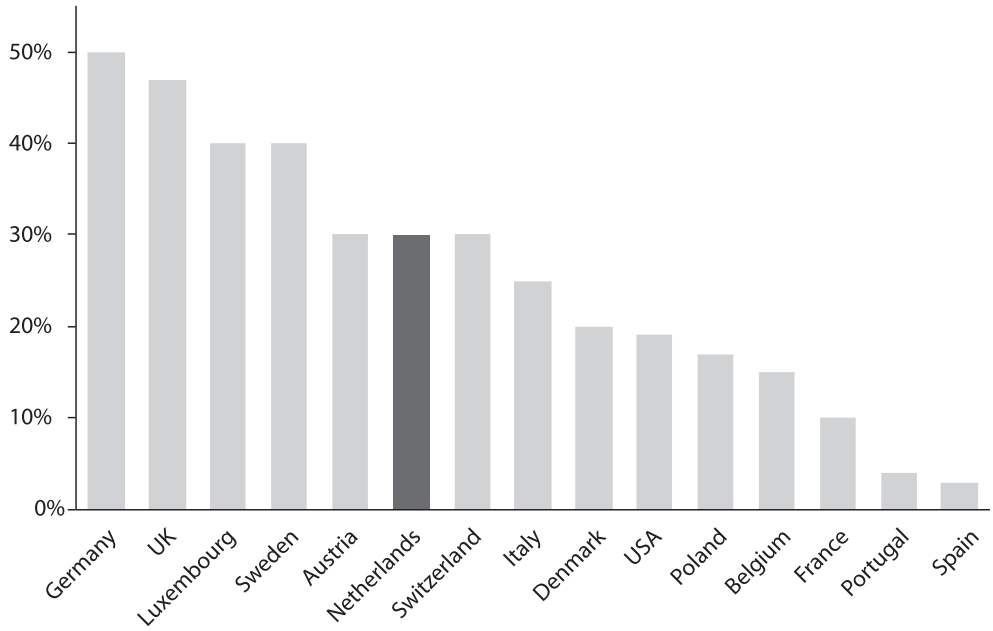

Figure - **Estimated percentage of eligible patients participating in Cardiac Rehabilitation programmes by country**

Source:
Eur J Cardiovasc Prev Rehabil 2010;17:410-418 http://www.cardiacrehabilitation.org.uk/docs/BHF_NACR_Report_2015.pdf
https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_493752.pdf

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Chapter 1

CARDIAC REHABILITATION IN PATIENTS WHO UNDERWENT PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR ACUTE MYOCARDIAL INFARCTION: DETERMINANTS OF PROGRAMME PARTICIPATION AND COMPLETION

M. Sunamura, N. ter Hoeve, M. L. Geleijnse, R. V. Steenaard, H. J. G. van den Berg-Emons, H. Boersma, R. T. van Domburg

Neth Heart J 2017;25:1039-3.

ABSTRACT

Background

Hospital length of stay after acute myocardial infarction (AMI) treated with primary percutaneous coronary intervention (pPCI) has reduced, resulting in more limited patient education during admission. Therefore, systematic participation in cardiac rehabilitation (CR) has become more essential. We aimed to identify patient-related factors that are associated with participation in and completion of a CR programme.

Methods

We identified 3,871 consecutive AMI patients who underwent pPCI between 2003 and 2011. These patients were linked to the database of Capri CR, which provides dedicated, multi-disciplinary CR. 'Participation' was defined as registration at Capri CR within 6 months after pPCI. CR as 'complete' if a patient undertook the final exercise test.

Results

In total, 1,497 patients (39%) were registered at Capri CR. Factors independently associated with CR participation included age (<50 vs. >70 year: odds ratio (OR) 7.0, 95% confidence interval (CI) 5.1–9.6), gender (men vs. women: OR 1.9, 95% CI 1.3–1.8), index diagnosis (ST-elevation myocardial infarction [STEMI] vs. non-ST-elevation myocardial infarction [NSTEMI]: OR 2.4, 95% CI 2.0–2.7) and socio-economic status (high vs. low: OR 2.0, 95% CI 1.6–2.5). The model based on these factors discriminated
well (c-index 0.75). CR programme completion was 80% and was inversely related with diabetes, current smoking and previous MI. The discrimination of the model based on these factors was poor (c-index 0.59).

Conclusions

Only a minority of AMI/pPCI patients participated in a CR programme. Completion rates, however, were better. Increased physician and patient awareness of the benefits of CR are still needed, with focus on the elderly, women and patients with low socio-economic status.

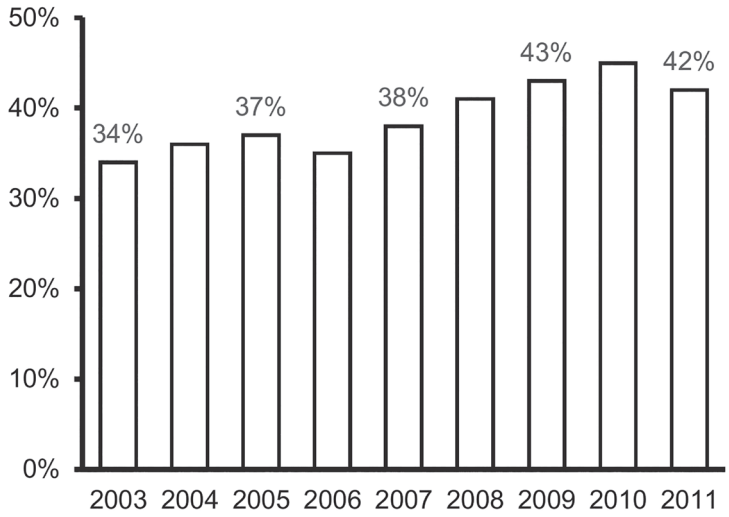

Fig. 1 Fig. 1.1 Participation rate over the years. Percentages of patients after primary percutaneous coronary intervention for acute myocardial infarction who participated in cardiac rehabilitation

BACKGROUND

Standard care for patients with an acute myocardial infarction (AMI) consists of immediate primary coronary percutaneous intervention (pPCI) [1]. Usually, patients with an uncomplicated AMI are then referred to a non-pPCI hospital for further care within a few hours, and discharged home within 2 to 4 days. Although a short hospital length of stay implies a lesser burden on the patient, it does result in more limited time for patient education. Therefore, participation in a cardiac rehabilitation (CR) programme is essential for AMI patients [2].

CR is a class I recommended intervention in coronary artery disease (CAD) patients [3, 4] with beneficial effects on physical fitness, quality of life, cardiovascular risk factors, and cardiovascular mortality and morbidity [5]. Nevertheless, merely one third of CAD patients are referred to CR in the Netherlands [6]. Better understanding of referral and participation patterns is essential to improve utilisation of CR. We therefore aim to identify patient-related characteristics that are predictive of CR participation and completion in AMI patients treated with pPCI.

METHODS

Study population and data collection

We identified all AMI patients who underwent pPCI in the Erasmus Medical Center Rotterdam between 2003 and 2011. These patients were linked to the database of Capri CR, which provides dedicated CR for patients who undergo pPCI in the Erasmus MC. Data on cardiac risk factors, clinical patient characteristics and treatment were prospectively collected in a database as part of the ongoing pPCI registry at the Erasmus MC. Capri CR provided information on participation and completion of the CR programme. This study was approved by the Erasmus MC Ethics Committee (MEC-2009-080).

Cardiac rehabilitation

Capri CR provides standardised outpatient CR according to the European Society of Cardiology (ESC) guidelines on CR [2]. The multi-disciplinary programme focuses on improving physical condition, self-confidence and social integration. The programme consists of 1.5-hour group exercise sessions twice a week during a maximum of 12 weeks, plus courses on how to deal with exercise, diet, smoking cessation and stress management. The aim is to improve adherence to lifestyle modification and help patients to adopt a positive role in the care of their own health. The exact length of a CR programme is determined by a multidisciplinary team together with the patient, with a minimum of 6 weeks. 'Participation' was defined as registration at Capri CR within 6 months after pPCI. CR 'completion' was defined as at least 75% attendance at the physical programme, based on the methodology described by Beauchamp et al. [7].

Statistical analysis

Normality of continuous variables was not rejected by Shapiro-Wilk tests. Hence, continuous variables are presented as mean and standard deviation. Categorical variables are summarised as numbers and percentages. Differences in characteristics between patients with and without CR participation, and with and without CR completion were evaluated by Student's t-tests (continuous variables), and Chi-square or Fisher's exact tests (categorical variables).

Univariate and multivariate logistic regression analyses were applied to investigate which baseline characteristics were related with CR participation or CR completion. We considered age, gender, body mass index, cardiac history (prior MI, prior coronary artery bypass graft, pri or PCI), diabetes, hypertension, dyslipidaemia, smoking, family history, socio-economic status and disease presentation as potential explanatory variables. Variables that reached statistical significance in univariate analysis entered the multivariate stage. Socio-economic status was based on the patient's postal code. We applied the 4-category classification developed by the Netherlands Institute for Social Research, which accounts for the average income in the corresponding city district, the percentage of people with a low income, the

percentage of people with low-level education and the percentage of people without a paid job. Regression analysis results are reported as odds ratios (OR) and 95% confidence intervals (CI). We used the C-index to assess the discriminatory ability of the multivariate models.

All statistical tests were two-tailed and p-values were considered statistically significant at $p < 0.05$. Analyses were performed using IBM SPSS Statistics version 21.

RESULTS

During 2003–2011, 4,260 AMI patients underwent pPCI in the Erasmus MC. A total of 352 died within 60 days, whereas another 37 were lost to follow-up. The remaining 3,871 patients were eligible for analysis.

Capri CR participation

The number of patients participating in the Capri CR programme amounted to 1,497 (39%). This percentage remained fairly consistent during the 8-year study period (Fig. 1.1) with a tendency to improvement. Capri CR participants were younger, had a better socio-economic status and a more favourable CAD risk profile (except smoking) than non-participants (Table 1.1). Participants were less often female. While 27% of the AMI patients were women, this percentage was lower (20%) in the CR group than in the non-CR group (32%). Furthermore, participants less often had a history of cardiovascular disease. Age, socio-economic status and diagnosis were independently associated with Capri CR participation (Table 1.2). Patients below the age of 50 years had a 6.9 times higher chance of participation than patients aged 70^{+}. The chance of CR participation was 2.0 times higher in patients who belonged to the upper social-economic class (as compared with the lowest class), and 2.4 times higher in those presenting with ST-elevation myocardial infarction (STEMI). The c-index of the multivariate model that predicted Capri CR participation based on these three characteristics was 0.75, implying a fair discriminatory performance.

Table 1.1 Clinical and socio-economic characteristics of the study population according to participation in and completion of the CAPRI cardiacrehabilitation program

	Participation	No participation	*P*-value	Completion	No completion	*P*-value
Number of patients	1497	2374		1193	304	
Age, years	56.9 (10.3)	64.5 (12.4)	<0.001	57.0 (10)	56.4 (11)	0.38
Age in categories						0.26
<50	400 (27%)	285 (12%)	<0.001	308 (26%)	92 (30%)	
50–60	800 (53%)	937 (40%)		652 (55%)	148 (49%)	
60–70	120 (8%)	280 (12%)		96 (8%)	24 (8%)	
>70	177 (12%)	866 (36%)		137 (11%)	98 (13%)	
Men	1198 (80%)	1614 (68%)	<0.001	963 (81%)	235 (77%)	0.2
Socio-economic status			<0.001			<0.005
Lower class	702 (47%)	1358 (57%)		543 (46%)	159 (52%)	
Lower middle class	344 (23%)	535 (23%)		273 (23%)	71 (23%)	
Upper middle class	184 (12%)	246 (10%)		149 (12%)	35 (11%)	
Upper class	265 (18%)	232 (10%)		226 (19%)	39 (13%)	
Diabetes	173 (12%)	513 (22%)	<0.001	123 (10%)	50 (16%)	<0.005
Hypertension	594 (40%)	1193 (50%)	<0.001	473 (40%)	121 (40%)	1.00
Dyslipidaemia	629 (42%)	1306 (55%)	<0.001	500 (42%)	129 (42%)	0.87
Current smoking	614 (41%)	719 (30%)	<0.001	465 (39%)	149 (49%)	<0.001
BMI			0.007			0.65
<18.5	4 (0%)	15 (1%)		3 (1%)	1 (1%)	
18.5–25.0	344 (23%)	625 (26%)		277 (23%)	67 (22%)	
25.0–30.0	928 (62%)	1348 (57%)		739 (62%)	189 (62%)	
>30	219 (15%)	383 (16%)		172 (14%)	47 (15%)	
Prior MI	220 (15%)	689 (29%)	<0.001	161 (13%)	59 (19%)	<0.001
Prior CABG	30 (2%)	236 (10%)	<0.001	23 (2%)	7 (2%)	0.70
Prior PCI	158 (11%)	600 (25%)	<0.001	116 (10%)	42 (14%)	0.04
Presentation with STEMI	1070 (71%)	1072 (45%)	<0.001	862 (72%)	208 (68%)	

Continuous data are presented as mean (standard deviation)
Categorical data are presented as numbers (%)
BMI bodymassindex, *MI* myocardialinfarction, *CABG* coronary artery bypassgraft, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction

Capri CR completion

Altogether 1,193 (80%) participants completed their CR programme. Programme completion was associated with socio-economic status, and inversely associated with CAD risk factors and CAD history (Table 1.1). In multivariate analysis, diabetes, current smoking and a history of MI were inversely related with the odds of CR programme completion (Table 1.3). However, the multivariate model that aimed to predict CR completion had poor discriminatory performance (c-index 0.59).

Table 1.2 Predictors of participation in the CAPRI cardiac rehabilitation program *Age, years*

	Univariateanalysis	Multivariateanalysis		
OR	95%CI	OR	95% CI	
Age, years				
<50	6.9	5.50–8.57	7.0	5.06–9.57
50–60	4.2	3.46–5.04	3.6	2.90–4.55
60–70	2.1	1.60–2.74	2.3	1.67–3.17
>70	1	1		
Men	1.9	1.62–2.20	1.5	1.26–1.77
Socio-economic status				
Lower class				
Lower middle class	1.2	1.06–1.46	1.3	1.09–1.57
Upper middle class	1.4	1.17–1.79	1.3	1.01–1.60
Upper class	2.2	1.81–2.69	2.0	1.60–2.48
Diabetes	0.47	0.39–0.57		
Hypertension	0.65	0.57–0.74		
Dyslipidaemia	0.59	0.52–0.67		
Currentsmoking	1.6	1.40–1.83		
BMI				
<18.5	0.48	0.16–1.47		
18.5–25.0	1			
25.0–30.0	1.3	1.07–1.46		
>30	1.0	0.84–1.28		
Prior MI	0.42	0.36–0.50		
PriorCABG	0.18	0.13–0.27		
PriorPCI	0.35	0.29–0.42		
Presentation with STEMI	3.0	2.65–3.49	2.4	2.03–2.77

OR odds ratio, *CI* confidence interval*, BMI* body mass index*, MI* myocardial infarction, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction

DISCUSSION

Only two out of five AMI patients who underwent pPCI during 2003–2011 in the Erasmus MC participated in the Capri CR programme. Apparently, patients and physicians did not adhere to the ESC guidelines recommendations for long-term management after CAD [3, 8]. Patient's adherence to CR fails to a larger extent. Particularly, elderly patients, female patients, patients presenting without ST-elevation and patients with lower socio-economic status were underrepresented among CR participants. Once started, an encouraging four out of five patients appeared able to complete Capri CR. Nevertheless, there is room for improvement, since non-completion was frequent in patients who could have benefited the most: diabetics, smokers and those with a past MI.

The observed low participation rate of 39% is consistent with earlier studies. It is even estimated that, on average, less than 30% of all eligible patients attend CR [9]. This may be especially worrying in patients after pPCI, when there is little time for patient education due to the short hospital stay. The ESC guidelines provide a Class I recommendation for 'exercise-based rehabilitation', with level of evidence B. The ESC guidelines for non-ST-elevation myocardial infarction (NSTEMI) have a Class IIa recommendation for 'participation in a well-structured cardiac rehabilitation programme'. Indeed, it is underscored that 'the benefits were established in the era preceding modern treatment of STEMI', whereas'… in patients with an uncomplicated course, rehabilitation can often be performed on an outpatient basis with an efficacy similar to that of centre-based cardiac rehabilitation' [8]. We believe that these and similar judgements may not reduce reluctance among treating physicians to refer to CR, whereas dedicated CR programmes have scientifically demonstrated positive effects on patient well-being and prognosis, also in the 'modern era'[10].

In literature, the terms 'referral' and 'participation' are often incorrectly used in the same context. If a cardiologist refers a patient to CR, but the patient is not willing to participate, this is incorrectly counted as 'no referral'. We believe that 'participation' is the correct term in our study. The low participation rate in elderly is a consistent finding, perhaps due to a lower expected benefit of CR for older patients [11]. Furthermore, older patients are more likely to have orthopaedic, vascular or neurological comorbidities which could prohibit or limit CR participation. It is a challenge for CR programmes to find ways to facilitate these kind of patients: sometimes by offering an individualised rehabilitation programme. Whether this is as effective as standard CR, has yet to be studied.

In our study, and in several other studies, women were also less likely to participate [12]. However, this is not a consistent finding in the literature [13]. Women in our study were older, had a higher prevalence of cardiac risk factors and less often STEMI. All factors that were all predictive of lower participation to CR. Still female gender was independently associated with low participation to CR. The reasons why women are less likely to participate in CR or other cardiac interventions are yet still poorly understood [14].

Patients with a lower socio-economic status were less likely to participate. In American

studies, it is often reported that the low participation rate is caused by insurance problems [15]. In the Netherlands, however, CR is fully reimbursed in the compulsory basic health insurance with a participation rate of >99%. Nevertheless, in our study higher socio-economic status was still associated with higher CR participation. This may be due to a lack of understanding of the benefits of CR and/or logistical problems in patients with a lower socio-economic status [16]. It has been demonstrated that if logistical problems are solved by providing a tailored CR programme for this specific group of patients, outcomes may be different [6, 15, 17].

Based on the patient-related data we collected, CR completion could be poorly predicted. Our somewhat discouraging results regarding CR completion by diabetic patients are consistent with a recent study by Armstrong et al. [18]. Interestingly, they found that diabetics who completed CR had a significant mortality reduction. This emphasises the importance for diabetics to complete CR despite their complexity and higher incidences of co-morbidities, potentially precluding completion of the physical part of the CR programme. Also, it cannot be excluded that diabetics already have so many contacts with health care providers that they are physically or mentally not able to continue the twice weekly training sessions.

Non-completion of patients with a prior MI could be explained by former CR participation. However, similarly to diabetes, patients with a prior MI have adverse prognosis, which could be caused by impaired left ventricular function. That condition may hamper participation in CR. Although, like Forman et al. state, CR programmes see opportunities for this category of patients by starting home-based programmes using latest technologies [19]. The future will tell whether this is the solution.

A review by Gaalema et al. described identical findings as in our study regarding smokers, namely a higher participation rate but also a higher rate of premature quitting [20]. Why smokers do more frequently quit CR remains an unresolved issue.

Several interventions to stimulate participation and completion of CR have been studied. Reviews suggest that approaches aimed at motivating patients may be improving CR participation, for example invitation calls or visits early after discharge, followed by the use of self-management techniques [21, 22]. The 2014 Cochrane Database Systematic Review by Karmali et al. confirms these positive results of motivational calls and visits to increase participation [23]. To stimulate completion there were some positive but biased results on supervised or unsupervised exercise, accompanied by a variety of self-management techniques[24, 25].

The authors conclude that there is still not enough evidence to make practice recommendations for increasing participation and completion of CR. Particularly, studies to identify useful interventions to stimulate under-representing patient groups such as women and elderly are still missing. We hypothesise that individually tailored approaches may

increase the likelihood of success. Clark et al. conclude more or less the same by mentioning participation in CR as a consumer behaviour, in which interventions influencing family support, patient-friendly scheduling, and other socially and individually related factors can have a positive role [26].

Limitations

It should be noted that our study is observational, retrospective, and based on a single-centre experience (Erasmus MC/Capri CR). Some factors that might be related to participation in and not completion of CR may be missing in our study. For example, the influence of distance and transportation options to the CR location was not incorporated in our analysis. Patient socio-economic status was not based on individual data, but on area of residence, which is only a proxy for socio-economic status. In addition, physician's endorsement of the benefits of CR was not analysed in our study. We did not find written records in patient files stating that the patient had indeed been referred. The fact that younger age, male gender, STEMI and higher socio- economic status were predictive of participation to CR suggest that cardiologists have the idea that these patients most likely benefit from CR. The use of an automatic referral system may aid in increasing referral rates by helping to disregard personal feelings of the referring physician [27, 28].

Although not completing a CR programme might be related to poor outcome, it should be emphasised that the duration of CR should always be tailored to the individual patient. At one end of the spectrum, a short CR period of six weeks for a patient who is already physically active and participating at work may suffice, whereas improvements in physical and mental health may require more than the traditional 12 weeks of CR in the socially vulnerable patient [29].

Table 1.3 Predictors of completion of the CAPRI cardiac rehabilitation program

	Univariateanalysis		Multivariateanalysis	
	OR	95%CI	OR	95% CI
Age, years				
<50	0.98	(0.64–1.49)		
50–60	1.28	(0.87–1.92)		
60–70	1.16	(0.66–2.08)		
>70	1			
Men	1.23	(0.35–1.96)		
Socio-economic status				
Lower class	1			
Lower middle class	1.12	(0.82–1.54)		
Uppe rmiddle class	1.25	(0.83–1.89)		
Upper class	1.69	(1.16–2.50)		
Diabetes	0.59	(0.41–0.83)	0.59	(0.40–0.88)
Hypertension	1.00	(0.77–1.28)		
Dyslipidaemia	1.00	(0.76–1.25)		
Currentsmoking	0.67	(0.52–0.85)	0.59	(0.46–0.78)
BMI				
<18.5	0.71	(0.75–7.14)		
18.5–25.0	0.91	(0.69–1.28)		
25.0–30.0	0.91	(0.58–1.35)		
>30	1			
Prior MI	0.67	(0.52–0.85)	0.63	(0.40–0.84)
PriorCABG	0.83	(0.35–1.96)		
PriorPCI	0.67	(0.46–0.98)		
Presentation with STEMI	1.20	(0.92–1.59)		

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *MI* myocardial infarction, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction

CONCLUSION

Participation in cardiac rehabilitation after pPCI for AMI was poor. Even with better completion rates, only a minority of total AMI patients completed a CR programme. Patients who are elderly, female or of low socio-economic status appear to be particularly at risk of CR non-participation and non-completion. Therefore, these patient groups should be targeted in order to enhance their participation and completion of CR.

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Chapter 2

CARDIAC REHABILITATION IN PATIENTS WITH ACUTE CORONARY SYNDROME WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION IS ASSOCIATED WITH IMPROVED 10-YEAR SURVIVAL.

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ABSTRACT

Aims

We aimed to assess the effects of a multidisciplinary cardiac rehabilitation program (CR) on survival after treatment with primary percutaneous coronary intervention (pPCI) for acute coronary syndrome (ACS).

Methods and results

Using propensity matching analysis, a total of 1,159 patients undergoing CR were 1:1 matched with ACS patients who did not undergo CR and survived at least 60 days. Kaplan-Meier analyses and multivariate Cox regression analysis were applied to study differences in survival.

During follow-up, a total of 335 patients (14.5%) had died. Cumulative mortality rates at 5 and 10 years were 6.4% and 14.7% after CR and 10.4% and 23.5% in the no CR group ($p<0.001$). CR patients had 39% lower mortality than non-CR controls (10-year mortality 14.7% versus 23.5 %; adjusted hazard ratio [aHR] 0.61; 95% confidence interval [CI] 0.46-0.81). A total of 915 patients (78.9%) completed CR and had 46% lower mortality than those who did not complete CR. (10-year mortality 13.6% versus 18.9%; aHR 0.54; 95% CI 0.42-0.70).

Conclusions

Patients who underwent pPCI for ACS, with a CR program had lower mortality than their non-CR counterparts. Mortality was particularly low in patients who completed the program. In conclusion, CR is still beneficial in terms of survival.

Keywords

Cardiac rehabilitation, prognosis, PCI

INTRODUCTION

The beneficial effects of cardiac rehabilitation (CR) that have been reported for more than 40 years (1) are not universally accepted. In particular, early reported mortality effects are disputed. Recently, West et al. argued (2) that pooled data of studies published after the landmark WHO European multi-centre collaborative trial (early 1970's) did not evidently show a mortality reduction by CR in myocardial infarction (MI) patients. Also, in the recent Rehabilitation After Myocardial Infarction Trial (RAMIT), conducted in Great Britain, no beneficial effects of CR on short-term and long-term mortality were seen in MI patients mainly treated with thrombolysis(2).

An additional concern for the need of CR in modern era acute coronary syndrome (ACS) patients may be the excellent overall prognosis of treated patients with an ACS with clear improvements in invasive and non-invasive, medical treatment. Modern era AMI patients are in particular at lower risk because treatment with primary percutaneous coronary intervention (pPCI) has substantially reduced mortality (3, 4). On top of this, nowadays medical therapy is (close) to optimal from peri- and post pPCI, including standard treatment with statins and dual antiplatelet therapy (5). So, it may be expected that such patients even less benefit from CR (6). Therefore, Taylor et al suggested to focus on seeking for evidence of reduction in hospital readmission and health-related quality of life, rather than on a reduction of mortality (6). But, surprisingly, De Vries et al recently reported in a retrospective analysis, beneficial effects of CR on mortality in a subset of patients with an ACS, included from 2007 to 2010 (7). It might be that due to the early discharge of this relatively low-risk modern-time ACS patients CR can be valuable to guide patients towards a personal health plan, for which there is little time during the short hospitalization(8). Also, a major flaw in many CR trials that may explain contradictory findings is that it is not clear what part of the CR program was actually followed by the patient because the definition of participation was lacking (2) or attendance of at least only one session was already defined participation. Because of the concerns and contradictory findings of the beneficial effects of CR on mortality in the modern era ACS patient, we conducted a large study to assess the effects of CR in patients after ACS treated with pPCI on long-term mortality, in particular in patients who completed the CR program, compared with those patients who did not complete the CR program.

METHODS

Patients

The Erasmus Medical Centre (EMC) is one of the 2 hospitals in the Rotterdam-Rijnmond area that offers a 24/7 pPCI service for MI patients. Capri Cardiac Rehabilitation Centre Rotterdam (Capri CR) provides dedicated CR at five different locations in the city of Rotterdam (www.caprihr.nl).

Capri CR provides standardized outpatient CR according to the European Society of Cardiology (ESC) guidelines (9). In the database at Capri CR 1159 consecutive patients were identified with pPCI after an ACS between 2003 and 2011. Matching patients were found in the database of EMC: In total 3958 patients. Patients with cardiogenic shock (2,3%) were excluded: also patients with early (within 60 days post PCI) death(5.2%). Early death was defined as death within 60 days post PCI, because patients in the CR group started CR 4-6 weeks post PCI (median period) : so none of the early death could be caused by CR participation This study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. Moreover, the study was conducted according to the Helsinki Declaration. All patients consented participation in this study.

CardiacRehabilitation

The program focuses on improving physical condition, self-confidence and social integration. The multi-disciplinary CR program is led by a physician, specialized physiotherapists, nurses and social workers. The core of the program consists of 1.5 hours group exercise sessions 2 times a week during a maximum of 12 weeks at local sport's accommodations. Besides the exercise program, both verbal and written instructions are given on how to deal with exercise, diet, smoking cessation and stress management. The aim is to improve adherence to lifestyle modification and to help patients to adopt a positive role in the care of their own health. If necessary, individual consultations with psychiatrist, psychologist, social workers and dieticians are provided. The exact length of a CR program is determined by a multidisciplinary team together with the patient but with a minimum of 6 weeks. Upon completion of the CR program, a maximum (symptom-limited) bicycle stress test is performed. Patients who had completed CR program had attended at least 75 % of the physical program: this was our definition of "completed CR"(10).

Statisticalanalysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent t- test for continuous variables and Pearson's chi-square test for categorical variables. All statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whilst log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression analysis was performed to adjust CR effect for the following potential confounders: to generate a propensity score for CR participation using the following characteristics (table 2.1): age, sex, ST Segment Elevation Myocardial Infarction (STEMI), hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease, current smoking, prior myocardial infarction (MI), prior history of PCI or coronary artery bypass graft (CABG), proximal left anterior descending (LAD) lesion, socio economic status (11, 12). Using the generated propensity score, each patient from the CR group was 1:1 matched with a patient without CR. Statistical analysis was performed with SPSS 16 for Windows (SPSS Inc., Chicago , Il, USA). The results are presented as unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Primary endpoint

For information about mortality municipality live registries were studied. 9 Patients were lost to follow-up (0.9%)

RESULTS

CR participants versus non-CR-participants

After 1:1 propensity matching no differences in clinical characteristics between CR patients and controls were found (Table 2.1). The mean age of the study patients was 58.8 years and 77% were men. During a median (25^{th} - 75^{th}percentile) follow-up of 10 (range 4-12) years a total of 335 out of 2,318 patients (14.5%) had died: 211 in the no CR group (18.2%) and 124 in the CR group (10.7%). Throughout the entire follow-up period, mortality was lower in patients with CR and continued to diverge (Fig. 2.1). Cumulative mortality rates at 5 and 10 years were 6.4% and 14.7% after CR and 10.4% and 23.5% in the no CR group. Patients with CR had a 44% lower 10-year mortality than non- CR controls (HR 0.56, 95% confidence interval (CI) 0.43-0.73). After adjustment CR patients had a 39% lower 10-year mortality (HR 0.61 with 95% CI 0.46-0.81; p-value<0.001) than non-CR controls. 10 year mortality 14.7% vs 23.5%.

CR participants: complete versus non-completeCR

Nine-hundred-and-fifteen patients (78.9 %) completed CR. Clinical characteristics between complete CR and non-complete CR patients are displayed in Table 2.2 Patients who did not complete CR had more often diabetes (12.3% vs. 18.4%). Cumulative mortality rates at 5 and 10 years were 5.5 % and 13.6% in the complete CR and 8.6 % and 18.9 % in the non-complete CR patients group (Fig. 2.2). Complete CR patients had a 48% lower 10-year mortality than non-complete CR patients (HR 0.521, 95% confidence interval (CI) 0.405-0.672). After adjustment complete CR patients had a 46% lower 10-year mortality (HR 0.54 with 95% CI 0.42- 0.70; p<0.001) than non-complete CR patients.

DISCUSSION

The main findings of this study in ACS patients treated with pPCI are 1) patients who attended a CR program had significantly lower 10-year mortality than their no-CR counterparts and 2) patients who completed CR had a lower 10-year mortality compared to patients who started but did not complete CR. This confirms that despite major changes in ACS treatment, CR programs may still be beneficial in terms of 10-year survival in the pPCI era.

To the best of our knowledge our propensity matched study is the first which studied the relationship between long-term effects of CR on mortality in ACS patients treated with pPCI which is the currently recommend treatment for not only STEMI patients but also in most patients with non- STEMI (13, 14). Despite these major changes in treatment in the acute phase of ACS beneficial effects of CR seem still prominent, evidenced by a 39% reduction in mortality. One of the reasons for failure to demonstrate positive effects on mortality by others in different populations may be the existing different definitions and lengths of CR programs attendance (7). Sometimes, attendance of only one session was already defined as participation Therefore, we also assessed the outcome of patients who did and did not complete CR. Patients who completed CR had a 10-year mortality of 13.6% against 18.9% in patients who did not complete CR. Thus, there seems to be a “dose response curve” with greater reduction in mortality with full completion of CR. This was already mentioned by Beauchamp et al (10) who studied patients undergoing bypass surgery. Patients who attended less than 25% of the CR program had a mortality risk over twice that of patients who attended more than 75% of the program. In our experience patient motivation is the most important reason in completing CR, although we cannot substantiate this with scientific evidence. Compared to the recent study by de Vries et al we did have information on cardiovascular risk factors whereas they did not: but this was not a major confounder in our study. Logistic reasons such as transportation facilities and the distance to the nearest CR centre have shown to be crucial in CR participation (15, 16). Finally, the expected effects of CR by the patient may play an importantrole.

One of the main challenges in post-ACS management is to increase patient participation in CR programs. As we recently demonstrated, in the Rotterdam-Rijnmond region, only 39% of eligible patients participated in CR, which is exemplary for a broad range of clinical practices. (15, 17) Target populations including women, elderly and patients with low socio-economic status have poorer than average participation rates and need specific attention. (18) Therefore, before patients can get the benefits of CR, and even better completion of CR, they first have to be referred by their cardiologists. This is still a challenge worldwide.

Since there seems to be a “dose response curve” with greater reduction in mortality with full completion of CR, we strongly advocate a strict definition of CR. Rauch et al (19) in their systematic review and meta-analysis (“CROS – analysis”) already emphasize the need for defining internationally accepted CR standards, since they found a wide heterogeneity of CR

programmes . Given the results of our current study, we plea that CR be defined 'complete' if a patient participated in at least 75% of the full multidisciplinary CR program. Our work can be considered a valuable contribution to review by Rauch et al, as our follow up period was much longer and even then survival benefit was sustained. Furthermore, our patients constituted a more homogeneous population. In particular, all patients had ACS that was treated with pPCI, and there were no differences in the use of guideline-recommended 'optimal' medical therapy between the patients with complete and incomplete CR. Even in such a homogeneous group, CR in the new millennium showed to be beneficial for long-term survival.

Limitations

Our study had an observational retrospective design. Although we performed propensity matching and multivariate Cox regression, we could not control for all confounders.

Conclusion

ACS patients treated with pPCI who attended a CR program had significantly lower 10-year mortality than their no-CR counterparts. Also, patients who completed CR had a better prognosis compared to patients who started but did not complete CR. This suggests that despite changes in treatment of ACS, CR programs are still beneficial. However, only a formal RCT can provide definite evidence.

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Conflicts of interest

none

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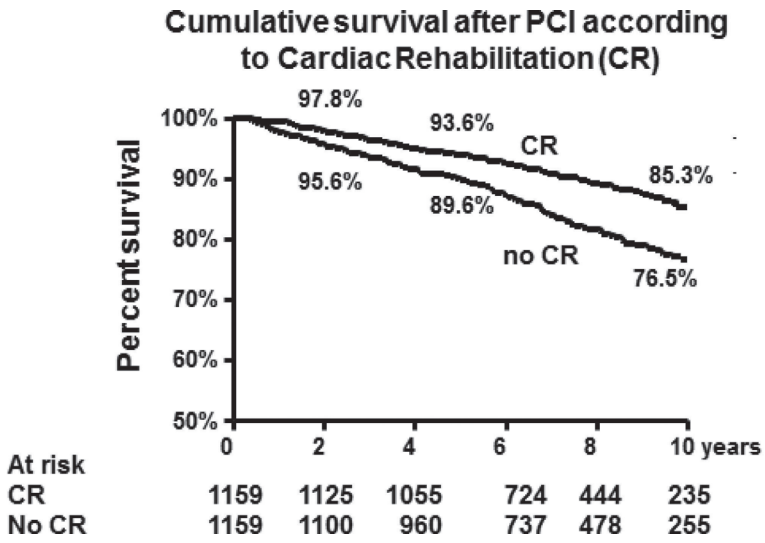

Figure 2.1: Cumulative survival after PCI according to Cardiac Rehabilitation (CR) Cardiac Rehabilitation (upper line) No Cardiac Rehabilitation (lower line)

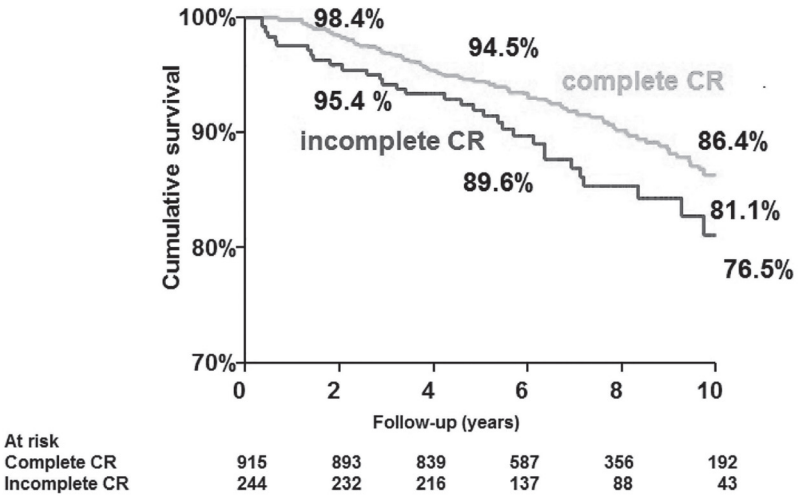

Figure 2.2: Cumulative survival after completing (upper line) or not completing Cardiac Rehabilitation (CR) after PCI (lowwer line).

Table 2.1. Baseline characteristics of patients who did and did not undergo CR

	CR	noCR	p-value
Age (SD)	59.0 (9,9)	58.8(11,83)	0.91
Male (%)	892 (77)	898(78)	0.80
STEMI (%)	760 (66)	754(65)	0.83
MVD	476 (41)	465(40)	0.67
Smoking	447 (39)	481(42)	0.16
Diabetes	158 (14)	153(13)	0.81
Hypercholesterolemia	522 (45)	519(45)	0.93
Hypertension	489 (42)	484(42)	0.87
Family History	418 (36)	422(36)	0.90
Prior MI	8 (2)	6(1)	0.88
Prior PCI	151 (13)	153(13)	0.95
Prior CABG	30 (3)	18(2)	0.11
Proximal LAD lesion	475 (41)	484(42)	0.74
Socio economic status:			
Upper class	172 (15)	162(14)	0.84
Upper middle class	143 (12)	150 (13)	
Lower middle class	262 (23)	252 (22)	
Lower class	580 (50)	594 (51)	
Use of medication:			
Aspirin	1112 (96)	1093(94)	0.07
Statins	1107 (95)	1096(94)	0.3
B blockers	1113(96)	1099(95)	0.1
ACE	1127 (97)	1122(97)	0.5
Diuretics	15(1.3)	27 (2.3)	0.06
Anticoagulants	2 (0.2)	5 (0.4)	0.2

Table 2.2: Baseline characteristics of patients who completed and who did not complete CR

	Complete CR (N=915)	non complete CR (N=244)	P-value
Age (SD)	59,0 (9,9)	58,2 (11,2)	
Male (%)	711 (77,7)	181 (74,2)	0.24
STEMI (%)	611 (66,8)	149 (61,1)	0.09
MVD	363 (39,7)	113 (46,3)	0.06
Smoking	340 (37,2)	107 (43,9)	0.06
Diabetes	113 (12,3)	45 (18,4)	0.01
Hypercholesterolemia	405 (44,3)	117 (48,0)	0.30
Hypertension	384 (39,5)	105 (43,0)	0.76
Family history	338 (36,9)	80 (32,8)	0.23
Prior MI	6 (0,7)	2 (0,8)	0.15
Prior PCI	110 (12,0)	41 (16,8)	0.05
Prior CABG	23 (2,5)	7 (2,9)	0.76
Proximal LAD lesion	380 (41,5)	95 (38,9)	0.46
Socio economic status:			
High	143 (15,7)	29 (11.9)	0.23
Less high	117 (12,8)	26 (10,7)	
Less low	208 (22,8)	54 (22,1)	
Low	445 (48,7)	135 (55,3)	

Chapter 3

AGE DOES MATTER: YOUNGER PPCI PATIENTS PROFIT MORE FROM CARDIAC REHABILITATION THAN OLDER PATIENTS

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ABSTRACT

Background

Cardiac rehabilitation (CR) is recommended as secondary prevention in primary percutaneous coronary intervention (pPCI) patients. This study was conducted to expand the knowledge about age-effects of CR in pPCI patients. The aim of this study was to compare changes in subjective health status (SHS) during and after CR between patients b60 years and patients ≥60 years, who underwent pPCI after myocardial infarction.

Methods

Between 2009 and 2011, in total 282 pPCI patients who participated in CR were included. Patients completed the Short Form12 (SF-12) questionnaire at baseline (pre-CR), 3 months (post-CR) and 12 months followup. Patients were divided into two age-groups, <60 years versus ≥60 years. To compare improvements in SHS between groups, Generalized Estimating Equations (GEE) analyses were performed.

Results

Themean physical component summary (PCS) score improved over time in both groups and even reached mean levels of the normative Dutch population. The improvement on the PCS score was equal in both age groups. The mental component summary (MCS) score also improved in both groups. Patients <60 years reported on average more improvement on the MCS score than patients ≥60 years (Exp(B) 1.019; 95%CI 1.009–1.030; P b 0.001). However, mean levels of the normative Dutch population were not reached by patients <60 years.

Conclusion

Even though pPCI patients <60 years reported more improvement on the MCS score, mean levels of the normative Dutch population were not reached. Therefore, a tailored CR program with more focus on their mental status, may be beneficial in younger patients.

INTRODUCTION

Nowadays, primary percutaneous coronary intervention (pPCI) is the treatment of choice in patients who suffer from acute coronary syndrome. Cardiac rehabilitation (CR) is recommended for secondary prevention of cardiac problems in these patients [1], as meta-analyses and reviews demonstrated that CR reduces cardiovascular mortality [2–4], all-cause mortality [2,4,5], hospital admissions [2,3] and recurrent myocardial infarction [5]. Moreover, CR has a positive effect on total cholesterol levels [4], triglyceride levels [4], systolic blood pressure [4] and subjective health status (SHS) [2–6]. Although not confirmed by all studies, improvements in SHS possibly remain at follow-up [2]. Improving the subjective health status is an important objective, as a poor subjective health status is associated with a worse prognosis [7,8].

CR programs in older coronary artery disease patients have a positive influence on lipids [9], obesity indexes and exercise capacity [9, 10]. The improvement in exercise test results of older patients is comparable to younger patients [10,11]. Unfortunately, little research has been done into whether this pattern (comparable age-effects of CR) also applies to the SHS [11–14], and more specifically if it also applies to long term-results in pPCI patients. Knowledge about the age-effects of CR may help to improve CR by offering tailored programs.

To bridge this gap in knowledge, the aim of this study was to investigate the change in SHS in pPCI patients participating in CR over a 12 months period and to compare SHS changes in the group of patients <60 years to changes in the group of patients ≥60 years.

METHODS

Consecutive series of patients treated with pPCI between January 2009 and March 2011 and who participated in CR were prospectively included. The study was approved by the local research ethics committee (MEC-2009-080) and was conducted according to the Helsinki Declaration. All patients provided informed consent. The study design has been published elsewhere [15].

Cardiac rehabilitation

All patients participated in an outpatient CR program offered by Capri Cardiac Rehabilitation Rotterdam in accordance to the Dutch guidelines [16]. The program consisted of 1.5 h of supervised group exercise sessions given twice a week at a local sport accommodation. The sessions consisted of strength and aerobic exercises. Depending on the patients improvements, the CR program took for 4 to 13 weeks. In addition to the exercise sessions, there were group education sessions regarding medical background, cardiovascular risk factors, diet and emotions. Moreover, patients could attend counselling sessions for smoking cessation, healthy diet and stress management. If indicated, individual consults with a psychiatrist, psychologist, social worker or dietician were provided.

Data collection

Patients received by postal mail questionnaires before the start of CR (T0), post-CR (T1) and at 12 months follow-up (T2). A postal reminder was sent out after 4 weeks of no response. Socio-demographic and clinical characteristics included age, gender, diabetes mellitus, smoking, hyperlipidemia, hypertension, body mass index, family history and medical history. This data was obtained from the medical charts.

Subjective health status

Subjective health status was assessed with the Dutch version of the Short Form 12 (SF-12), an internationally widely used and validated questionnaire [17]. The SF-12 consists of a physical component summary (PCS) score and a mental component summary (MCS) score. The PCS includes physical functioning, role functioning physical, bodily pain and general health. The MCS includes social functioning, role functioning emotional, vitality and mental health. Both the PCS and MCS score range from 0 to 100. The mean score is 50 in a normative Dutch population [18]. A higher score is interpreted as a better subjective health status.

Statistical analyses

Patients were only included in analysis when they had at least completed questionnaires at baseline and a minimum of 1 follow-up moment. Categorical variables were summarized as percentages and differences between categorical variables were compared with the Chi-square test or Fisher's exact test when appropriate. Continuous variables were presented as means with standard deviation. The student's t-test was used to compare differences between continuous variables. In case of three or less missing answers on the SF-12 questionnaire, an imputation method was used [19]. A one sample t-test was used to compare the mean PCS and MCS scores at T2 to those of the Dutch normative population. Based on the mean age of the study sample (59.1 years), age was dichotomized into patients <60 years and ≥60 years. The student's t-test was used to compare the change in PCS and MCS scores in one year between both age groups. Changes over time in PCS and MCS between groups were compared with Generalized Estimating Equations (GEE) analyses with an autoregressive structure and with PCS andMCS as dependent outcome variables and time and group as categorical variables. A GEE model was chosen because it adjusts for the dependency of observations within one individual and it corrects for missing values [20]. An autoregressive structure was selected because measurement times were unequally spaced. The PCS and MCS scores were not normally distributed. Therefore, a log link function was used. For the dependent variable, outcomes were displayed as the exponent of the regression coefficients EXP(B), which indicates the ratio between the SHS change in the group of patients <60 years and the group of patients ≥60 years. Confounders were based on the literature and include; sex, PCS and MCS score at baseline, acute myocardial infarction (AMI), smoking, hypertension, diabetes mellitus, family history, completion of CR (≥18 training sessions) and individual sessions with a psychologist, psychiatrist and social worker. A 2-sided *P* value of b0.05 was considered significant. All analyses were performed using SPSS version 21.

RESULTS

Study sample

A total of 413 patients participated in a CR program following pPCI after MI. The mean time between pPCI and the start of the CR program was 42 days. Of these patients, 63 did not respond to the SF-12 questionnaire at baseline and were excluded. The 68 patients who did not respond at both T1 and T2 were also excluded. The 282 remaining patients were used in the analysis (Fig. 3.1). No differences were found in age, gender, cardiac history and risk factors between responders and non-responders at baseline. Whereas the group of non-responders at both T1 and T2 consisted of more smokers (57% vs. 43%; *P*=0.041) and younger patients than the group of responders (56.0 vs. 59.1; P = 0.021).

Patient characteristics

In the group of patients <60 years were more men and smokers and there were more patients with a positive family history than in the group of patients ≥60 years. Moreover, less patients in the younger group had hypertension or a history of AMI. The group of patients <60 years also reported a lower PCS and MCS score at baseline than the group of older patients. Both age groups attended a similar amount of training sessions. More patients in the group <60 years visited a psychologist, psychiatrist and social worker than in the group ≥60 years (Table 3.1).

Subjective health status

Fig. 3.2 shows changes in PCS and MCS scores in both age groups. At baseline, the mean PCS and MCS scores of both groups were lower, thus more unfavorable, compared to Dutch normative data. At T2, so after CR, both groups reached the mean levels of the normative PCS score (mean PCS score b 60 years 50.3 (SD ± 9.5); *P* = 0.744. ≥60 years 50.5 (SD ± 8.7); *P* = 0.512). However, at T2, the group of patients <60 years had a lower MCS score than the mean levels of the normative Dutch population (mean MCS score 47.6 (SD ±10.8); *P*=0.018). The group of patients ≥60 years did reach the mean levels of the normative Dutch population (mean MCS score ≥ 60 years 49.3 (SD ± 9.4); *P* = 0.460) (Fig. 2). Unadjusted, a greater improvement at one year follow-up was found in the group of patients <60 years on the MCS score as well as on the PCS score (Fig. 3.2). Because of baseline differences, changes on MCS and PCS scores were also compared using a multivariable GEE-analysis. The group of patients <60 years had less improvement on the PCS score over time than the group of patients ≥60 years (Exp(B) 0.961; 95%CI 0.935–0.988; P=0.005).However, the group of younger patients differed on several baseline characteristics. After adjustment the difference was no longer significant (Exp(B) 1.007; 95%CI 0.987–1.027; *P* = 0.489). A greater improvement over time on the MCS score was found in the group of patient < 60 years than in the group of patients ≥60 years (Exp(B) 0.931; 95%CI 0.901–0.963; *P* < 0.001). This difference in improvement remained significant after correcting (Exp(B) 1.019; 95%CI 1.009–1.030; *P* < 0.001).

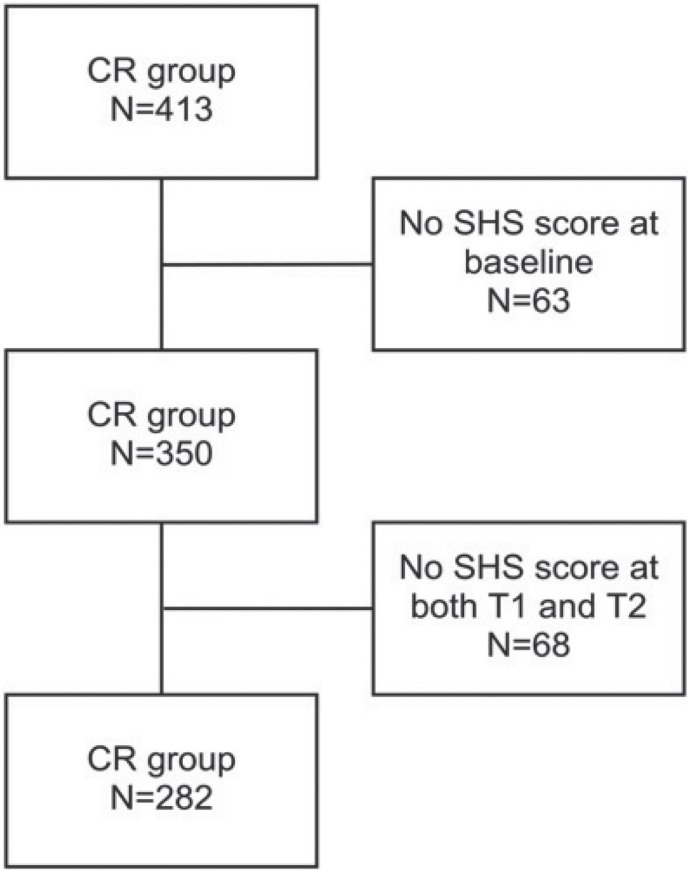

Fig. 3.1. Flowchart study sample. Abbreviations: CR, cardiac rehabilitation; SHS, subjective health status.

Table 3.1
Characteristics of the study sample.

	CR (*n* = 282)		
Age category	<60 years	≥60 years	*P*-value
	(*n* = 145; 51.4%)	(*n* = 137; 48.6%)	
Mean age ± SD	51.6 ± 6.1	67.0 ± 5.4	<0.001a
Mean BMI ± SD	27.7 ± 4.3	27.0 ± 3.6	0.148
Male gender, n(%)	126 (86.9)	104 (75.9)	0.017[a]
History			
CVA, n(%)	0 (0.0)	4 (2.9)	0.054
Cardiac event, n(%)	12 (8.3)	20 (14.6)	0.094
- AMI	5 (3.4)	14 (10.2)	0.027a
- PCI	9 (6.2)	15 (10.9)	0.159
- CABG	2 (1.4)	1 (0.7)	1.000
Risk factors			
Smoking, n(%)	83 (57.2)	40 (29.2) <0.001[a]	
Hypercholesterolemia, n(%)	51 (35.2)	59 (43.1)	0.173
Hypertension, n(%)	45 (31.0)	61 (44.5)	0.019[a]
Diabetes mellitus, n(%)	15 (10.3)	20 (14.6)	0.278
Family history, n(%)	93 (64.1)	67 (48.9)	0.010[a]
Baseline SHS			
Mean PCS baseline ± SD	44.3 ± 8.9	47.3 ± 9.0	0.006[a]
Mean MCS baseline ± SD	42.3 ± 11.5	47.2 ± 10.2	<0.001[a]
Cardiac rehabilitation			
Training sessions ± SD	23.7 ± 9.2	21.9 ± 8.7	0.089
Individual consults[b], n(%)	21 (14.5)	8 (5.8)	0.017[a]

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; MCS, mental component summary; PCI, percutaneous coronary intervention; PCS, physical component summary; SHS, subjective health status.

[a] P-value b 0.05 was considered significant.

[b] Individual consults with psychiatrists, psychologists and social workers.

DISCUSSION

Although an improvement in MCS score over time in both age groups was found, younger patients benefited more, whereas the improvement in PCS score was equal between both groups.

The MCS and PCS scores improved in both groups and, with exception of the MCS score in the group of younger patients, the MCS and PCS scores even reached the mean score of the normative Dutch population. This indicates a recovery of the SHS in patients participating in a CR program. Not reaching the mean MCS score of the normative Dutch population in the group of patients <60 years might be due to the fact that the MCS score at baseline was lower in this group compared to the score in the older group of patients, thus a greater improvement was necessary to reach this score. It cannot be ruled out that the lower MCS score in the group of patients <60 years contributed to the occurrence of the cardiac event, as some previous studies found a relationship between the SHS and ischemic heart disease incidence [21–23]. However, a more recent study did not confirm the relationship between SHS domains on a validated questionnaire and ischemic heart disease [24].

Our findings are in line with Saeidi et al. [12]. They also found greater improvements in some mental components of the SHS after CR in a group of patients b65 years compared to a group of patients ≥65 years,whereas the improvement on the physical component was equal between both groups [12].

It should be taken into account that the MCS and PCS scores only improved between the range of 1.20 and 6.00 points and, even though the change in MCS score was significantly different between both groups, it is a relatively small difference. The minimal clinically important difference in both the MCS and PCS score is in the range of 3 to 5 points [25]. Therefore, some of the improvements might not be clinically relevant.

The question arises to what extend the SHS improvement is due to CR or whether similar results would have been achieved without CR. Two studies showed that older patients depend more on CR to improve their SHS [13,14]. In contrast to the group of younger patients, previous studies show that SHS in the group of older patients did not improve without CR [13,14]. As a result, older patients have a greater need for CR, since this group has less natural recovery.

Limitations

The present study has several limitations. Our study design,without a control group, does not allow us to compare the improvement in SHS to the natural improvement. Therefore, it is not possible to determine which portion of the improvement in SHS is due to CR. Another limitation of this study is that selection bias may be present, given that the group of non-responders at both T1 and T2 consisted of more smokers and younger patients than the responders. In case of a difference in quality of life between the included and excluded patients, the results of the younger patients could have been influenced more than the results of the older patients.

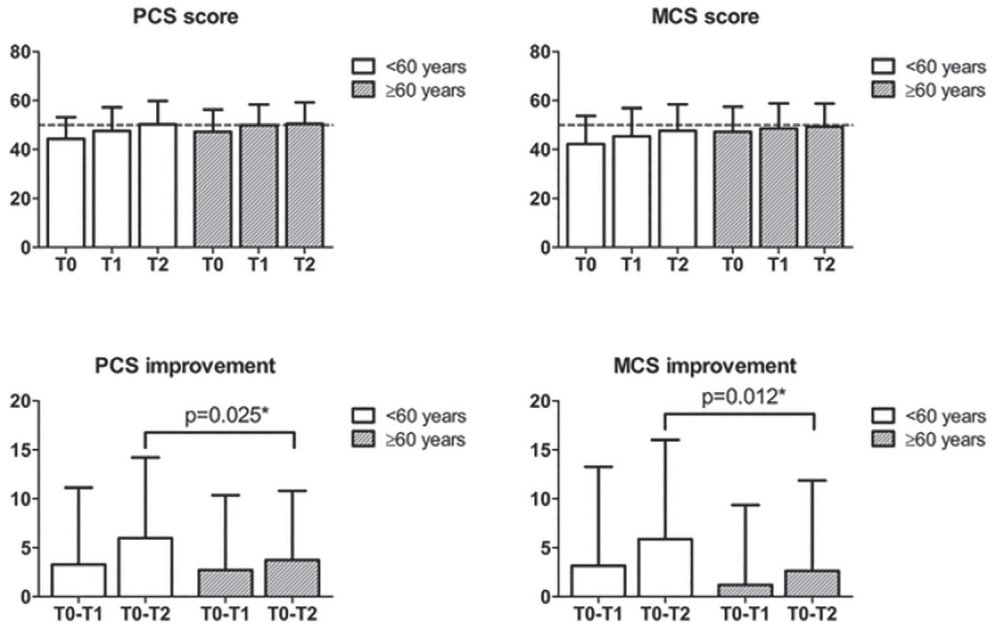

Fig. 3.2. Changes in PCS andMCS scores. *P-value b 0.05 was considered significant. P-values represent the difference in improvement between T0 and T2 between patients b60 years and patients ≥60 years. The dotted line represents the mean score of the normative Dutch population (50). Abbreviations: MCS, mental component summary; PCS, physical component

CONCLUSIONS

Even though, greater improvement on the MCS score was found in CR patients <60 years, this group did not reach the mean MCS score of the normative Dutch population. This may display the need of a tailored CR program for younger patients, focusing slightly more on their mental status. Whereas, this study does not show the need for change in the current CR program for patients ≥60 years to improve SHS.

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Conflicts of interest

All authors declare no conflicts of interest and sources of support.

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Chapter 4

CHANGES IN PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR DURING CARDIAC REHABILITATION.

Ter Hoeve N, Sunamura M, van Geffen ME, Fanchamps MH, Horemans HL, Bussmann JB, Stam HJ, van Domburg RT, van den Berg-Emons HJG.

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ABSTRACT

Objective
To objectively measure changes in both moderate-to-vigorous physical activity (MVPA) and sedentary behavior (SB) during and after standard cardiac rehabilitation (CR).

Design
Prospective cohort study

Setting
Outpatient CR center

Participants
Patients (n=135) with acute coronary syndrome (ACS) who completed CR.

Intervention
Multidisciplinary CR according to current guidelines

Main outcome measures
The proportion of time spent in MVPA and SB was objectively measured with an accelerometer. The distribution of time in MVPA and SB was also determined (e.g. average length of time periods spent in MVPA and SB). All measurements were obtained prior to CR, following CR and at one-year follow-up.

Results
Patients' time in MVPA during waking hours increased by 0.65% (≈5 min) during CR ($p=0.002$), and remained increased at one-year follow-up ($p=0.037$). The MVPA distribution did not change. During CR, time spent in SB decreased by 2.49% (≈22 min; $p<0.001$), and SB time became more fragmented with more breaks and shorter SB periods ($p<0.001$). These SB improvements were maintained at one-year follow-up ($p<0.001$).

Conclusions
Patients with ACS achieved a small improvement in MVPA time during CR, but MVPA distribution remained unchanged. More substantial improvements occurred for SB time and distribution. However, by the end of CR, patients still spent relatively little time in MVPA and a long time in SB, which is known to be detrimental to cardiovascular health. Although CR programs have the potential to improve physical behavior, our findings highlight the need to develop adjusted CR targets that address amount *and* distribution of MVPA *and* SB.

INTRODUCTION

Physical behavior comprises both physical activity (PA) and sedentary behavior (SB).[1] PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure.[2] SB is defined as behavior that consist mainly of sitting or lying and that requires very low energy expenditure.[3] Recent studies show that PA and SB should be considered as distinct behaviors related to health outcomes.[4,5] In a general population, low levels of moderate-to-vigorous intensity PA (MVPA) have been identified as a leading risk factor for mortality and cardiovascular disease.[6] Increased levels of SB are independently related to an increased risk of diabetes, cardiovascular disease, and mortality.[3-5,7] In addition to volume (total time) of MVPA and SB, increasing evidence suggests that the distribution of this behavior over time may also be important. For example, the health benefits of daily, short bursts of MVPA may be smaller than those of less frequent, longer periods of MVPA.[8,9] Taking regular active breaks during sedentary time can counteract the harmful effects of prolonged sedentary periods.[10,11]

In patients with Acute Coronary Syndromes (ACS), it has been shown that more MVPA is related to a better cardiovascular risk profile[12,13] and lower cardiac mortality.[14] Standard Cardiac Rehabilitation (CR) generally addresses MVPA, but not SB. Few studies have focused on SB in patients following ACS. Cross-sectional studies show that patients with cardiovascular disease spend more time sedentary per day compared to healthy individuals,[15] and that longer sedentary time at CR completion is associated with poorer fitness and higher body mass index.[16]

Studies using objective measurement tools to evaluate changes in MVPA and SB volume and distribution during standard CR are lacking. Knowledge of these changes may help formulate recommendations on future PA and SB targets. Therefore, the objective of the present study was to evaluate longitudinal changes in PA and SB volume *and* distribution in patients with ACS during and after CR participation.

METHODS

Study sample

The cohort investigated in the current study was originally recruited for a randomized controlled trial (RCT) in which they were assigned to the control group, receiving treatment as usual (standard CR). Patients with ACS who were referred to Capri CR between September 2011 and August 2014 were invited to participate in this study. Inclusion criteria were: diagnosis of ACS; age >18 years; proficiency in Dutch; and absence of physical and cognitive impairments that could limit CR participation. Only patients who completed standard CR were included in the current study. Additionally, patients needed at least two valid physical behavior measurements (of which one was a baseline measurement) for inclusion in the analysis. All participants provided written informed consent. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam, The Netherlands.

Measures

Physical behavior

Physical behavior (PA and SB) was measured with a tri-axial accelerometer (ActiGraph GT3X+[a]). Patients were asked to wear the accelerometer on the right side of their waist for eight consecutive days during waking hours, except when showering or swimming. Patients recorded the times they wore the accelerometer in a logbook.

Data processing

Consensus in accelerometer data processing is lacking. There is wide variability in the choices made for epoch length, wear time validation and intensity cut-off points, for example. We made our choices after extensively reviewing the literature.[17-25]

Accelerometer data were sampled with a frequency of 30 Hz. The ActiGraph[a] measures raw accelerations on three axes and converts this into activity counts and steps. Step numbers were processed using Actilife software.[26] Counts were summed over 15s time sampling intervals (epochs) using Actilife software and converted to Matlab format for further processing (Matlab version R2011b). A composite measure called vector magnitude was calculated ($\sqrt{(x^2+y^2+z^2)}$) and used for analysis. Non-wear time was defined as >60 minutes of consecutive zeros, with no allowance of epochs with counts above zero. Data were analyzed only for patients who wore the accelerometer for ≥4 days and ≥660 min/d. After subtracting the non-wear time from the data, each epoch was categorized as:

- MVPA: activities of ≥672.5 counts [17]
- Light activity: activities of >37.5 and < 672.5 counts[17]
- SB: activities of ≤37.5 counts[18]

Outcome measures

Volume of physical behavior

Total activity counts were calculated by summation of counts in epochs, and expressed as counts per minute. Total time spent in MVPA, light activity, and SB was calculated and expressed as a percentage of total daily wear time. The amount of steps was expressed as steps per minute.[26] In addition, we calculated the percentage of patients meeting a step target of at least 6500 steps/day. According to recent studies, 6500 steps/day is needed to prevent cardiovascular disease progression.[27,28]

Distribution of physical behavior

The mean length of all uninterrupted bouts (time periods) of MVPA and SB with a minimum length of 15s (1 epoch) was calculated. Because the lengths of these bouts were not normally distributed, the natural logarithm of lengths was taken and geometric means were calculated. A fragmentation index for both MVPA and SB was calculated as the total number of bouts divided by the total volume in minutes. A higher fragmentation index indicates that the number of bouts was high and time in MVPA or SB relatively low. In other words, time is more fragmented in frequent, shorter bouts than in fewer prolonged periods.[19,20]

Also, we were interested in prolonged bouts of MVPA and SB. In accordance with recommendations[6,12,29-31], prolonged MVPA was defined as periods ≥10 min. Short MVPA interruptions may occur in daily life situations such as waiting for a traffic light.[21-23] The exact length of MVPA interruptions to consider the bout as continuous remains unclear.[23] We chose to allow a maximum of four interruptions (*not necessarily consecutive*) of 15s epochs with counts below 672.5 during a single bout of MVPA. Likewise, because there is no standard definition of prolonged SB, we defined prolonged SB as those bouts >30 min. During a sedentary period, we chose to allow a maximum of three consecutive interruptions of 15s epochs with counts above 37.5 during a single bout of SB. Thus, we analyzed a prolonged SB bout as ending after at least 1 min of continuous non-SB. In making this choice, we considered that interrupting SB every 30 min with a 1 min break of non-SB seems a feasible target for interventions. The total time spent in prolonged MVPA and SB was calculated and expressed as a percentage of total wear time. We also calculated whether participants met the American College of Sports Medicine (ACSM) target of ≥150 min of prolonged MVPA bouts per week.[30] This guideline is consistent with those addressing secondary prevention of cardiovascular disease.[6,14,29] Because the accelerometer was not always worn for a full week, we calculated the percentage of participants reaching an average of 21.4 min prolonged MVPA/day (150 min/ 7 days). There are no guidelines currently for recommended volume of SB.

Procedures

Cardiac rehabilitation

All patients participated in multi-disciplinary outpatient CR lasting 10-13 weeks, as per Dutch guidelines. The program was terminated when individual physical and psychosocial goals were met, as evaluated by an exercise stress test and consultation by a multidisciplinary team consisting of physical therapists, social workers, and cardiologists. The program consisted of a 75-min group exercise sessions (twice weekly with a strength and aerobic program); and group educational sessions about the medical background and risk factors for cardiovascular disease, dietary advice, and emotional coping. If indicated each patient could participate in group counseling sessions on smoking cessation, healthy diet, and stress management. If needed, patients were referred for individual consultations with a psychologist, social worker, psychiatrist, or dietician. During CR, there was no specific MVPA coaching, but general information was given on the health benefits of an active lifestyle. There was no specific focus on changing SB.

Patients also attended usual follow-up appointments with their cardiologist, during which general information on the health benefits of PA might be given. We do not have exact information on this aspect.

Data collection

Data on physical behavior were obtained the week before CR (T0), during the last week of CR (T1), and at follow-up one year after the start of CR (T2). Data on age, gender, and working status were collected at T0.

Statistical analysis

Descriptive statistics were used to present baseline characteristics. Independent *t*-tests and Chi-square tests were used to test for differences in baseline characteristics between the original study sample and the sample with sufficient valid physical behavior measures.

For continuous variables, mean differences between T0 and T1 and between T0 and T2 were analyzed using paired t-tests, after checking whether the within-subject changes met the assumptions of normality. For dichotomous variables, chi-square tests were used to test for mean differences between T0 and T1 and between T0 and T2

A two-sided p-value <0.05 was considered significant. All analyses were performed using SPSS (version 20).

RESULTS

Subjects

A flow diagram of inclusion is shown in Figure 4.1. A total of 245 patients were randomized to standard CR and included in this study. Data from 45 patients who did not complete CR, for reasons such as lack of time and unwillingness, were excluded. An additional 54 patients were excluded because fewer than two valid physical behavior measurements were available, and 11 patients because baseline physical behavior measurements were lacking. These 65 patients with insufficient physical behavior measurements were on average four years younger (p=0.001). Most of the remaining 135 participants were male (80%), mean age was 59 years and the attendance rate was 23 CR exercise sessions. (Table 4.1). ActiGraph[a] wear time increased between T0 and T1 and between T0 and T2 (Table 4.2). Data from logbooks showed that at T0, during which patients are still in the acute phase after their cardiac event, patients go to bed earlier and wake up later. To compensate for these differences, all physical behavior outcomes were expressed relative to wear time.

Table 4.1 Baseline characteristics of the study population (n=135)

Characteristics	
Male , %	78.5
Age (years), mean ± SD	58.8 ± 8.5
Body Mass Index (kg/m^2), mean ± SD	28.0± 3.8
Employment status, %	
Full time	45.1
Part time	12.4
Not employed	42.5
Number exercise sessions, mean ± SD	23.1 ± 5.0

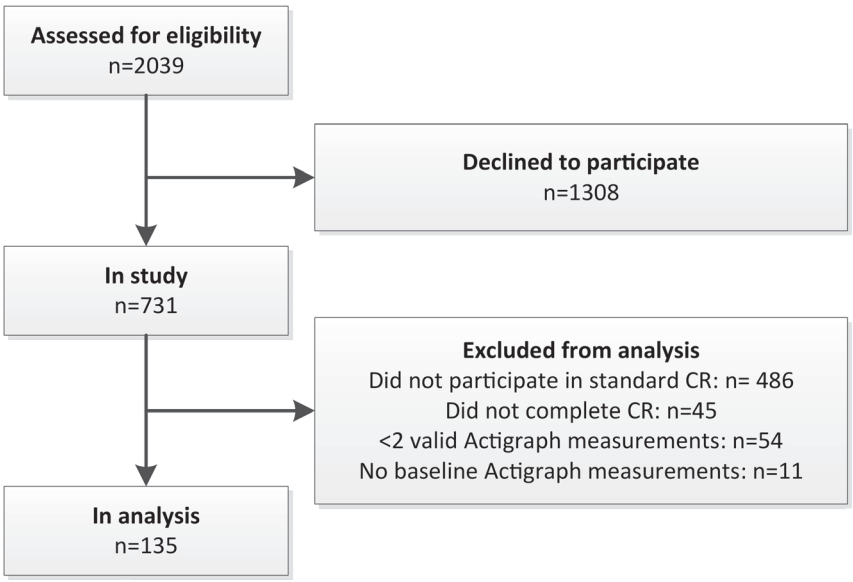

Figure 4.1 Flow diagram of participants

Changes in physical behavior during cardiac rehabilitation

Table 4.2 shows the observed data and outcomes of the paired t-tests for mean changes over time in the volume of physical behavior (graphically depicted in Figure 4.2).

Total activity counts per minute significantly increased between T0 and T1 (mean difference=50.56 counts/min, p<0.001), and between T0 and T2 (mean difference=55.04 counts/min, p<0.001). The step count also increased between T0 and T1 (mean difference=0.67 steps/min, p=0.002) and between T0 and T2 (mean difference=0.55 steps/min, p=0.017). At T0, 39.3% of participants were compliant with a daily step target of 6500. This compliance increased to 51.4% (p<0.001) at T1 and was 46.5% at T2 (p<0.001 vs T0).

Between T0 and T1, the time spent in MVPA and light activity increased (mean difference=0.65% of waking hours, p=0.002 and mean difference=1.84%, p=0.001 respectively) and time in SB decreased (mean difference=-2.49%, p<0.001). During an average day with a wear time of 14.5 hours, this equals a change of +5.7 min in MVPA, +16.0 min in light activities and -21.7 min in SB. Differences remained significant between T0 and T2.

Distribution of physical behavior

Table 4.3 shows the observed data and the outcomes of the paired t-tests for mean changes over time in the distribution of physical behavior.

Table 4.2 Physical behavior over time

	T0 (n=135)	T1 (n=111)	T2 (n=114)	T0-T1 (n=111)		T0-T2 (n=114)	
Variable	Mean ± SD	Mean ± SD	Mean ± SD	Mean difference ± SD	P*	Mean difference ± SD	P*
Wear time							
Valid days	6.5 ± 1.1	7.0 ± 1.1	7.1 ± 1.1	0.30 ± 0.95	0.001	0.46 ± 0.98	<0.001
Daily wear time (hours)	14.2 ± 1.0	14.6 ± 1.0	14.7 ± 1.0	0.43 ± 1.37	0.001	0.52 ± 1.21	<0.001
Total volume of physical activity							
Activity counts /min	544.7 ± 169.6	599.0 ± 152.0	596.0 ± 164.2	50.56 ± 128.2	<0.001	55.04 ± 148.2	<0.001
Steps/min	7.3 ± 2.9	8.1 ± 2.6	7.8 ± 2.8	0.67 ± 2.21	0.002	0.55 ± 2.44	0.017
Categories of physical behavior							
MVPA (% wear time)	6.3 ± 3.0	7.0 ± 2.7	6.7 ± 3.0	0.65 ± 2.21	0.002	0.50 ± 2.51	0.037
Light activity (% wear time)	28.1 ± 7.1	30.2 ± 6.4	31.0 ± 7.6	1.84 ± 5.65	0.001	2.98 ± 6.49	<0.001
SB (% wear time)	65.6 ± 8.3	62.8 ± 7.4	62.3 ± 8.4	-2.49 ± 6.57	<0.001	-3.48 ± 7.75	<0.001

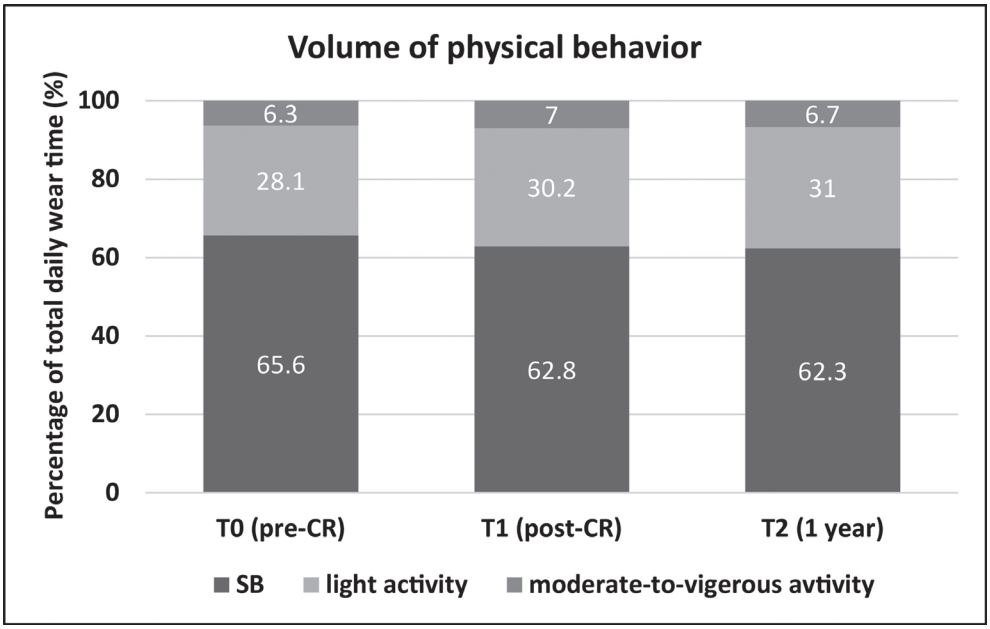

Figure 4.2 Percentage of waking hours spent in SB, light activities, and MVPA

With regard to MVPA, there were no significant changes in distribution outcomes. Compliance with the ACSM guidelines decreased over time from 17.8% of participants at TO to 13.5% at T1 ($p<0.001$) and 13.2% at T2 ($p<0.001$ vs T0).

SB bout distribution changed between T0 and T1. The mean length of bouts decreased (mean difference=-0.05 min, $p<0.001$), the fragmentation index increased (mean difference=0.04, $p=0.001$), and time spent in prolonged SB bouts >30 min decreased (mean difference=-3.10%, $p=0.001$). These changes were also significant between T0 and T2. For an average day with a wear time of 14.5 hours, the change in time spent in prolonged SB was -26.0 min/day between T0 and T1 and -44.4 min/day between T0 and T2.

Table 4.3 Distribution of physical behavior over time

Variable	T0 (n=135)	T1 (n=111)	T2 (n=114)	T0-T1 (n=111)		T0-T2 (n=114)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean difference ± SD	P*	Mean difference ± SD	P*
Distribution of MVPA bouts							
Mean length MVPA bouts (min)[a]	0.38 ± 0.06	0.39 ± 0.05	0.39 ± 0.06	0.008 ± 0.05	0.111	0.004 ± 0.05	0.381
Fragmentation index[b]	1.79 ± 0.53	1.73 ± 0.42	1.86 ± 0.55	-0.05 ± 0.42	0.173	0.05 ± 0.46	0.235
MVPA bouts >10 min (% of wear time)[c]	0.66 (0:8.26) †	0.77 (0:7.79) †	0.49 (0:6.87) †	-0.03 ± 1.45	0.805	-0.21 ± 1.34	0.096
Distribution of SB bouts							
Mean length SB bouts (min)[a]	0.87 ± 0.16	0.82 ± 0.14	0.80 ± 0.15	-0.05 ± 0.14	<0.001	-0.07 ± 0.16	<0.001
Fragmentation index[b]	0.49 ± 0.15	0.53 ± 0.14	0.54 ± 0.16	0.04 ± 0.12	0.001	0.06 ± 0.14	<0.001
SB bouts >30min (% of wear time)[d]	39.0 ± 12.0	35.2 ± 11.4	34.5 ± 11.5	-3.10 ± 10.0	0.001	-5.11 ± 10.7	<0.001

** t-tests*

[a] Uninterrupted bouts with a minimum length of 15 seconds (equal to epoch length).

[b] Total number of bouts divided by total volume of MVPA/SB in minutes. A higher fragmentation index indicates that time is more fragmented with shorter periods of uninterrupted MVPA or SB.

[c] Prolonged MVPA bouts with a minimum duration of 10 min with allowance for interruptions of 60 non-consecutive seconds of non-active time.

[d] Prolonged SB bouts with a minimum duration of 30 min with allowance for interruptions of 45 consecutive seconds of non-sedentary behavior.

† Since the outcomes violated normality assumptions, median (range) values are displayed.

DISCUSSION

Our results show a small, but lasting, increase in MVPA time during CR. Distribution measures revealed that patients with ACS tend to break up their MVPA time into short bouts. This pattern did not change during CR. SB volume and distribution changed. During CR, SB time decreased nearly 22 min and sedentary time became more fragmented with shorter bouts. These improvements were maintained.

The exact changes in MVPA and SB required to gain health benefits are unclear, making it difficult to determine the clinical relevance of our findings. Nevertheless, our results indicate that MVPA remains low despite CR. For example, at the end of CR, only half of the participants achieved a daily step target of 6500.[27,28] Recognizing that PA volume, intensity and distribution are all important[8], the ACSM guidelines recommend 150 min of MVPA per week, in bouts of 10 min or longer. Again, only a minority of our participants attained this level and compliance to this guideline even decreased over time. Compliance rates might be underestimated, because these guidelines are based on questionnaires, whereas our data were objectively measured.[23] However, the MVPA volume was also relatively low at the end of CR compared to that of healthy adults measured by objective accelerometers (7.0% vs 10.2% MVPA, respectively).[20] Moreover, although MVPA time improved during CR, there were no improvements in the distribution of this behavior.

Interpreting the SB outcomes is even more difficult, as there are no existing guidelines for comparison. The improvements in volume and distribution of SB during CR seem quite substantial and lasting. Less time was spent in SB and this time was more fragmented with shorter periods, as is suggested to gain health benefits.[10,11] This improvement in SB is surprising, as interventions without an SB focus usually do not result in SB changes.[33] However, despite the SB improvements during CR, time in SB was still long (62.8% which equals approximately 9 hours) when compared to that of healthy adults (57.5%).[20] Moreover, a meta-analysis has shown that every hour increase in SB beyond seven hours is associated with a 5% increase in all-cause mortality.[5] Although no reference data are available, time spent in prolonged SB also seemed long (> 5 h/day).

The results of our study are in line with those of other studies showing that cardiac patients tend to be sedentary and inactive.[15,34,35] Studies focusing on the effects of CR and using objective measurement tools are scarce. A recent longitudinal study reported comparable small improvements in MVPA after eight weeks of CR;[36] however, in contrast to our study, patients showed no improvement in SB. Another cross-sectional study showed post-CR, step counts and MVPA levels comparable to ours; for SB, lower values were found (56% vs 62.8% in our study).[33] Differences can partly be explained by differences in choices related to data processing of accelerometers. This general issue of methodological differences in PA and SB research limits comparisons between studies.[21,24,37,38]

Our findings highlight the need to focus on further improvements in PA and SB in patients

with ACS. Multidisciplinary CR teams that specialize in directing lifestyle changes can have an important role in helping to improve physical behavior. The focus of CR should be to reach more substantial and lasting changes in total MVPA time, but also to accrue MVPA time in longer-lasting bouts. Targets for SB improvement should be to lower total SB time and frequently interrupt this time. Behavioral interventions containing self-regulation components (e.g. self-monitoring, goal-setting) seem promising.[31,33,39]

Study Limitations

Our study has some limitations. The ActiGraph[a] cutt-off points we used for the PA intensity categories were developed for a healthy population. Patients entering CR often have lower cardiovascular fitness levels compared to healthy individuals, which may result in under classification of PA intensity.[40] Furthermore, the ActiGraph[a] is not water-resistant and could not be worn during swimming activities. Because our participants rarely swam, we made no attempt to correct for this limitation. Finally, although the ActiGraph GT3X+[a] was found to fairly accurately detect SB, misclassifications such as designating "standing still" as "SB" cannot be ruled out.[18] Despite these limitations, the use of accelerometers is still a major strength of our study.

Another limitation is that our study was performed at a single-center with no control group. Caution is required when attributing the observed effects to the CR program. Baseline measurements were taken after hospital discharge, when patients had not yet returned to their daily life activities. The observed improvements might, therefore, partly reflect a return to participants' physical behavior situations that existed before the cardiac incident.

Lastly, patients who did not have sufficient physical behavior measurements to be included in the analysis were younger on average, which may have biased the results. In addition, the cohort may consist of higher motivated patients that were willing to participate in this trial. Information on patients who did not provide informed consent is lacking.

CONCLUSIONS

Patients with ACS achieved small, but lasting, improvements in MVPA volume during CR. More substantial and lasting improvements in SB volume and distribution were observed. However, at the end, CR participants still spent a relatively short time in MVPA and a long time in SB, which has been shown to be detrimental to cardiovascular health. Although CR programs have the potential to improve physical behavior, our findings highlight the need to develop adjusted CR targets focusing on volume *and* distribution of MVPA *and* SB.

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Chapter 5

PARTICIPATION IN SOCIETY IN PATIENTS WITH CORONARY ARTERY DISEASE BEFORE AND AFTER CARDIAC REHABILITATION

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ABSTRACT

Objective
To asses changes in participation in society (frequency, restrictions, satisfaction) during and after cardiac rehabilitation (CR) and to asses associations between participation and health-related quality of life (HRQoL).

Design
Prospective cohort study.

Setting
Outpatient CR center.

Participants
Patients with coronary artery disease (N=121; mean age, 57y; 96 men [79%]).

Intervention
Multi-disciplinary CR.

Main outcome measures
Participation in society was assessed with the Utrecht Scale for Evaluation of Rehabilitation-Participation and HRQoL with the MacNew heart disease health-related quality of life questionnaire. All measurements were performed pre-CR, post-CR, and 1 year after the start of CR.

Results
Frequency of participation did not change during and after CR. The proportion of patients experiencing restrictions in participation decreased from 69% Pre-CR to 40% post-CR ($p<0.001$) and 29% at one year ($p<0.001$, vs post-CR). Pre-CR, 71% of patients were dissatisfied with their participation. This improved to 49% post-CR ($p<0.001$) and 53% at 1 year ($p<0.001$, vs pre-CR). Experienced restrictions explained 5% to 7% of the improvement in HRQoL during CR and satisfaction with participation explained 10% to 19%.

Conclusions
Participation in society improves in patients undergoing CR. Despite these improvements, the presence of coronary artery disease is associated with persistent restrictions and dissatisfaction with participation. Because experienced restrictions and dissatisfaction are related to changes in HRQoL, it is important to address these aspects of participation during CR.

INTRODUCTION

Cardiac rehabilitation (CR) is multidisciplinary, focusing on improving physical and psychosocial functioning of patients with cardiac disease. An important goal of CR is to optimize participation in society with regard to different aspects of daily life, such as domestic, occupational, and recreational activities.[1,2] This goal can be achieved either directly, or by improving the conditions for participation, in particular physical capacity and mental status.[3-7]

Only few studies have looked at participation in society in patients attending CR. Most of these studies focused solely on work resumption and showed that about 80% of participants attending CR have returned to work 1 year after hospitalization.[8] Return to work is, however, only one aspect of daily life. Participation in society also involves domestic and recreational activities such as social contacts, going out and housekeeping. Because most of the participants attending CR are retired, it is especially important to also focus on these non-work-related aspects of daily life as outcome measures of CR.

Besides being limited in number and merely focusing on work-related aspects, previous studies measured only one dimension of participation in society: either frequency or restrictions to participation experienced by participants. Participation is, however, a multidimensional concept that also consists of the participants' satisfaction with participation.[9-11] It is important to take into account all 3 dimensions, since they are only weakly related to each other.[12]

Research in several patient populations has shown that patients who participate in society more often and who have greater satisfaction with participation, have a higher health-related quality of life (HRQoL).[13-15] Similarly, in patients with coronary artery disease (CAD), work resumption is associated with an improved HRQoL[6,16] whereas their experience of restrictions in household tasks is related to a lower HRQoL.[17] Because HRQoL is not only an indicator of a patient's well-being, but also an important outcome measure for the success of a treatment,[18] knowledge about determinants of HRQoL is essential for developing successful interventions.

The primary aim of this study was to undertake a multidimensional assessment of participation in society (frequency, restrictions and satisfaction) for various aspects of daily life (domestic, occupational and recreational activities) before and after CR in patients with CAD. When significant time effects were observed for participation, the mediating effects of physical capacity and mental status were explored. Our secondary aim was to study the mediating effects of participation in society on changes in HRQoL.

METHODS

Study sample

From October 2010 until July 2012, patients who attended CR at Capri Cardiac Rehabilitation Center were included in this prospective cohort study. Patients were included if they had a diagnosis of acute myocardial infarction or angina pectoris (established ≤ 8 weeks before inclusion) and were treated with percutaneous coronary intervention, coronary artery bypass grafting, and/or medical treatment. Other inclusion criteria were age ≥18 years, proficiency in Dutch and signed informed consent. Exclusion criteria were left ventricular ejection fraction <40 % and physical and cognitive impairments that might limit CR.

Measures

Participation in society

Participation was assessed with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-Participation), which has been found to have good psychometric properties.[11,19,20] This questionnaire consists of 32 items (concerning domestic, occupational, and recreational activities) that address 3 different dimensions of participation: frequency, restrictions, and satisfaction. A score (0-100) is calculated for each dimension, with higher scores indicating better participation. The first 59 patients filled out a first version of the USER-Participation, whereas the subsequent 62 patients filled out the final version. Because both versions showed high agreement on all scales (intraclass correlation coefficients 0.947-0.982), they can be used interchangeably.[21]

To further quantify participation, item scores were dichotomized. For the frequency scale, “none at all” and “never” were defined as “not participating”, and participation for “≥ 1 hour per week” and “once or more than once a month” as “participating”. In line with the study of van der Zee et al,[12] the item scores for the restriction scale and satisfaction scale were dichotomized into restrictions/ no restrictions and satisfied/ not satisfied.[12] Although no reference values were available, in cases where 20% or more of the study sample did not participate, felt restricted or dissatisfied with regard to a certain aspect of daily life, this arbitrary proportion was considered relatively high.

Mediating variables

Two potentially mediating variables on time effects in participation in society were specified: physical capacity and mental status. Physical capacity was measured with a 6-minute-walk test, a reliable and valid submaximal-exercise test that was found to be responsive to relevant clinical changes during CR. The 6-minute walk distance correlates well with outcomes on the criterion standard maximum exercise test.[22] Mental status was measured using the subscale for depression of the Hospital Anxiety and Depression Scale (HADS). The HADS is a valid measurement for the screening of depressive mood in patients with CAD.[23,24]

Health-related quality of life

HRQoL was assessed with the MacNew heart disease health-related quality of life questionnaire. The Dutch MacNew is valid and reliable[25] and has shown to be a useful evaluation instrument for CR.[18] The questionnaire consists of 26 items. A global score (1-7) was calculated, as well as subscores (1-7) for the physical, emotional and social domains, with higher scores indicating improved HRQoL.

Procedure

The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam.

All patients participated in a multidisciplinary-outpatient CR program. The core of the program consisted of group exercise sessions (strength and aerobic) twice a week. Participants were also offered group-education sessions on risk factors for cardiovascular disease. Participation in a smoking cessation program, nutritional counseling, and stress management were optional. If necessary, individual consultations with psychiatrists, psychologists, social workers and dieticians were provided. The duration of the program varied between 4 and 13 weeks. The CR program was terminated when individual physical and psychosocial goals were met, as evaluated by an exercise stress test and consultation of a multidisciplinary team that consisted of physical therapists, social workers, and cardiologists.

All measures were obtained at the start of CR (T0), after CR (T1), and at follow-up 1 year after the start of CR (T2).

Data on age, gender, employment before CR, marital status, risk factors (diabetes, smoking, hypertension, body mass index), and reason for referral (diagnosis) were obtained from the medical charts.

Statistical analysis

Scores on the restriction scale of the USER-Participation violated the normality assumption and showed severe negative skewness. For this reason, scores were dichotomized. A

maximum score of 100 was given the value of '1' (no restrictions) and a score <100 a value of '0' (restrictions experienced). Data on other measures were normally distributed.

Descriptive statistics were used to present baseline characteristics. To estimate changes in participation between baseline, post-CR and follow-up, three generalized estimating equation (GEE) analyses were performed with frequency of participation, restrictions and satisfaction as dependent outcome variables and time as a categorical predictor. A GEE model was chosen because it corrects for missing values and because corrections are made for the dependency of observations within 1 individual.[26] In case of significant time effects, additional analyses were performed to evaluate possible mediating effects of physical capacity and depressive mood.

To assess whether participation in society is mediating changes in HRQoL, another GEE model was used with HRQoL as outcome variable and time as predictor. In case of significant time effects, participation was added to the model as possible mediator. The model was corrected for mediating effects of physical capacity and depressive mood on participation in society.

Since time points were unequally spaced, an autoregressive structure was used in all models. All baseline variables (Table 5.1) were considered possible confounders for all models. In case the variable changed the regression coefficient or odds ratio (OR) >10%, this variable was included in the model as a confounder.

For continuous variables, outcomes are displayed as regression coefficients (B), which indicate the change in the dependent variable that is associated with an increase in the specified time unit. For dichotomized variables outcomes are displayed as OR's, which indicates the increase (over the specified time period) in the odds that the dependent variable changes. Mediation was expressed as the percentage of change in the overall time effect after adding the potential mediator to the model. A 2-sided p-value <0.05 was considered significant. All analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois).

RESULTS

Subjects

A total of 163 patients started CR and were eligible for this study (Figure 5.1). Data from 35 patients who did not complete CR for reasons such as lack of time and unwillingness were excluded. The number of dropouts in this study was similar to that described in the literature (20% - 25%).[27,28] Data from another 7 patients were excluded, because they failed to return any of the questionnaires. There were no significant differences in baseline characteristics between patients excluded from analysis and those included. Of the remaining 121 patients, a total of 17 patients were lost to follow-up, for reasons such as lack of time, illness, and unwillingness.

Most of participants were men (n=96, 79%), mean age was 57 years, and 79 participants (65%) were employed. For further baseline characteristics see Table 5.1.

Table 5.1 Baseline characteristics of the study population (n=121)

Baseline Characteristics	
Demographics	
Sex, number of men (%)	96 (79)
Age in years, mean ±SD	56.6 ± 9.1
Employment, n (%)	
Employed (full time/part time)	79 (65)
Unemployed	8 (7)
Home/retired	34 (28)
Marital status, n (%)	
Married/partner	93 (77)
Single	28 (23)
Risk factors	
Blood pressure in mmHG, mean ±SD	
Systolic	134.0 ± 19.4
Diastolic	79.5 ± 11.4
BMI, mean ±SD	28.0 ± 5.8
Diabetes, n (%)	17 (14)
Smoking, n (%)	29 (25)
Rehabilitation characteristics	
Diagnosis, n (%)	
Myocardial infarction	91 (75)
Angina pectoris	30 (25)
Number of training sessions, mean ±SD	22 ± 4.6

SD= standard deviation

Participation in society

Frequency of participation

Table 5.2 lists the outcomes of the GEE regression model for time and frequency, which is graphically depicted in Figure 5.2a. Frequency of participation did not change during and after CR (see Table 5.2).

Table 5.3 shows the results of the dichotomized item scores (prevalence of nonparticipation). Although total participation time did not change, we did see some changes in percentage of patients that did not participate in a certain activity. At T0, 39% of patients were not working (paid employment), and at T1 this decreased to 34%. At follow-up (T2), 42% were not working. With regard to leisure and social activities, at T0 >20% of patients participated less than once a month in going out, outdoor activities, and physical exercise. At T1 and T2, this only remained above 20% for going out.

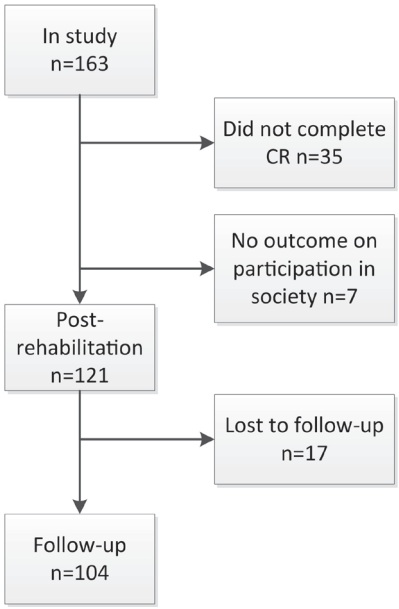

Figure 5.1 Patient flowchart

Table 5.2: Results of GEE analysis for changes in frequency of participation, satisfaction with participation and restrictions in participation

Scale	time period	Regression coefficient B[†]	95% Confidence interval	P-value
Frequency[1]	T0-T1	2.121	-0.086: 4.328	0.060
	T0-T2	0.155	-2.454: 2.763	0.908
	T1-T2	-1.966	-4.595: 0.663	0.143
Satisfaction[2]	T0-T1	6.915	4.125: 9.706	*<0.001*[§]
	T0-T2	8.435	4.903: 11.967	*<0.001*[§]
	T1-T2	1.520	-1.506: 4.546	0.325
Scale	**time period**	**Odds ratio[‡]**	**95% Confidence interval**	**P-value**
Restrictions[2,*]	T0-T1	3.077	1.952: 4.848	*<0.001*[§]
	T0-T2	5.843	3.363: 10.152	*<0.001*[§]
	T1-T2	1.899	1.186: 3.040	*0.008*[§]

[1]GEE model corrected for confounding effect of age, smoking status and employment; [2] no confounders identified. [*] Because scores violated the normality assumption, dichotomized scores were used in the analysis; [†] regression coefficients (B) indicate that for an increase in the specified time unit, the outcome variable changes with the regression coefficient B; [‡]odds ratio indicates the increase (over the specified time period) in the odds of feeling unrestricted; [§]P<0.05 considered significant.

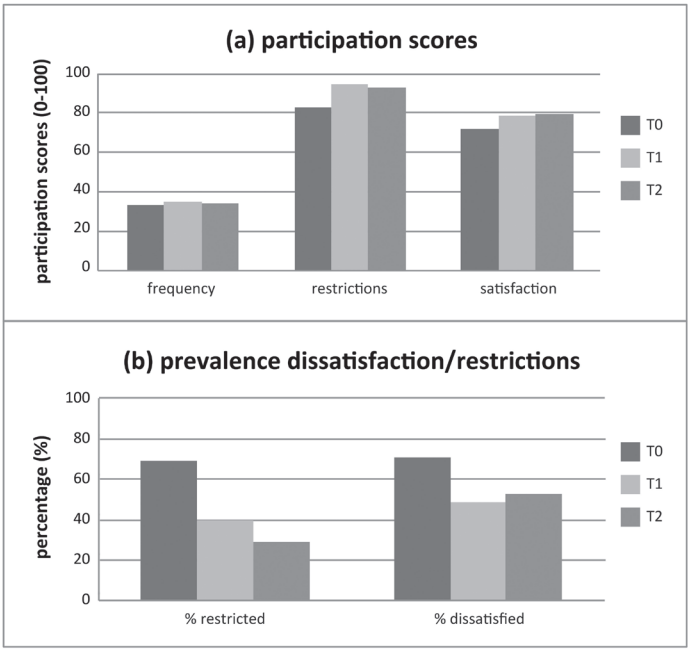

Figure 5.2 (A) Improvements in mean score for frequency, restrictions, and satisfaction scale during and after CR. **(B)** Improvements in prevalence of restrictions and dissatisfaction during and after CR.

Participation restrictions

At T0, the mean score on the restriction scale was 82.8 ± 18.3 (median 85.4). This increased to 94.5 ± 8.9 (median 100) at T1 and 93.0 ± 17.2 (median 100) at T2 (see Figure 5.2a and Table 5.2). Because scores violated the normality assumption, dichotomized scores (restrictions experienced/no restrictions experienced) were used in the analysis. At T0, most patients experienced restrictions (69%) in one or more aspects of daily life. At T1, this improved to 40% (OR=3.077, 95% confidence interval (95% CI) =1.952-4.848) and at T2 this improved further to 29% (OR=1.899, 95% CI=1.186-3.040). See Figure 5.2b.

At T0, restrictions were experienced mainly during work (33% of patients involved in this activity), housekeeping (38%), physical exercise (49%), and outdoor activities (36%). At T1, restrictions persisted for work (28%) and physical exercise (22%). At T2, during work this improved to 9%, but 21% still experienced restrictions during physical exercise (Table 5.3).

Satisfaction with participation

At T0, the mean score on the satisfaction scale was 71.8 ± 16.1 (median 75.0). This increased to 79.0 ± 14.6 (median 80.0) at T1 (B = 6.862, p<0.001). There were no significant changes between T1 and T2 (mean score 79.6 ± 15.8, median 82.5), see Figure 5.2a and Table 5.2. At T0, 71% of patients were dissatisfied with one or more aspects of daily life. This improved to 49% at T1 and was 53% at T2 (see Figure 5.2b).

At T0, dissatisfaction was seen in work (27% of working patients dissatisfied), housekeeping (37%), physical exercise (44%), going out (36%), outdoor activities (37%), and contact with friends/acquaintances (33%). At T1, dissatisfaction persisted only in contact with friends (27%). However, at follow-up (T2) more than 20% of patients were once more dissatisfied with housekeeping, physical exercise, going out, and contact with friends (Table 5.3).

Mediating effects

Physical capacity explained 1.6% of changes in satisfaction with participation and 9% of changes in restrictions. Depressive mood explained 20% of changes in satisfaction and had no mediating effect on restrictions (Table 5.4).

Mediating effect of participation in society on changes in HRQoL

Table 5.5 lists the outcomes of the GEE regression model with HRQoL and the mediating effects of participation in society. Both global HRQoL and subscores improved significantly over time. Satisfaction with participation explained changes over time in global HRQoL (19%), physical HRQoL (18%), emotional HRQoL (25%), and social HRQoL (10%), whereas experienced restrictions explained 5%, 7%, 1%, and 2% respectively. Frequency of participation did not explain changes in HRQoL.

Table 5.3 Prevalence of nonparticipation, restrictions and dissatisfaction in different aspects of daily life (dichotomized item scores)

	Not participating (%)		
Frequency	T0	T1	T2
Paid work	39*	34*	42*
Unpaid work	80*	77*	69*
Education	93*	95*	89*
Housekeeping	5	0	1
Physical exercise	22*	3	9
Going out	45*	28*	24*
Outdoor activities	33*	19	18
Leisure indoors	14	11	19
Visits to family/friends	13	8	5
Visits from family/friends	7	14	9
Telephone/computer contact	6	6	5
	Restrictions (%)		
Restriction scale	T0	T1	T2
Work/education	33*	28*	9
Housekeeping	38*	19	16
Mobility	21*	6	15
Physical exercise	49*	22*	21*
Going out	21*	4	6
Outdoor activities	36*	9	12
Leisure indoors	8	6	3
Partner relationship	17	16	15
Visits to family/friends	23*	4	5
Visits from family/friends	14	6	5
Telephone/computer contact	9	1	1
	Dissatisfied (%)		
Satisfaction scale	T0	T1	T2
Work/education	27*	18	12
Housekeeping	37*	18	20*
Mobility	19	10	13
Physical exercise	44*	15	23*
Going out	36*	16	20*
Outdoor activities	37*	14	16
Leisure indoors	18	14	10
Partner relationship	8	10	13
Family relationships	8	8	11
Friends & acquaintances	33*	27*	36*

**A percentage above 20% was considered high.*

Table 5.4 Mediating effects of physical fitness and depressive mood on changes in participation in society*

	Participation in society	
Mediating variable	Satisfaction	Restrictions
Physical fitness (6-minute walk test)	2%	9%
Depressive mood (HADS)	20%	†

*Mediation was expressed as the percentage of change in the overall time effect after adding the potential mediating variable to the GEE model.
†No mediating effect found.

Table 5.5 Mediating effects of participation in society on changes in HRQoL

	Time effect		**Mediating effect participation scores** *		
Outcome variable	**Regression coefficient B‡ (95% Confidence interval)**	**P-value**	Frequency	Restriction	Satisfaction
Global HRQoL[1]	0.224 (0.123: 0.326)	<0.001§	†	5%	19%
Physical HRQoL[2]	0.323 (0.192: 0.454)	<0.001§	1%	7%	18%
Emotional HRQoL[3]	0.141 (0.037: 0.245)	0.008§	†	1%	25%
Social HRQoL[4]	0.212 (0.085: 0.340)	0.001§	1%	2%	10%

*Mediation was expressed as the percentage of change in the overall time effect after adding the potential mediator to the GEE model.
‡*Regression coefficients (B) indicate that for a unit increase in the specified predictor variable, the outcome variable changes with the regression coefficient B.*
[1]*GEE models corrected for confounding effect of physical fitness, depressive mood and smoking status.*
[2]*GEE model corrected for confounding effect of physical fitness, depressive mood, smoking status and body mass index.*
[3]*GEE model corrected for confounding effect of physical fitness, depressive mood, age, sex, smoking status and marital status.*
[4]*GEE model corrected for confounding effect of physical fitness, depressive mood, age, smoking status, body mass index and blood pressure.*
§*P<0.05 considered significant.*
†*No mediating effect found.*

DISCUSSION

This study shows that participation in society improves during CR. Although no changes were seen in frequency of participation, considerable improvements were seen for experienced restrictions and satisfaction. Despite these improvements, 1 year after the start of CR one third of patients still felt restricted and half of the patients were dissatisfied with one or more aspects of daily life. Improvements in HRQoL during CR were for a considerable extent (10%-25%) explained by satisfaction with participation and were also influenced by experienced restrictions (1%-7%). Frequency of participation did not explain improvements in HRQoL. These findings underline the importance – both when conducting research and during rehabilitation – of also considering the restrictions experienced by patients and their satisfaction with participation, instead of focusing solely on frequency of participation.

Few comparable studies have focused on participation in society during CR. Our results at follow-up are similar to the results from a validation study of the USER-participation in patients with cardiac disease obtained 4 months after CR.[11] Scores at T2 are higher in our population than in those with other disorders such as chronic pain and neurological disorders.[11] This is to be expected because these patient groups have more severe mobility problems. Our HRQoL results are also comparable to the results of studies in other patient groups. In a study with older adults and patients with brain injuries, results also suggested that mainly experienced problems in participation and not the frequency of participation are related to changes in HRQoL.[14,15]

There was no control group in this study, so caution is required when attributing the improvements observed in participation directly to CR. Part of the improvements could also be due to spontaneous recovery over time. Besides spontaneous recovery or direct improvements, changes in participation could also be reached indirectly during CR by improving the conditions for participation, in particular physical capacity and depressive mood. There is plenty of evidence found in controlled studies that CR does lead to changes in physical capacity and depressive mood.[29,30] Improvements in physical capacity could lead to lower physical strain[4] and subsequently explain the decrease in restrictions and dissatisfaction. Depressive mood was shown in other studies to be a predictor of work resumption in patients with cardiac disease.[5,6] Additional analysis in our study indeed showed that changes in satisfaction with participation were for a considerable extent mediated by depressive mood. Improvements in restriction were influenced by physical capacity. So, the improvements observed in participation are partially achieved indirectly by improvements in physical capacity and depressive mood achieved during CR. Because we could explain only 9% of improvements in experienced restrictions and 20% of improvements in satisfaction, further improvements could be a direct effect of CR or spontaneous recovery. However, other possible mediators such as fatigue and self-efficacy should be investigated in future studies. Knowing more about these factors could help to improve CR to target persisting restrictions and dissatisfaction.

In this study we found persistent restrictions and dissatisfaction with participation. Because restrictions and dissatisfaction are related to HRQoL, it is important to address these aspects of participation during CR. We explored in what areas of daily life most problems were experienced. Previous studies focused mainly on work resumption. In our study, one third of patients was not working before diagnosis and most patients who worked before the event returned to work at the completion of CR without experiencing major problems. This finding is in line with previous studies.[8] The high percentage of patients being retired demonstrates the importance to not only focus on work resumption but also on other aspects of daily life.

Persisting restrictions (and dissatisfaction) were mainly experienced during the performance of physical exercise. It might be that the strain of these activities is high and physical training during CR inadequate for problem-free resumption. However, because we found that physical capacity was only weakly related to changes in experienced restrictions, other factors responsible for the persisting restrictions must be explored.

For going out and taking part in outdoor activities, restrictions were low 1 year after CR, but dissatisfaction was high and frequency of performance low. In this respect, our results are somewhat contrasting with a previous study that showed that most patients have returned to outdoor activities 12 weeks after diagnosis.[31] During housekeeping tasks we also found high dissatisfaction. Problems might even have been underestimated, because most of our study participants were men. Woman are in general more involved in and responsible for household tasks and report more stress and limitations.[17] The dissatisfaction seen during exercise, going out, outdoor activities, and housekeeping could partly be caused by depressive feelings. We found that depressive mood is related to dissatisfaction with participation. A more individualized approach during CR focusing on these areas in which problems are experienced might help to optimize patients' participation and consequently HRQoL.

The fact that the aspect of daily life with which patients were most dissatisfied 1 year after CR was their contact with friends and acquaintances (36% dissatisfied) – while satisfaction with partner and family relationships was high – suggests that there is also room for improvement in social contact outside the family home. As social support is important because it is related to health outcomes,[32-34] future studies should focus on this topic, to find out whether CR could help.

Study limitations

Studies investigating participation in society are limited by the lack of a standard scale for measuring this concept.[9,35] The USER-Participation measures not only frequency, but also restrictions and satisfaction; it also has good psychometric properties.[11,19,20]

Another limitation is the lack of a control group in this study and caution is required when attributing the effects that we found to CR. To our knowledge, there are no randomized trials that published results of changes in several aspects of participation in society (more than return to work) during CR.

CONCLUSIONS

Although no changes were seen in frequency of participation, considerable improvements were seen for experienced restrictions and satisfaction. Despite improvements, the presence of CAD is associated with persistent restrictions and dissatisfaction with participation. Because experienced restrictions and dissatisfaction are related to HRQoL, it is important to also address these aspects of participation in society during CR, and not only frequency of participation. A more individualized approach during CR focusing on areas in which restrictions and dissatisfaction are experienced might help to optimize patients' participation and HRQoL.

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Chapter 6

FATIGUE DURING AND AFTER CARDIAC REHABILITATION

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ABSTRACT

Objective

To estimate fatigue during and after a multidisciplinary cardiac rehabilitation programme and its association with aerobic capacity.

Design

Longitudinal cohort study.

Patients

A total of 121 patients with coronary artery disease (79% men), mean age 57 years.

Methods

Fatigue was measured with the Fatigue Severity Scale (FSS) and aerobic capacity with the 6-min walk test (6MWT). FSS scores ≥ 4 were defined as fatigue and > 5.1 as severe fatigue. Measurements were taken before (T0) and after rehabilitation (T1) and at 1-year follow-up (T2).

Results

Fatigue decreased from 3.49 at baseline to 3.03 post-rehabilitation ($p=0.002$) and decreased further to 2.75 at follow-up ($p<0.001$ vs T0). At baseline, 17.7% of patients were classified as severely fatigued. After cardiac rehabilitation, the prevalence decreased to 10.6% ($p<0.001$) and to 8.1% at follow-up ($p=0.011$ vs T0). Although the prevalence of severely fatigued patients decreased, it was still high compared with healthy individuals (3.5%). Aerobic capacity was weakly associated with a reduction in fatigue ($p=0.030$).

Conclusions: Fatigue decreased during and after cardiac rehabilitation. However, the prevalence of severely fatigued patients remained high after cardiac rehabilitation. Fatigue should be identified at an early stage in order to provide additional programmes aiming to reduce severe fatigue.

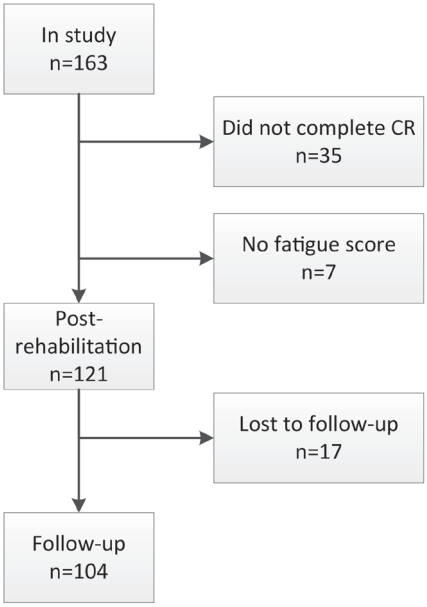

Figure 6 .1 Patient inclusion in study
CR= cardiac rehabilitation.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide.[1] In 2008, 17.3 million people died from CVD, which represents 30% of global deaths.[1] The most common form of CVD is coronary artery disease (CAD), which caused 7.3 million deaths in 2008.[1] The economic impact of CAD is high, due to high healthcare costs and sickness absence.[2]

Cardiac rehabilitation (CR) is known to improve the physical and psychological status of patients with CAD, thereby reducing both cardiovascular mortality and total mortality.[3] Physical improvements are often seen in aerobic capacity, for which previous intervention studies have shown favourable effects directly after exercise-based CR.[3,4]

Studies[5,6] have shown that illness-related fatigue is one of the most disturbing symptoms experienced by patients with CAD.[6] This type of fatigue is difficult to manage, because it differs from any earlier experience with fatigue unrelated to CAD.[6] Another reason for the often quite considerable impact of fatigue is that fatigue negatively influences physical and mental capacity and therefore quality of life.[5] Despite the impact fatigue might have, only 2 studies have examined the severity of the problem in patients with CAD.[5,6] One study[6] found that fatigue decreases over time without participation in CR. Nevertheless, half of patients still reported fatigue 4 months to 2 years after myocardial infarction. It appears that additional interventions, such as CR, are necessary to improve long-term fatigue after CAD. Besides the direct influence on fatigue, participation in CR may also indirectly improve fatigue. A study[5] showed that fatigue levels seem to be associated with aerobic capacity in patients with CAD. It may therefore be hypothesized that improvements in aerobic capacity, which are known to occur during exercise-based CR, lead to a decline in fatigue. However, those studies that have examined the effect of CR on fatigue focused only on patients with heart failure and, indeed, reported less fatigue after exercise-based CR.[7,8]

The primary aim of this study was to estimate fatigue in patients with CAD before and after CR and at 9 months follow-up. A secondary aim was to explore whether aerobic capacity was associated with fatigue. Because fatigue or loss of energy is one of the main symptoms of depression[6] and depression is common in patients with CAD[9], depression seems to overlap with illness-related fatigue.[6,10] Thus, all analyses were controlled for depression.

METHODS

Patients and design

Inclusion criteria were: (I) a diagnosis of acute myocardial infarction or angina pectoris; (II) scheduled to participate in the regular CR programme; (III) 18 years of age or older; (IV) provided signed informed consent; and (V) proficient in Dutch language. Exclusion criteria were: (I) comorbidities; (II) left ventricle ejection fraction of < 40%; and (III) psychological or cognitive impairments that might impair participation in the rehabilitation programme.

Between October 2010 and July 2012, 163 consecutive patients were included in this single-centre prospective observational cohort study. Of these, 121 patients who had completed the CR programme and who had at least 1 fatigue score were included in the analysis (Fig. 6.1). Reasons given by patients (n=17) for not participating in the follow-up measurements were: (I) lack of time, (II) immobility; and (III) unwillingness.

Measurements were taken at the following time-points: pre-rehabilitation (T0), post-rehabilitation (T1), and 1 year after the start of rehabilitation (9-month follow-up) (T2). The study was approved by the medical ethics committee of the Erasmus Medical Centre in Rotterdam.

Cardiac rehabilitation programme

The rehabilitation programme at Capri cardiac rehabilitation centre is based on the Dutch guidelines for CR.[11] The duration of CR varied from 4 to 13 weeks, depending on the patient's individual improvement. The CR programme was completed when an individual's physical and psychosocial goals were achieved. This was evaluated with an exercise test on a bicycle ergometer and a consultation with the multidisciplinary team that consisted of a social worker, physical therapist and nurse.

The patients exercised twice a week. One training session lasted 75 min; the other session had additional relaxation exercises and lasted 105 min. The exercise sessions consisted of: (I) warming-up exercises; (II) gymnastics exercises; (III) an aerobic programme of 12 min, which involved a combination of brisk walking and jogging with increasing the component of jogging over time; (IV) sports activities; and (V) cooling-down exercises.

In addition to the regular exercise programme, patients could voluntarily attend educative medical sessions, risk factor sessions, healthy diet sessions or emotional advice sessions. Stress management modules, dietary advice modules and smoking cessation programmes were also provided to help adjust the lifestyle behaviour of the patients.

MEASURES

Fatigue

The primary outcome measure was fatigue, which was measured with the Fatigue Severity Scale (FSS). The FSS consists of 9 questions. Answers are given on a 7-point scale from "totally disagree" to "totally agree". A higher FSS score indicates more severe fatigue.[12,13] Both the mean FSS score, indicating the level of fatigue, and the prevalence of fatigued patients and severely fatigued patients were calculated. Patients were classified as being fatigued if their FSS score was ≥ 4 and ≤ 5.1[12] and as being severely fatigued if their FSS score was > 5.1.[13] The FSS has been found reliable and valid in healthy subjects[12], in patients with multiple sclerosis[12,14] and in patients with recent ischaemic stroke.[12]

Aerobic capacity

Aerobic capacity was measured with the 6-min walk test (6MWT). The 6MWT is a submaximal exercise test for measuring aerobic capacity.[15] During this test, patients walk as fast as they can over a distance of 30m during a period of 6 min. The distance walked is recorded. Patients were not allowed to run, and standardized words of encouragement were given every minute. The 6MWT has been found moderately reliable and moderately valid in patients with CAD undergoing CR.[16] The 6MWT has been shown to be responsive to the relevant clinical changes that occur during CR.[16]

Depression

Depression was measured with the Hospital Anxiety and Depression scale (HADS). This questionnaire has subscales for depression and anxiety, each comprising 7 items. Answers are given on a 4-point scale from "never" to "almost always". Higher scores on the depression subscale indicate higher levels of depression.[17] Patients with a score ≥ 8 are considered to have signs of depression.[18] The HADS is a valid instrument for the screening of depression in patients with CAD.[17,19]

Baseline characteristics

Data on age, gender, body mass index (BMI), waist circumference, blood pressure, cardiac diagnosis for referral, smoking, diabetes and medication were obtained from the patients' medical files for the purpose of descriptive statistics. In addition, the number of training sessions was recorded.

Procedure

Depending on their individual preferences, patients completed the questionnaires either on paper or digitally. The questionnaires were completed at home. The 6MWT was performed either at Capri cardiac rehabilitation centre or at Erasmus Medical Centre under the supervision of a nurse, physical therapist or researcher.

Statistical analysis

Descriptive statistics were used to present baseline characteristics, level and prevalence of fatigue, level of aerobic capacity and depression. To test the difference in baseline characteristics between the patients who completed CR and the patient who did not, independent t-tests and $\chi 2$ tests were performed. To assess the changes in prevalence of fatigue during and after CR, a $\chi 2$ test was performed. To investigate the changes in the level of fatigue during and after CR, a generalized estimated equation (GEE) model was performed with fatigue as dependent outcome variable and time as categorical predicator. A GEE model corrects for missing values and the dependency of observation within a subject is taken into account.[20] In case time effects in fatigue were found, a second GEE model was performed to test whether the changes in fatigue were mediated by aerobic capacity and depression. In this second model, fatigue was used as dependent outcome variable and time, aerobic capacity and depression were used as predictors. All models were adjusted for age, gender and cardiac diagnosis. Since the time between the measurements was not equal, an autoregressive structure was used in all models. The outcomes of the GEE analysis are regression coefficients (B), which indicate the change in the dependent variable that is associated with a 1 unit change in the predictor variable. To examine the difference in baseline characteristics between patients who were severely fatigued at follow-up and those who were not, post-hoc independent t-tests and $\chi 2$ tests were performed. SPSS version 20 was used for data analysis. An overall 2-sided α of 0.05 was set for all analyses.

RESULTS

Patients

The majority of patients were men (79%) and mean age was 56.6 years (Table 6.1). The main diagnosis for referral to CR was myocardial infarction (75%). The mean number of training sessions was 22 (Table 6.1). There were no differences in baseline characteristics between the 121 patients who completed the rehabilitation programme and the 35 patients who did not complete the programme and who were excluded from analysis.

Fatigue

Patients with AP (mean FSS 4.05 (standard deviation (SD) 1.59)) were significantly more fatigued at baseline than patients with MI (mean FSS 3.31 (SD=1.38), p=0.024). There was no difference at baseline in prevalence of fatigued patients between patients with AP (21.4% fatigued, 28.6% severely fatigued) and MI (21.2% fatigued, 14.1% severely fatigued, p=0.131). The mean level of fatigue significantly decreased in the total study population from 3.49 (SD=1.5) at baseline to 3.03 (SD=1.3) post-rehabilitation (B=-0.42, p=0.002) and to 2.75 (SD=1.4) at follow-up (B=-0.68, p<0.001 vs T0) (Table 6.2 and Fig. 6.2). At baseline, 21.2% of the patients were classified as fatigued (mid-grey) and 17.7% as severely fatigued (dark-grey). The prevalence of fatigued patients decreased to 12.8% post-rehabilitation (p<0.001) and to 10.5% at follow-up (p=0.011 vs T0, p<0.001 vs T1). The number of severely fatigued patients decreased to 10.6% post-rehabilitation (p<0.001) and to 8.1% at follow-up (p=0.011 vs T0, p<0.001 vs T1) (Fig. 6.2). Those patients who were classified as severely fatigued at follow-up, were also severely fatigued prior to CR. Therefore, the fatigued and non-fatigued patients did not change into severely fatigued patients.

Post-hoc analysis revealed differences in baseline characteristics between patients who were severely fatigued at follow-up and those who were not. The severely fatigued group consisted of significantly more patients with diabetes and women compared with fatigued and non-fatigued patients (Table 6.3). At follow-up, the patients with severe fatigue walked a shorter distance on the 6MWT; 449.4m (SD=109.66) compared with 613.9m (SD=84.8) for those who were not severely fatigued (p=0.026). In addition, the severely fatigued patients showed significantly more depressive symptoms (66.7%), compared with 16.7% in mildly fatigued patients and 3.3% in non-fatigued patients.

Table 6.1 Baseline characteristics of the study population (n=121)

Baseline characteristics	
Men, n (%)	96 (79)
Diagnosis, n (%)	
Myocardial infarction	91 (75)
Angina pectoris	30 (25)
Age (years), mean ± SD	56.6 ± 9.1
BMI (kg/m^2), mean ± SD	28.1 ± 5.8
Waist circumference (cm), mean ± SD	100.9 ± 13.8
Systolic blood pressure (mmHg), mean ± SD	133.9 ± 19.4
Diastolic blood pressure (mmHg), mean ± SD	79.5 ± 11.4
Number of training sessions, mean ± SD	22 ± 4.6
Smoking, n (%)	29 (25)
Diabetes, n (%)	17 (14)
Medication, n (%)	
Aspirin	116 (95.9)
Statin	118 (97.5)
Beta blocker	101 (83.5)
ACE inhibitor	79 (65.3)
ADP antagonist	99 (81.8)

SD= standard deviation; BMI= body mass index; ACE= angiotensin-converting enzyme; ADP= adenosine diphosphate.

Table 6.2 Generalized estimating equation model for changes in fatigue scores during and after cardiac rehabilitation

	B[a]	95% CI	P-value
T0-T1	-0.42	-0.68; -0.15	0.002
T0-T2	-0.68	-1.00; -0.36	<0.001
T1-T2	-0.26	-0.51; -0.01	0.042

CI= confidence interval.
T0: n= 113. T1: n= 94. T2: n= 86.
[a]B coefficients are unstandardized regression coefficients.

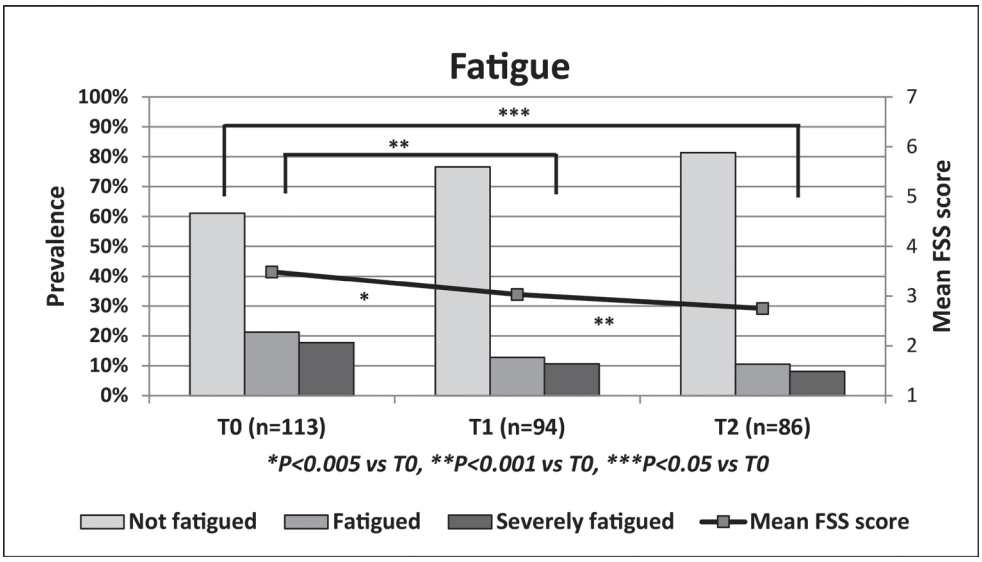

Figure 6.2 Prevalence and level of fatigue
FSS= fatigue severity scale.

Table 6.3 Difference in baseline characteristics between severely fatigued patients and fatigued and non-fatigued patients at follow-up

	Severely fatigued patients	Fatigued and non-fatigued patients	P-Value
Men, %	42.9	83.5	0.010
Diagnosis, %			0.790
Myocardial infarction	71.4	75.9	
Angina pectoris	28.6	24.1	
Age (years), mean ± SD	58.4 ± 7.6	57.7 ± 9.3	0.845
BMI (kg/m^2), mean ± SD	30.6 ± 5.69	28.1 ± 6.5	0.328
Waist circumference (cm), mean ± SD)	104.1 ± 19.2	101.0 ± 9.8	0.688
Systolic blood pressure (mmHg), mean ± SD	72.1 ± 14.1	80.6 ± 10.6	0.054
Diastolic blood pressure (mmHg), mean ± SD	132.9 ± 25.3	135.9 ± 19.5	0.701
Smoking (number), %	14.3	23.0	0.597
Diabetes (number), %	57.1	10.1	0.001

SD= standard deviation; BMI= body mass index.

Aerobic capacity and depression

The distance walked during the 6MWT increased by 7.1%, from 581 m (SD=81) at baseline to 622 m (SD=87) at post-rehabilitation (B=36.59, p<0.001). At follow-up, the distance walked decreased by 3.4% to 601m (SD=93) (B=-18.34, p=0.011 vs T1) (Table 6.4), but was still higher compared with baseline (B=18.25, p=0.006).

The mean level of depression decreased from 3.57 (SD=3.6) at baseline to 2.87 (SD=2.9) at post-rehabilitation (B=-0.56, p=0.026). This lower level of depression was maintained at follow-up (2.67 ± 3.1, B =-0.77, p=0.008 vs T0) (Table 6.4).

An association was found between distance walked during the 6MWT and fatigue (B=-0.002, p=0.030) when adjusted for depression. A mean increase in the 6MWT of 1m was associated with a mean decrease of 0.002 in the fatigue score (Table 6.4). An association was also found between depression and changes in fatigue (B=0.203, p<0.001) (Table 6.4). A mean decrease of 1 in the score on the depression subscale was associated with a mean decrease of 0.203 in the fatigue score.

Table 6.4 GEE model for changes in six minute walking test and depression before and after CR

	B[a]	95% CI	P-value
6MWT			
T0-T1	36.59	22.16; 51.02	<0.001
T0-T2	18.25	5.34; 31.16	0.006
T1-T2	-18.34	-32.55; 4.12	0.011
Depression			
T0-T1	-0.56	-1.06; -0.07	0.026
T0-T2	-0.77	-1.34; -0.21	0.008
T1-T2	-0.21	-0.74; 0.32	0.440
Associations			
6MWT and fatigue	-0.002	-0.005; 0.000	0.030
Depression and fatigue	0.203	0.145; 0.260	<0.001

CI= confidence interval; 6MWT= 6-minute walk test.
T0: n=99; T1: n=70; T2: n=67.
[a]B coefficients are unstandardized regression coefficients.

DISCUSSION

This study estimated fatigue during and after CR. The level and the prevalence of fatigue both decreased. However, one year after the start of rehabilitation, the prevalence of severely fatigued patients remained high. In this group of severely fatigued patients, the prevalence of depressive symptoms was also high. As hypothesized, aerobic capacity was associated with reductions in fatigue scores, even after correction for depressive symptoms.

Our finding of a mean baseline level of fatigue of 3.49 indicates that, on average, this patient group is not fatigued. However, since the mean FSS score in healthy populations is 3.00 ± 1.08[12], the level of fatigue in patients with CAD is higher at baseline. After rehabilitation and at follow-up, FSS scores were equal to scores in the healthy population.

Examination of the prevalence of fatigue showed that the findings were encouraging for the fatigued patients, but are still a cause of concern for the severely fatigued patients. In a healthy population, the prevalence of fatigued individuals (including severely fatigued patients) is 18%.[12] While the prevalence in patients with CAD was higher than this at baseline, this difference was no longer present at follow-up. In contrast, the prevalence of severely fatigued patients in the current study was higher than the figure of 3.5% seen in the healthy population[12], not only at baseline, but also after rehabilitation and at follow-up. The current CR programme thus seems inadequate for reducing fatigue in this subgroup of severely fatigued patients. Since fatigue might negatively influence physical and mental capacity and thus quality of life[6], it is important to know whether CR can be optimized to reduce fatigue in this group. The most striking factor shown by the characteristics of this subgroup was the very high occurrence of depressive symptoms at follow-up. Since one of the main symptoms of depression is fatigue or loss of energy[21], an extra intervention that focuses on the treatment of depression is likely to be beneficial.

To the authors' knowledge, no previous studies have explored levels of fatigue after CR in patients with CAD. However, a treatment effect of CR on vital exhaustion was found by one study.[5] The features of vital exhaustion are fatigue and loss of energy.[22] Another study reported a decrease in fatigue from baseline to 4 months and 2 years after infarction on the Multidimensional Fatigue Inventory scale.[6] Since the patients in this second study did not participate in CR, it seems that the improvements in fatigue reported in our study cannot completely be attributed to CR. It should be noted, however, that while 48% of the patients in the second study still reported fatigue at 4 months and at 2 years after a myocardial infarction[6], this was only 23% in our study after participation in CR.

Besides a direct result of CR on fatigue, CR could also indirectly lead to improvements in fatigue. According to the results of previous studies, our study demonstrated a significant increase in aerobic capacity during CR. This increase has been shown to improve a patient's ability to perform activities of daily living, including work and leisure activities.[23] These improvements influence the patient's psychological condition and thus improve their quality of life.[23] A small decline in aerobic capacity was seen at follow-up; however, the distance

walked was still higher than baseline. These results are in line with a previous study.[24] Also consistent with our hypothesis was the finding of a positive association between aerobic capacity and changes in fatigue. To achieve a level of fatigue equal to that of healthy individuals, patients with CAD had to reduce their FSS score on average by 0.5. Based on the model, patients would therefore have had to increase the distance walked in the 6MWT on average by 250 m. Since the mean improvement was only 33 m, the reduction in fatigue was also clearly influenced by other factors.

Previous research has indicated a strong, positive association between scores on the HADS depression subscale and fatigue scores.[5] The prevalence of depression is high in patients with CAD and overlaps with fatigue.[6] In line with these findings, the results of our study showed that changes in fatigue were significantly associated not only with aerobic capacity, but also with depression. A reduction in depression was associated with a decline in fatigue. Whereas aerobic capacity was only a weak mediator for changes in fatigue, the decline in fatigue during and after CR seems to have been caused mainly by a reduction in depression. This again underlines the importance of focusing on depressive symptoms in the group of severely fatigued patients for whom CR does not seem to be effective in terms of reducing fatigue.

Further research is required into more causes of fatigue and severe fatigue. Fatigue is likely to be influenced not only by the patient's disease, but also by factors such as socio-economic factors and comorbidities.[6] It is also important to identify patients with severe fatigue at an early stage of the rehabilitation programme so that other additional fatigue-relieving strategies can be provided for this group.

Study limitations

This study has some limitations. First, since there was no control group, the effects of CR on fatigue remain unclear. The changes in fatigue could be attributed to time rather than to exercise-based CR. Ideally, future research should study the effect of CR on fatigue in a randomized controlled trial. However, since CR is currently seen as standard care, it would be unethical to exclude patients from CR.

A second limitation is our use of the 6MWT to assess aerobic capacity. The gold standard for determining aerobic capacity is measuring oxygen consumption during cardiopulmonary exercise testing. This test could, however, not be performed for logistic reasons. Instead, we used the 6MWT, a test that is often recommended in patients undergoing CR. It is well known from previous research that the 6MWT is a valid instrument to estimate aerobic capacity in patients undergoing CR.[16] Nevertheless, previous research has also shown that there is a learning effect for repeated 6MWTs, which can also result in improvements.[16] We attempted to reduce this effect by performing a practice session at baseline. Despite this, patients who walk only a short distance in the 6MWT at baseline have more scope for improvement than those who walk a greater distance, in whom a "ceiling effect" may therefore occur.[16]

A final limitation is that, since someone's experience of fatigue may differ during the day, their answers may depend on when the questionnaire was completed.[6]

CONCLUSIONS

This is the first study, to our knowledge, which investigated the level and prevalence of fatigue in patients with CAD during and after CR. Levels of fatigue were improved both post-rehabilitation and at follow-up. On average, patients obtained levels of fatigue equal to those in a healthy population. However, after rehabilitation the prevalence of severe fatigue remained higher in patients with CAD than in healthy individuals. This suggests that the current CR programme might be inadequate for these patients in terms of fatigue. Although aerobic capacity was found to be associated with a decline in fatigue, the association was weak. Since a stronger association was found between fatigue and depression, interventions that focus on reducing depression might also have a positive influence on reducing fatigue in patients with CAD. Patients with severe fatigue should be identified in an early stage of rehabilitation so that additional programmes to relieve fatigue can be provided.

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Chapter 7

MARITAL QUALITY AND LONELINESS AS PREDICTORS FOR SUBJECTIVE HEALTH STATUS IN CARDIAC REHABILITATION PATIENTS FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Background

Low marital quality is associated with adverse health outcomes and lower personal well-being. Loneliness increases the risk of cardiovascular disease and mortality and predicts poor quality of life. The aim of this study was to investigate the association between marital quality and loneliness and subjective health status in primary percutaneous coronary intervention (pPCI) patients who underwent cardiac rehabilitation (CR).

Design/Methods

In a prospective cohort study, pPCI patients that followed CR were included between 2009-2011. A total of 223 patients responded to the SF-12 (subjective health status), MMQ-6 (marital quality) and UCLA-R (loneliness) questionnaires at baseline (pre-CR) and at 3 months (post-CR) or at 12 months follow-up. Subjective health status is displayed by a physical component summary (PCS) score and a mental component summary (MCS) score. Generalized estimating equations (GEE) analyses were performed to test improvements in subjective health status.

Results

Changes over time in subjective health status scores were similar between patients with optimal marital quality vs. patients with less optimal marital quality and non-lonely patients vs. lonely patients. The MCS level at one year follow-up of both patients with less optimal marital quality and lonely patients was lower compared with a healthy Dutch population (respectively; mean MCS score 47.3 (SD 10,5); p=0.013 and mean MCS score 46.1 (SD 11,2); p=0.010).

Conclusion: Both patients with less optimal marital quality and lonely patients did not reach the MCS level of a healthy Dutch population. Therefore, extra care and support should be given to these patients in a CR program.

Keywords

percutaneous coronary intervention, cardiac rehabilitation, subjective health status, marital quality, loneliness

This study was approved by the Medical Ethical Committee of the Erasmus Medical Center Rotterdam (MEC-2009-080 and MEC_2009-081).

INTRODUCTION

Cardiovascular disease is an important form of chronic disease that has a large contribution to mortality worldwide.[1] Chronic diseases such as cardiovascular disease are associated with lower levels of subjective health status. [2,3] Metabolic factors like hypertension, hypercholesterolemia and diabetes have been known to increase the risk of cardiovascular disease since the 20th century.[4,5] Interestingly, psychosocial risk factors (e.g. depression and anxiety) also increase the risk of coronary heart disease.[6]

A recent paper has stated the importance of psychosocial risk factors in relation to cardiovascular disease and cardiac rehabilitation (CR).[7] Marital quality is a psychosocial factor that might have an influence on subjective health status in CR patients. It has been shown that marital communication, conflict and strain are associated with adverse health outcomes.[8] Being married has a beneficial effect on long term survival in coronary artery bypass graft patients (CABG). Furthermore, a high- satisfaction marriage was associated with a significantly higher survival at 15 years follow-up than a low-satisfaction marriage.[9] A higher marital quality has also been shown to improve personal well-being.[10] Current numbers show that the divorce rate in the Netherlands increased from 3.0 per 1000 married couples in 1950, to 9.9 per 1000 married couples in 2013.[11] This makes marital quality an interesting parameter to investigate.

Another factor that might have an influence on the outcome of CR is loneliness. Loneliness is an important predictor of poor quality of life in older people.[12] Lonely patients are also at increased risk for cardiovascular disease and mortality.[13-15] The influence of marital quality and loneliness on subjective health status after CR is still unknown. The aim of the present study was to investigate the association between marital quality and loneliness and subjective health status in pPCI patients who underwent cardiac rehabilitation.

METHODS

Patient population

From January 2009 until March 2011 prospectively, a consecutive series of patients who participated in CR (Capri Cardiac Rehabilitation Rotterdam) following percutaneous coronary intervention after a myocardial infarction (primary PCI or pPCI) were included into this study. The study was approved by the local research ethics committee (MEC-2009-080 and MEC-2009-081). Moreover, this study was conducted according to the Helsinki Declaration. All patients consented participation in this study.

Cardiac rehabilitation

Patients were referred to cardiac rehabilitation by their physician in conjunction with their own preference. The dropout was 20 percent. Referral to our rehabilitation center was 38 percent in our region. In order to be eligible for inclusion, patients had to have completed at least half of the cardiac rehabilitation program.

Data collection

All patients received a set of questionnaires before the start of CR (T_0), post-CR (T_3, 3 months later) and at follow-up; 12 months after the start of CR (T_{12}). When patients did not respond to the questionnaires, a postal reminder was sent out after 4 weeks.

Data on age, gender, risk factors (diabetes, smoking, hyperlipidemia, hypertension, body mass index (BMI), family history), and medical history were obtained from the medical charts.

Marital quality (MMQ-6)

Marital quality was assessed by a 6-item Dutch version subscale of the Maudsley Marital Questionnaire (MMQ-6).[16] The MMQ-6 consists of 6 questions, 6-point Likert scale about marital strain, marital conflict and marital satisfaction. Maximum score is 36 and minimum score is zero. A higher score corresponded with lower marital quality.

Loneliness (UCLA-R)

Loneliness was assessed by a 10-item, 4-point Likert scale Dutch version subscale of the UCLA-R Loneliness Scale.[17] Questions concern social relationships and personal feelings. Maximum score is 40 and minimum score is 10. A higher score corresponded with more feelings of loneliness.

Subjective health status (SF-12)

Subjective health status was measured with the Short Form 12 (SF-12), a widely used questionnaire, consisting of a physical component summary (PCS) score and a mental component summary (MCS) score. Maximum score is 100 for both the PCS and MCS, mean score 50 in a normative Dutch population.[18] A higher score indicates a better health status. The Dutch version of the SF-12 health status scale was used, coupled with the normative data available for the Dutch population.[18,19]

Statistical analysis

Analyses were carried out for patients with complete questionnaires at minimally two measurement times (n=223). Patients with no answers at baseline were excluded from analysis, patients with no answers post-CR and at one year follow up were also excluded from analysis.

Descriptive statistics were used to present baseline characteristics. Categorical variables were summarized as percentages, continuous variables as means with standard deviation. The Chi-square test or student's t-test was used to calculate baseline differences between groups.

To distinguish between optimal marital quality and less optimal marital quality, the sum of the MMQ-scores at baseline was calculated. This score was then dichotomized, wherein the two highest tertiles (Sum-score > 0) corresponded with less optimal marital quality and the lowest tertile (Sum-score = 0) corresponded with optimal marital quality.

The sum of the UCLA-R scores at baseline was also calculated and dichotomized. The two lowest tertiles (Sum-score 10-20) corresponded with non-lonely patients and the highest tertile (Sum-score > 20) corresponded with lonely patients.

An imputation method was performed in case of missing items.20 Mean imputation was used to impute missing data for MMQ-6 and UCLA-R.

A one sample t-test was used to compare PCS and MCS scores at one year follow up with the subjective health status level of 50 points of the Dutch normative population.

To estimate changes in PCS and MCS between groups, GEE analyses were performed, with PCS and MCS as dependent outcome variables and time and group as categorical predictors. A GEE model was chosen because corrections are made for the dependency of observations within one individual.[21] Because time points were unequally spaced, an autoregressive structure was used in all models. The dependent variables, PCS and MCS, violated the normality assumption, therefore a log link function was selected. For the dependent variable, outcomes are displayed as the exponent of the regression coefficients EXP(B),

which indicates the change in percent in the dependent variable that is associated with an increase in the specified factor unit.

A multivariate GEE model was used to test differences in subjective health status scores between groups over time (optimal marital quality vs. less optimal marital quality and non-lonely patients vs. lonely patients). Confounders were selected à priori and include; age, sex, diabetes and a history of cardiovascular disease. In case of significant differences between groups, an interaction variable between group allocation and measurement time was added to the model. In this way, we correct for potential baseline differences. A 2-sided P value of <.05 was considered significant. All analyses were performed using SPSS version 21.

RESULTS

Patient flow

Of the 404 patients who were sent a mailing, 297 (73.5%) patients completed the SF-12, MMQ and UCLA-R at baseline (*Figure 7.1*). Since the outcome of this research is based on the SF-12 questionnaire, patients with >3 items missing at baseline and patients with >3 items missing at all measurement intervals were excluded from analysis. Ultimately, 223 patients were included in the analysis.

Baseline characteristics

Baseline characteristics are displayed in Table 7.1. Patients with an optimal marital quality and patients with less optimal marital quality only differed in PCS and MCS scores at baseline. PCS and MCS were both higher for patients with optimal marital quality. This was not seen between not-lonely and lonely patients. Compared to non-lonely patients, lonely patients were more likely to have a higher BMI and were more likely to have a history of cardiovascular disease.

Health status

Figure 7.2 shows mean physical and mental health status scores at baseline, post-CR and at one year follow up for each group. All groups showed an improvement in both PCS and MCS over time. Both less optimal marital quality patients (*mean MCS score 47.3 (SD 10,5); p=0.013*) and lonely patients (*mean MCS score 46.1 (SD 11,2); p=0.010*) did not reach the Dutch normative population level of 50 points at one year follow up.

Influence of marital quality on subjective health status

There was a difference in changes over time in MCS between patients with optimal marital quality and patients with less optimal marital quality (*Exp(B) 1.095; 95% CI 1.043 to 1.150*). Because patients with less optimal marital quality had a significantly lower MCS score at baseline, an interaction term between group allocation and time measurement was added. After correcting for the baseline difference, there was no difference between patients with optimal marital quality and patients with less optimal marital quality (*Exp(B) 1.030; 95% CI 1.000 to 1.062*).

Influence of loneliness on subjective health status

Non-lonely patients had a higher MCS score (*Exp(B) 1.076; 95% CI 1.017 to 1.139*) than lonely patients. Because there was a small, even though not significant, difference in MCS at baseline an interaction term was added for this model as well. The difference in MCS between non-lonely patients and lonely patients turned out to be insignificant after the interaction term was fitted in the model (*Exp(B) 0.994; 95% CI 0.961 to 1.027*). Implying that there was no difference between non-lonely and lonely patients when corrections for baseline MCS differences were made.

DISCUSSION

This study shows that improvements in subjective health status are not influenced by both marital quality and loneliness during cardiac rehabilitation.

Patients with less optimal marital quality improve more in subjective health status from a relative perspective than patients with optimal marital quality (*Figure 7.2*). However, patients with less optimal marital quality had a lower baseline value of PCS and MCS than patients with optimal marital quality, therefore there was more to gain. This hypothesis is supported by the results of our GEE analysis in which we correct for baseline differences (Table 7.2).

Although improvements in subjective health status were seen in all groups, less optimal marital quality patients as well as lonely patients did not reach the MCS level of a normative Dutch population at one year follow up. In contrast to patients with optimal marital quality and non-lonely patients. This difference might be explained by the baseline MCS difference.

Interestingly, PCS and MCS kept increasing even after the cessation of CR. This might be explained by the effect of exercise training and group education sessions. Besides, patients that completed the CR program are hypothetically more likely to maintain a healthy lifestyle.

Previous research has shown that poor marital quality is associated with adverse health outcomes and lower levels of personal well-being.[8,10] Loneliness is associated with increased cardiovascular disease and mortality and is a predictor of poor quality of life.[12-15] In this study lonely patients and patients with less optimal marital quality also showed lower subjective health status scores and are in line with these studies.

Social support has been shown to be important for improving mental health status.[22,23] Besides, a lack of social support is associated with persisting or worsening anxiety and depression after an acute cardiac event.[24] A CR program offers the opportunity for patients to have social interactions with other patients, clinicians, nurses and social workers. For lonely patients especially, CR might be good to reduce feelings of loneliness and thus, increase quality of life. Therefore, it is important to address marital quality and loneliness for each patient individually.

This research has shown that less optimal marital quality and loneliness are associated with a lower mental health status score one year after CR. These patients should receive extra care and support in a CR program to increase their mental health status in the long term.

Limitations

We used an imputation method for the SF-12, MMQ6 and UCLA-R in case of missing answers. However, for our dependent variables (SF-12) cases with more than three missing items were not imputed and therefore excluded from analysis. Another limitation is the amount of patients that were lost during follow up. Hence, a GEE model was used so data could be efficiently used and power of analysis could be maintained.

CONCLUSIONS

To our knowledge, this is the first study to examine marital quality and loneliness as possible predictors for subjective health status in combination with cardiac rehabilitation. No differences were found in changes over time in health status between patients with optimal marital quality compared to patients with less optimal marital quality and non-lonely patients compared to lonely patients. However, both patients with less optimal marital quality and lonely patients did not reach the MCS level of a healthy Dutch population. Therefore, extra care and support should be given to these patients in a CR program.

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Declaration of Conflicting Interests
None declared.

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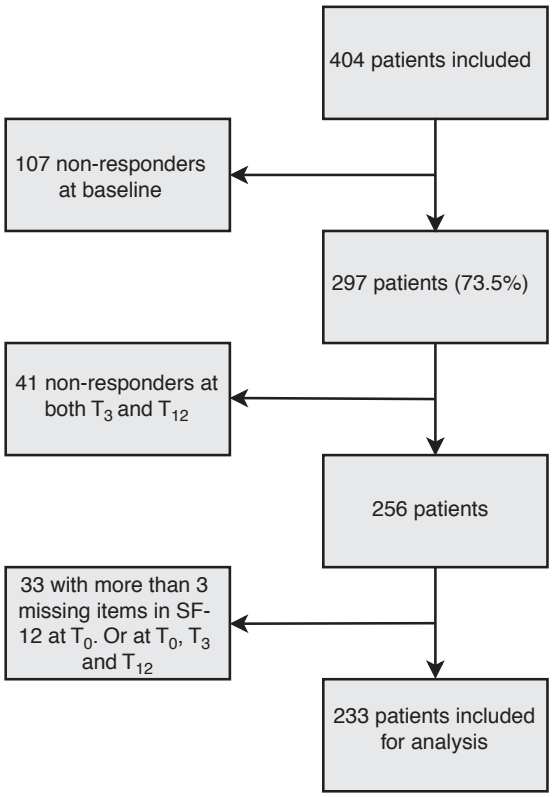
TABLES AND FIGURES

Figure 7.1. Patient flowchart



T_0: baseline; T_3: directly after cardiac rehabilitation; T_{12}: one year follow-up.

Table 7.1: Baseline characteristics of all included patients.

		Marital quality (*n*=223)			Loneliness (*n*=223)		
	Total group (*n*=223)	Optimal marital quality (*n*=102)	Less 0ptimal marital quality (*n*=121)	*p*-value	Not lonely (*n*=153)	Lonely (*n*=70)	*p*-value
Demographic Characteristics							
Age ± SD	57.7 (9.0)	58.9 (8.8)	56.6 (9.1)	0.056	57.1 (9.0)	58.9 (8.9)	0.173
BMI ± SD	27.2 (4.0)	27.3 (3.9)	27.2 (4.1)	0.870	26.8 (4.2)	28.3 (3.3)	**0.012***
Male Gender (%)	86.1	83.3	88.4	0.332	85.0	88.6	0.537
History:							
CVA (%)	1 (0.5)	1 (1.0)	0 (0.0)	0.452	1 (0.7)	0 (0.0)	0.688
Cardiac event (%)	23 (10.3)	10 (9.8)	13 (10.7)	1.000	11 (7.2)	12 (17.1)	**0.032***
- AMI (%)	15 (6.8)	7 (7.0)	8 (6.6)	1.000	8 (5.3)	7 (10.1)	0.147
- PCI (%)	18 (8.1)	8 (8.0)	10 (8.3)	1.000	10 (6.6)	8 (11.6)	0.287
- CABG (%)	2 (0.9)	1 (1.0)	1 (0.8)	0.698	1 (0.7)	1 (1.5)	0.521
Multivessel disease (%)	87 (39.0)	43 (42.2)	44 (36.4)	0.410	55 (35.9)	32 (45.7)	0.185
Risk Factors:							
Current Smoking (%)	98 (43.9)	39 (38.2)	59 (48.8)	0.137	63 (41.2)	35 (50.0)	0.246
Hypercholesterolemia (%)	83 (37.4)	39 (38.6)	44 (36.4)	0.781	58 (38.2)	25 (35.7)	0.767
Hypertension (%)	78 (35.1)	40 (39.6)	38 (31.4)	0.208	52 (34.2)	26 (37.1)	0.762
Diabetes Mellitus (%)	28 (12.6)	11 (10.9)	17 (14.0)	0.546	16 (10.5)	12 (17.1)	0.193
Family history (%)	130 (58.6)	54 (53.5)	76 (62.8)	0.173	91 (59.9)	39 (55.7)	0.562
Subjective Health Status							
PCS baseline ± SD	46.4 (9.1)	48.2 (9.3)	44.9 (8.8)	**0.008***	46.8 (8.6)	45.6 (10.2)	0.366
MCS baseline ± SD	45.2 (11.4)	48.7 (10.5)	42.3 (11.4)	**<0.001***	46.2 (11.0)	43.1 (12.1)	0.068

BMI: Body Mass Index; CVA: Cerebral Vascular Accident; AMI: Acute Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; PCS: Physical Component Summary; MCS: Mental Component Summary.
*P-value < 0.05 was considered significant

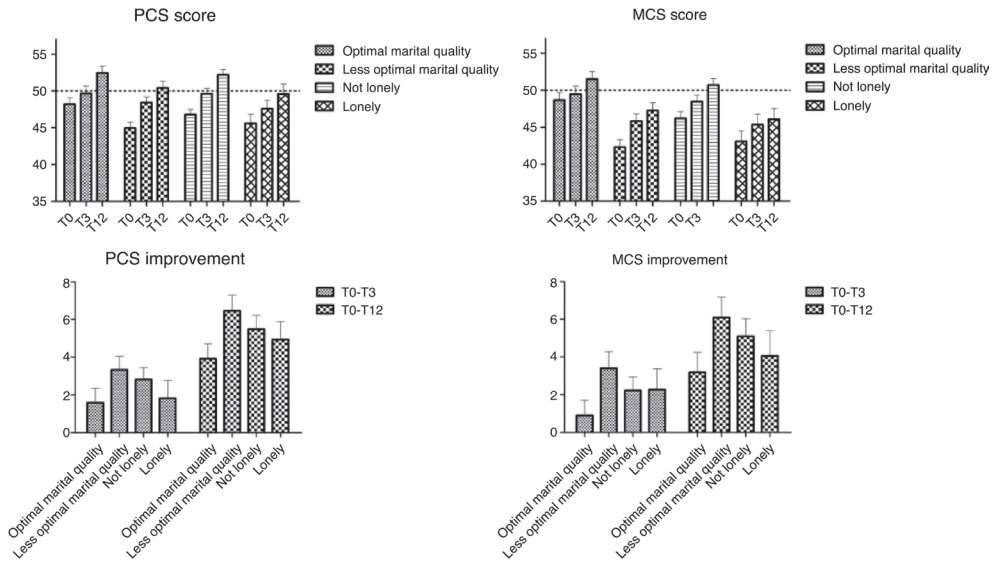


Figure 7.2. Average physical and mental health status scores at T_0 (baseline), T_3 (post-CR) and T_{12} (1 year follow-up) and average improvements between T0-T3 and T0-T12. Dotted line represents the mean score in a normative Dutch population. PCS: Physical component summary; MCS: Mental component summary.

Table 7. 2. Results of GEE analysis on health status scores.
Difference between groups (Overall effect)

Scale	Groups	EXP(B)[a]	95% CI	P p*
PCS[b,c]				
	Optimal marital quality vs. Less optimal marital quality	1.039	0.996 to 1.082	0.074
	Not lonely vs. lonely	1,035	0,988 to 1,084	0,150
MCS[b,c]				
	Optimal marital quality vs. Less optimal marital quality	1,095	1,043 to 1,150	**<0,001**
	Not lonely vs. lonely	1,076	1,017 to 1,139	**0,011**

Difference between groups corrected for baseline differences (interaction variable)

Scale	Groups	EXP(B)[a]	95% CI	P p*
PCS[b,c]				
	Optimal marital quality / Less optimal marital quality	1,021	0,998 to 1,044	0,080
	Not lonely / Lonely	0,990	0,967 to 1,013	0,389
MCS[b,c]				
	Optimal marital quality / Less optimal marital quality	1,030	1,000 to 1,062	0,054
	Not lonely / Lonely	0,994	0,961 to 1,027	0,703

GEE: Generalized Estimating Equations; PCS: Physical Component Summary; MCS: Mental Component Summary
[a] Exponent of the regression coefficients EXP(B), which indicates the difference in percent in the dependent variable between the two specified groups.
[b] GEE model corrected for the confounding effect of sex, age, diabetes mellitus and cardiac history.
[c] Because scores violated the normality assumption a log link function was chosen in the analysis.
* P < 0.050 was considered significant.

Chapter 8

SHORT- AND LONGER-TERM ASSOCIATION BETWEEN BODY MASS INDEX AND HEALTH STATUS IN CARDIAC REHABILITATION PATIENTS

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STRUCTURED ABSTRACT

Purpose

The association between body mass index (BMI) and subjective health status before and after cardiac rehabilitation (CR) and 1 year later were compared in primary percutaneous coronary intervention (pPCI) patients who did (CR group) and did not receive CR (no-CR group). The aim was to investigate the association between BMI and subjective health status based on the Short-Form 12 questionnaire.

Methods

Between 2009 and 2011, 242 pPCI patients with an acute myocardial infarction completed a CR program and were compared with 115 patients in the no-CR group. All patients completed the Short-Form 12 questionnaire at baseline, at 12 weeks, and at 1 year followup. The CR program consisted of a 2 sessions per week for 1.5 hours each for 12 weeks. Patients were categorized into 3 groups based on BMI: normal weight, overweight, and obese.

Results

Compared with patients in the no-CRgroup, CR group patients in the overweight group significantly improved their subjective health status after CR and these improvements were sustained at 1 year followup. CR patients in the normal weight and the obese group did not significantly improve subjective health status. The overweight patients had the highest improvement in subjective health status (odds ratio = 3.4 post-CR and 5.1 at 1 year of followup).

Conclusion

After CR, overweight patients showed the best improvement in subjective health status. CR did not significantly improve subjective health status in normal weight and obese patients.

Introduction

The association between body mass index and subjective health status in cardiac rehabilitation (CR) patients after primary percutaneous coronary intervention for an acute myocardial infarction was compared to patients who did not receive CR. Overweight patients showed the best improvement. CR did not improve subjective health status in obese patients.

Cardiac rehabilitation (CR) reduces overall morbidity and improves subjective health status in patients with coronary artery disease.[1] Obesity is an increasing problem, prevalent in one- third of adults in the United States,[2] and associated with increased cardiovascular morbidity and mortality.[3] In obese patients, CR results in improved exercise capacity, weight reduction, and improved lipid profiles.[4-9] Obesity may also influence subjective health status, which is frequently used as an outcome in evaluating treatments.[10] Poor subjective physical health status is a predictor of poor prognosis in patients with coronary artery disease.[11]

The association between body mass index (BMI) and subjective health status outcome after CR is unclear. Hence, the aim in this current study was to investigate the association between BMI and subjective health status outcome pre-CR, immediately post-CR, and 1 year after primary percutaneous coronary intervention (pPCI), in CR patients with myocardial infarction. These results were also compared to those with pPCI patients who did not undergo CR.

METHODS

Patient Sample

From January 2009 through March 2011, a consecutive series of prospective patients who underwent CR (CR group) in the Capri Cardiac Rehabilitation program, after pPCI, were included. A second group of patients who underwent pPCI but did not receive CR (no-CR group) was selected in the same time period from the PCI lab at Erasmus Medical Center, Rotterdam, The Netherlands. The no-CR group did not receive CR treatment because of no referral by the cardiologist, unwillingness of the patients to participate, or severe comorbidity hindering participation, (eg, advanced heart failure, chronic obstructive pulmonary disease Gold classification[12] ≥II, diabetes with organ damage). pPCI was defined as PCI in the acute phase of an acute myocardial infarction to restore blood flow through a coronary artery. This study was approved by the Medical Ethical Committee at the Erasmus Medical Center.

Exclusion criteria for the present study were: no available BMI score; and no available subjective health status data at baseline, post-CR and at 1 year follow-up. In addition, CR participants were excluded if they stopped CR <6 weeks (12 sessions) into the program. The CONSORT flow diagram is presented in Figure 8.1. A total of 1351 patients were eligible for inclusion (564 in the CR group and 787 in the no-CR group). After exclusion of 154 patients with no BMI score at baseline (21 in the CR group and 133 in the no-CR group) and exclusion of 840 patients with no complete follow-up (301 in the CR group and 539 in the no- CR group), the final patient sample consisted of 357 patients with complete data at all 3 time-points (242 patients in the CR group and 115 in the no-CR group).

To investigate response-bias, baseline characteristics and subjective health status at 12 weeks of follow-up for responders vs non-responders at 1 year were compared. Non-responders had more hypertension. The subjective health status at 12 weeks and all other baseline characteristics were similar between the responders and the non-responders.

Cardiac Rehabilitation

The Capri Cardiac Rehabilitation program provides standardized outpatient CR for coronary artery disease patients in the Rotterdam area. The program focuses on improving physical fitness, self-confidence, and social integration of the participants. The multidisciplinary CR program is led by specialized physiotherapists, nurses, and social workers. The core of the program consists of 1.5 hours group exercise sessions held 2 times per week over 12 weeks at a local sports facility. Besides the exercise program, both verbal and written instructions are provided on how to self-manage diet, smoking cessation, and stress management to improve adherence to lifestyle modification and help patients to adopt a positive role in their own health. If necessary, individual consults with psychiatrists, psychologist, social workers, and dietitians are provided.

Subjective Health Status

The Short-Form 12 questionnaire is widely used and measures subjective health status consisting of a physical component score (PCS) and a mental component score (MCS).[13] The mean score on both the PCS and MCS is 50 with a standard deviation of 10; a higher score means a better subjective health status. The Dutch version of the Short-Form 12 scale was used, for which normative data from the Dutch general population were available.[13,14]

All CR patients received a Short-Form 12 questionnaire before CR (T_0); 12 weeks after the start of CR (T_{12}), and after 1 year (T_{52}). The no-CR group received the same questionnaire at the same time intervals.

Follow-Up

Before approaching patients at T_0, T_{12}, and T_{52}, survival status was assessed through the civil registry. All patients alive were sent a questionnaire and, if necessary, a reminder after 4 weeks.

Statistical Analysis

Analyses were carried out for patients who completed all 3 questionnaires: baseline, 12 weeks, and 52 weeks (complete case analyses). BMI was grouped according to the World Health Organization (WHO) guidelines: normal weight, 18.5 to 24.99 kg/m^2; overweight, 25 to 29.99 kg/m^2; and obese, ≥30 kg/m^2.[14] There were no patients with a BMI <18.5kg/m^2.

Categorical variables were summarized as percentages and continuous variables as mean standard error of the mean. Chi-square test and Student's *t*-test were used. Univariate and multivariate regression analyses were performed using binary logistic regression. Since no standard cut-off was available, we chose to dichotomize the outcome on subjective health status (PCS and MCS). The highest tertile was used to indicate a better improvement in subjective health status and the 2 lowest tertiles were used to indicate a worse improvement in subjective health status.

Adjustments were made for the following baseline characteristics: subjective health status, age, gender, education level, number of diseased coronary arteries found during PCI, smoking, treated diabetes mellitus, family history, cardiac history (previous myocardial infarction, previous CABG and/or previous PCI) and depressive symptoms (a 2-item Patient Health Questionnaire score ≥2). Results were reported as odds ratio (OR) and 95% confidence interval (CI). All statistical tests were 2-tailed and *P* values <.05 were considered statistically significant.

RESULTS

Patient Characteristics

Table 8.1 describes the baseline characteristics of all 357 patients with completed Short-Form 12 questionnaires pre- and post-CR, and at the 1-year followup. The CR and the no-CR groups were different on a number of characteristics. The CR group was, on average, 5 years younger than the no-CR group, had less patients who previously had a cardiac event than the no-CR group, and had more smokers. No differences were found between the CR and no-CR group as to the distribution of the BMI categories or any of the other baseline characteristics.

PCS and MCS Improvement

The improvement in PCS and MCS between T_0 and T_{12} ($T_{0\text{-}12}$) and between T_0 and T_{52} ($T_{0\text{-}52}$) in PCS and MCS are presented in Figure 8.2. Both PCS and MCS improved at 12 weeks and at 52 weeks in the CR group, in contrast to the no-CR group for which subjective health status remained unchanged. After splitting up the subjective health status improvements for the 3 BMI categories, the improve-ments were predominantly present in the normal weight group at the 1- year follow-up and in the overweight group directly after CR and at the 1-year follow-up. No improvements were found in the obese group.

Adjustment for Baseline Characteristics

After adjustment for baseline characteristics, the total CR group had greater improvement in subjective health status at 12 weeks as well as at 52 weeks compared to the no-CR group, with the highest improvement found in the PCS (Figure 8.3). In the normal weight and obese group, no difference was found between patients in the CR and no-CR groups in subjective health status improvement at 12 weeks or at 52 weeks. The overweight group demonstrated the best improvement; between baseline and 12 weeks follow-up OR = 3.4, 95% CI 1.5-7.5 and between baseline and 1-year followup OR = 5.1, 95% CI 2.1-12.5.

DISCUSSION

Post-primary PCI patients who participated in a standardized CR program had greater improvement in subjective health status at 12 weeks than patients who did not undergo CR. This improvement was sustained at the 1-year followup. The improvement was observed in patients with overweight BMI, but not in normal weight and obese patients.

The results of our study support previous findings that cardiac rehabilitation improves subjective health status post-CR after pPCI compared to those who did not undergo cardiac rehabilitation.[1,5,8,9,15] However, little was known about the association between BMI and subjective health status after CR, especially regarding whether benefits would be sustained after a longer follow-up. Earlier studies demonstrated that obese patients experienced significantly less benefit aerobic capacity from CR[16,17] and subjective health status[17], but did not use a no-CR group. These studies recommended more investigation was needed regarding methods to improve CR outcomes in obese patients. Our results support the findings of earlier studies indicating that obese patients gain less benefit of CR. There were no significant differences between obese CR patients and obese patients who did not participate in a CR program. The additional value of this study was that we investigated the relationship between CR and subjective health status for different BMI categories separately and compared all the categories with the no-CR group.

Two previous publications used different cut-points for obesity (BMI = 27.8 kg/m^2 for men and 27.3 kg/m^2 for women) rather than the WHO guidelines, and found that CR improved subjective health status in obese patients.[4,7] Using these cut-points in analyzing the present data would have resulted in 67 of our original 180 overweight patients to be classified as obese and thus, the overweight patients in our trials would have had the best benefit of CR regarding the subjective health status. Other trials have used a variety of instruments to assess functional status, which also complicates the comparisons. These studies demonstrated improved exercise capacity, weight loss, and better lipid profiles after CR in obese patients.

The key question is why outcomes in patients with different BMI classes were different in our sample. Obese patients in the CR group scored worse on the mental health score than the obese patients in the control group after 12 weeks cardiac rehabilitation. At 1 year after ending CR, this difference had disappeared. It is possible that the cardiac rehabilitation program may have been a mental strain for them. Additionally, the workload intensity of the cardiac rehabilitation exercises was defined based upon the heart rate achieved during exercise. Obese patients usually had lower workload intensity training because of their higher heart rate responses. Thus, although the obese patient group did the same exercises as other patients, the workload intensity was lower. Perhaps 12 weeks of this "usually lower" workload intensity training was not enough to improve subjective health status. This lower workload intensity training was also used for elderly patients and patients with comorbidities, such as rheumatoid arthritis or chronic obstructive pulmonary disease.

Furthermore, 12 weeks may also not be long enough to reach the desired lifestyle changes. Because obese patients had to presumably change more lifestyle habits compared to normal and overweight patients, they may have felt like they were restricted in everything that they are used to do, requiring significant time commitment and motivation, and leading to frustration. This could be associated with an initially poorer subjective health status, especially in mental health.

Conversely, the overweight patients likely had to change fewer of their habits than the obese patients and thus, it was easier for them to change, which could be associated with a better subjective health status. These observations suggest that obese patients may require a tailored CR program with lower intensity training for a longer period, and with interventions that focus on their specific situation and needs, as they are challenged with a greater number and more challenging goals; as an example, providing additional psychological interventions.

Every patient who undergoes PCI should be referred to a CR program according to the guidelines.[18] However, some clinicians do not refer all their PCI patients and this results in lower participation rates.[19] Our CR group was 5 years younger, had less previous cardiac events, and more family history than the control group.

This study has some limitations. First, differences between baseline characteristics of the CR group and no-CR group could affect the outcomes. However, we adjusted for baseline characteristics. Second, the majority of patients were lost during follow-up. A third limitation is that BMI was only measured at baseline. Therefore, we were unable to investigate the association between changes in BMI and changes in subjective health status.

Conclusions and Future Directions

In this study, obese patients did not benefit from CR regarding subjective health status. Subjective health status is an important prognostic factor,[10] and therefore it is important to optimize cardiac rehabilitation for this patient group. Future research is needed to identify strategies for improving outcomes in obese patients undergoing a CR program after an acute myocardial infarction and pPCI. Furthermore, there are needs to clarify whether obese patients would benefit from a prolonged CR program that is longer than 12 weeks, as well as the use of psychological interventions to change lifestyle for improving better subjective health status.

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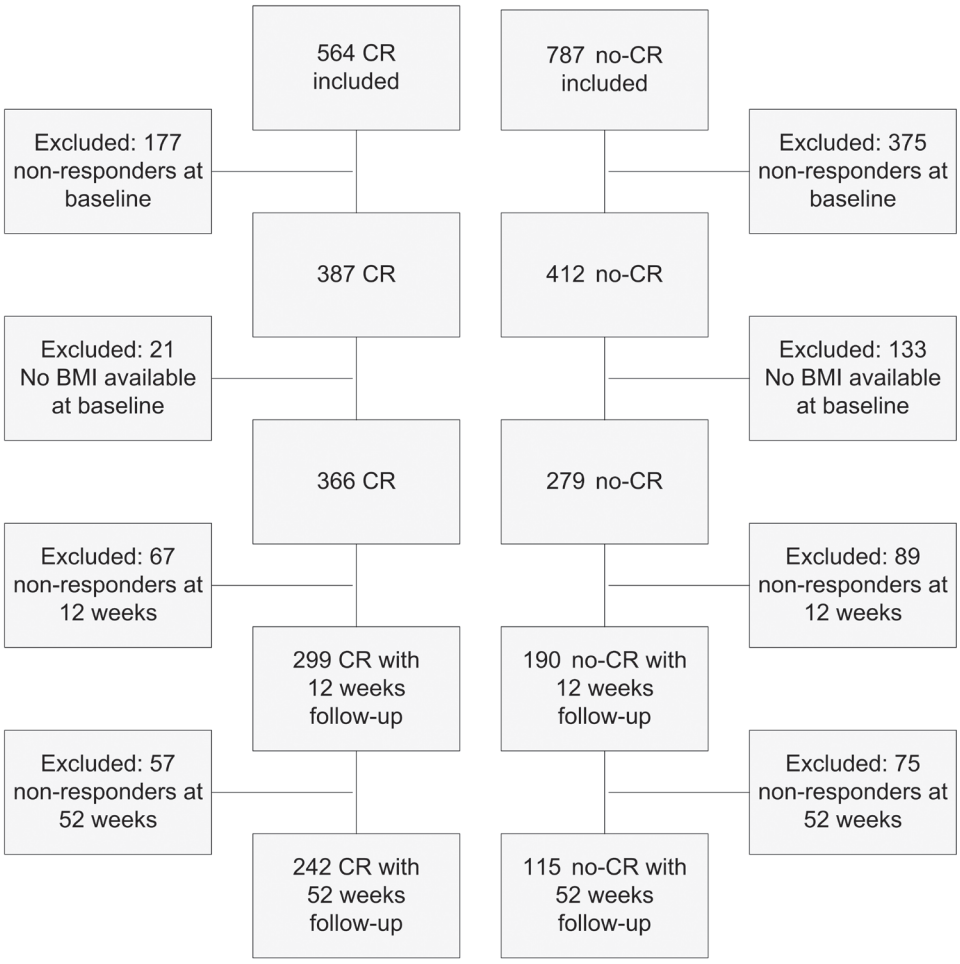

Figure 8.1. Patient flow diagram of the study sample. Abbreviations: BMI, body mass index; CR, cardiac rehabilitation group; no-CR, no cardiac rehabilitation group.

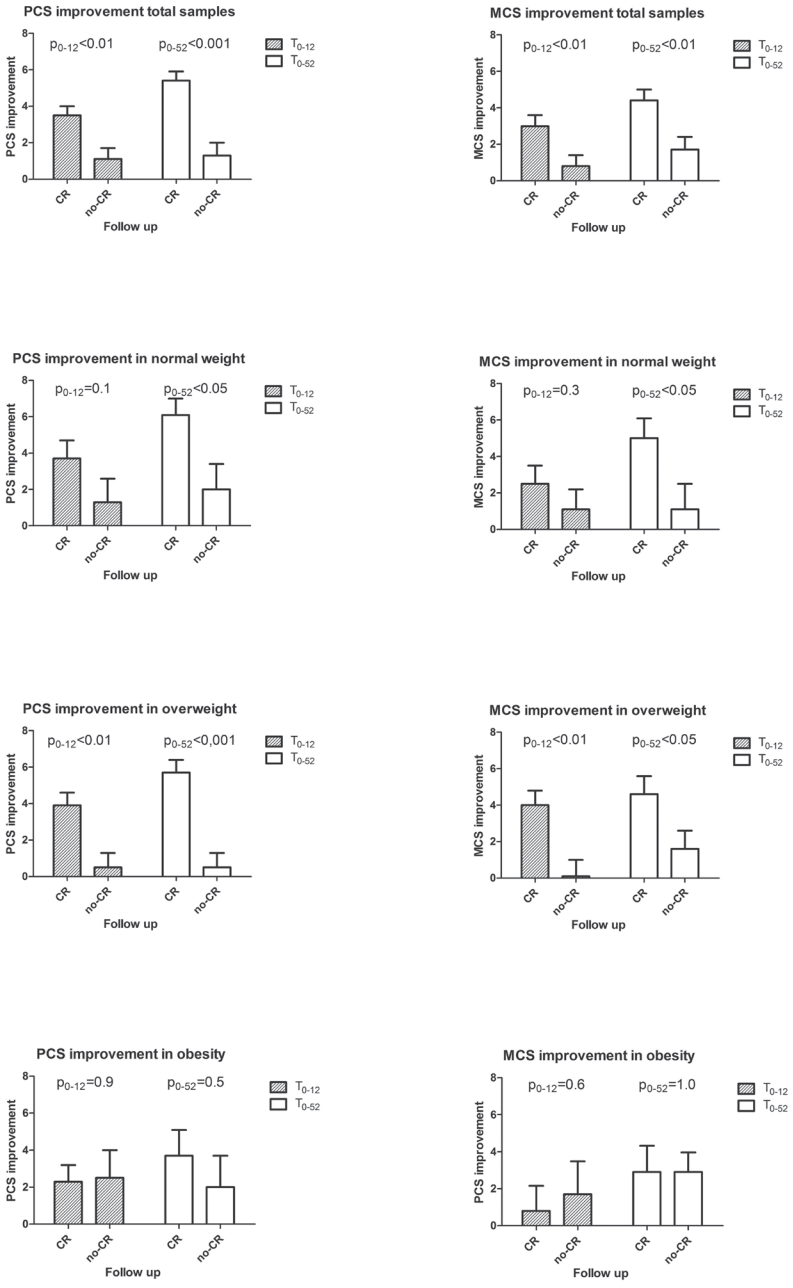

Figure 8.2. Changes in subjective health status for the CR and no-CR groups. Bars are mean scores and error bars represent standard deviations. Abbreviations: CR, cardiac rehabilitation group; MCS, mental component score; no-CR, no cardiac rehabilitation group; PCS, physical component score; $T_{0\text{-}12}$, changes in PCS or MCS between baseline and follow-up at 12 weeks; $T_{0\text{-}52}$, changes in PCS or MCS between baseline and follow-up at 52 weeks. *P*0-12 based on differences between CR versus no-CR for changes from $T_{0\text{-}12}$. $P_{0\text{-}52}$ based on differences between CR versus no-CR for changes from $T_{0\text{-}52}$.

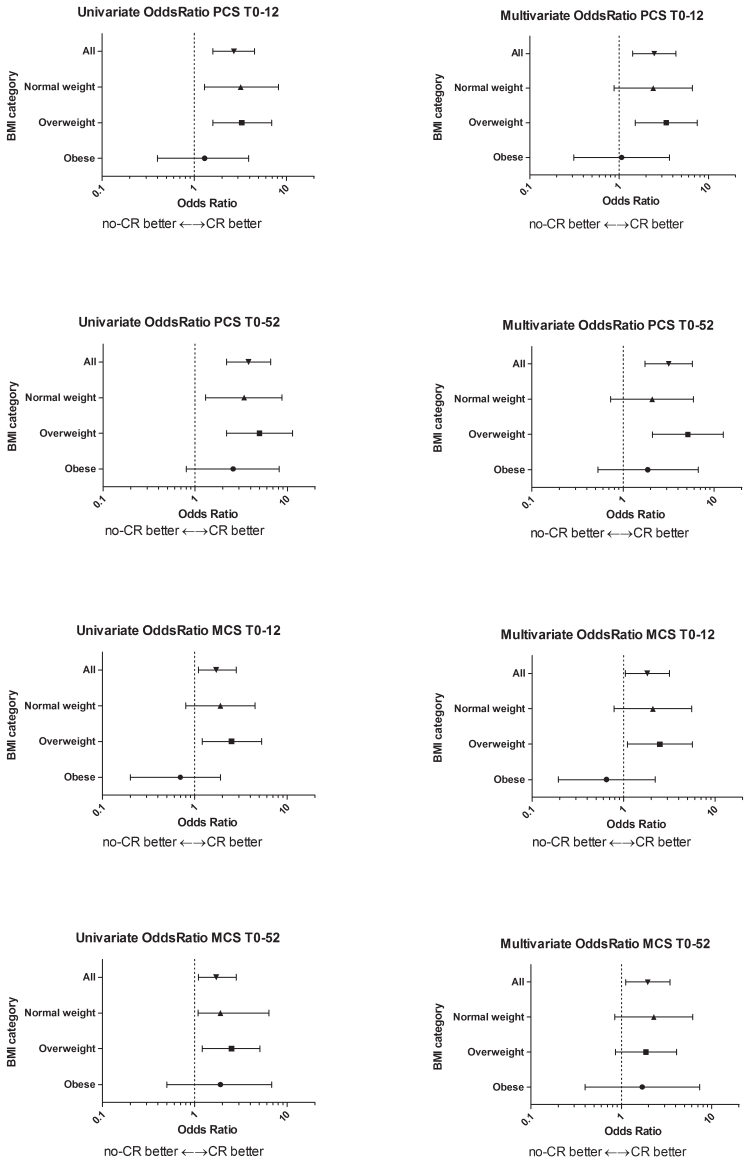

Figure 8.3. Association between CR vs no-CR groups and improvement in subjective health status for separate BMI categories. Univariate and multivariate odds ratios with 95% confidence intervals for CR compared to no-CR for being in the tertile with the best improvement in subjective health status. Multivariate analysis adjusted for age, gender, education level, number of diseased coronary arteries found during PCI, smoking, diabetes mellitus, family history, cardiac history (previous myocardial infarction, previous coronary artery bypass grafting and/or previous percutaneous coronary intervention) and depressive symptoms (a 2-item Patient Health Questionnaire score ≥2). Abbreviations: BMI, body mass index; CR, cardiac rehabilitation group; MCS, mental component score; no-CR, no cardiac rehabilitation group; PCI, percutaneous coronary intervention; PCS, physical component score; $T_{0\text{-}12}$, change in subjective health status between baseline and follow-up at 12 weeks; $T_{0\text{-}52}$, change in subjective health status between baseline and follow-up at 52 weeks.

Table 8.1 Patient Characteristics[a]

BMI Category	CR n = 242 (68%)			no-CR n = 115 (32%)			Total CR/no-CR n = 357		
	Normal Weight n = 75 (31%)	Overweight n = 122 (50%)	Obese n = 45 (19%)	Normal Weight n = 36 (31%)	Overweight n = 59 (51%)	Obese n = 20 (17%)	CR n = 242 (68%)	no-CR n = 115 (32%)	*P* Value
Age, y	58 ± 10	59 ± 9	58 ± 9	66 ± 12	63 ± 11	62 ± 10	59 ± 10	64 ± 11	<.001
BMI, kg/m^2	23 ± 1	27 ± 1	33 ± 2	23 ± 2	27 ± 1	33 ± 3	27 ± 4	27 ± 4	.7
Male, n (%)	52 (69)	107 (88)	40 (89)	27 (75)	54 (92)	15 (75)	199 (82)	96 (83)	.9
History, n (%)									
CVA	1 (1)	2 (2)	0 (0)	1 (3)	3 (5)	0 (0)	3 (1)	4 (3)	.2
Cardiac event[b]	9 (12)	15 (12)	4 (9)	6 (17)	15 (25)	4 (20)	28 (12)	25 (22)	<.05
AMI	6 (8)	9 (7)	1 (2)	6 (17)	7 (12)	4 (20)	16 (7)	17 (15)	<.05
PCI	8 (11)	10 (8)	3 (7)	5 (14)	11 (19)	2 (10)	21 (9)	18 (16)	.07
CABG	1 (1)	0 (0)	1 (2)	1 (3)	1 (2)	1 (5)	2 (1)	3 (3)	.3
Multivessel disease	24 (32)	44 (36)	15 (33)	15 (42)	26 (44)	10 (50)	83 (34)	51 (44)	.1
Risk factors, n (%)									
Smoking	29 (39)	51 (42)	21 (47)	13 (36)	18 (31)	3 (15)	101 (42)	34 (30)	<.05
Cholesterol	27 (36)	50 (41)	19 (42)	12 (33)	24 (41)	8 (40)	96 (40)	44 (38)	.8
Hypertension	26 (35)	41 (34)	24 (53)	9 (25)	17 (29)	12 (60)	91 (38)	38 (33)	.4
Diabetes mellitus	6 (8)	15 (12)	10 (22)	3 (8)	8 (14)	3 (15)	31 (13)	14 (12)	.9
Family history	41 (55)	78 (64)	25 (56)	12 (33)	25 (42)	8 (40)	144 (60)	45 (39)	<.001
COPD	4 (5)	4 (3)	0 (0)	4 (11)	1 (2)	1 (5)	8 (3)	6 (5)	.4
Depression[c]	11 (15)	26 (22)	17 (38)	4 (12)	12 (20)	5 (25)	54 (23)	21 (19)	.4
Baseline HRQL									
PCS baseline	46 ± 8	46 ± 9	45 ± 9	46 ± 11	49 ± 9	46 ± 8	46 ± 9	48 ± 10	.06
MCS baseline	46 ± 10	44 ± 11	44 ± 12	49 ± 9	49 ± 11	47 ± 10	45 ± 11	49 ± 10	<.01

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; CVA, cerebral vascular accident; HRQL, health-related quality of life;
MCS, mental component score; no-CR, no cardiac rehabilitation group; PCI, percutaneous coronary intervention; PCS, physical component score.

[a] Data are reported as mean ± standard deviation unless otherwise noted.

[b] PCI, CABG and/or AMI.

[c] Depression was defined as a score ≥2 on the 2-item Patient Health Questionnaire.

Chapter 9

OPTIMAL CARDIAC REHABILITATION (OPTICARE) FOLLOWING ACUTE CORONARY SYNDROMES: RATIONALE AND DESIGN OF A RANDOMIZED CONTROLLED TRIAL TO INVESTIGATE THE BENEFITS OF EXPANDED EDUCATIONAL AND BEHAVIOURAL INTERVENTION PROGRAMS

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ABSTRACT

The majority of cardiac rehabilitation (CR) referrals consist of patients who have survived an acute coronary syndrome (ACS). Although major changes have been implemented in ACS treatment since the 1980s, which highly influenced mortality and morbidity, CR programs have barely changed and only few data are available on the optimal CR format in these patients. We postulated that standard CR programs followed by relatively brief maintenance programs and booster sessions, including behavioural techniques and focusing on incorporating lifestyle changes into daily life, can improve long-term adherence to lifestyle modifications. These strategies might result in improved (cardiac) mortality and morbidity in a cost-effective fashion. In the OPTImal CArdiac REhabilitation (OPTICARE) trial we will assess the effects of two advanced and extended CR programs that are designed to stimulate permanent adoption of a heart-healthy lifestyle, compared with current standard CR, in ACS patients. We will study the effects in terms of cardiac risk profile, levels of daily physical activity, quality of life and health care consumption.

INTRODUCTION

Healthy lifestyle management is becoming increasingly important in the Western world, as the incidence of obesity, hypertension, and diabetes is taking on epidemic proportions.[1-3] According to the World Health Organisation, 75% of cardiovascular diseases could be prevented by optimal lifestyle management.[4] Indeed, the INTERHEART investigators have demonstrated that 90% of (first) myocardial infarctions (MI's) could be attributed to nine modifiable risks, including hypertension, diabetes, and hypercholesterolemia.[5] Furthermore, smoking cessation, physical activity, moderate alcohol consumption and combined dietary changes are associated with mortality risk reductions of 20–45% in patients with coronary artery disease (CAD).[6]

Several cardiac rehabilitation (CR) programs have been developed since the 1980s for CAD patients, which offer a variety of interventions that aim to stimulate an active and healthy lifestyle. In meta-analyses it has been demonstrated that these programs effectively reduce the 1-year incidence of total mortality, cardiovascular mortality and nonfatal MI.[7,8] However, these initial beneficial results were not maintained during longer-term follow-up.[9] The lifestyle changes adopted during the rehabilitation period were probably not incorporated into daily routine.

Throughout the past decades, patients who are referred for CR constitute a heterogeneous and dynamically changing population. Nowadays, the majority of CR referrals consist of patients who have survived an acute coronary syndrome (ACS). Major changes have been implemented in ACS treatment since the 1980s, which have highly influenced mortality and morbidity. Currently, most ACS patients undergo percutaneous coronary intervention (PCI) in the acute phase, and receive antiplatelet therapy, lipid lowering therapy and other cardio protective medication during long-term follow-up. As a result, ACS patients usually have preserved left ventricular function and, consequently, a good survival.[10,11] Also, the duration of the hospital stay after ACS is considerably reduced; the current average is approximately only 5 days.[12] Interestingly, CR programs have barely changed since the 1980s, and only few data are available on the optimal CR format in ACS subjects.[13-15]

The favourable developments in ACS treatment have, however, an important downside: ACS patients have less time for reflection on the event they experienced. The contact time with healthcare professionals during the acute phase is limited, whereas in this period patients might be most open to accept (lifestyle) advice to avoid future cardiac events. In order to adapt and maintain a heart-healthy lifestyle, ACS patients therefore probably need more guidance in the subacute phase than is currently offered in CR programs. Recently, some successful maintenance programs have been presented.[16-18] However, these programs consist of high frequency contacts during long-term follow-up, and may therefore not be cost-effective. We postulated that CR programs followed by relatively brief maintenance programs and booster sessions, including behavioural techniques and focusing on incorporating lifestyle changes into daily life, can also improve long-term adherence to

lifestyle modifications.[16,19,20] These strategies might result in improved (cardiac) mortality and morbidity in a cost-effective fashion.

In the OPTImal CArdiac REhabilitation (OPTICARE) trial we will assess the effects of two advanced and extended CR programs that are designed to stimulate permanent adoption of a heart-healthy lifestyle, compared with current standard CR, in ACS patients. We will study the effects in terms of cardiac risk profile, levels of daily physical activity, quality of life and health care consumption.

OBJECTIVES

Primary objectives

The primary objective of OPTICARE is to evaluate the effectiveness of extended CR programs in patients who have experienced an ACS. The programs combine physical activities, psychosocial counselling and personal coaching. Effectiveness will be expressed in terms of levels of daily physical activity and (reduction in) estimated cardiovascular risk, which will be measured by the Systematic Coronary Risk Evaluation (SCORE) function.[21]

Secondary objectives

We have defined the following secondary objectives:

- To evaluate the effects of the extended CR programs on physical fitness, body mass index (BMI), waist circumference, health care consumption, quality of life, return to work, occurrence of anxiety and depression, and cardiovascular events;
- To evaluate which health benefits (cardiac risk profile, physical fitness, quality of life, anxiety, depression, participation, fatigue, health care consumption) are associated with improved levels of physical activity;
- To investigate whether extended CR is more cost-effective than standard care.

METHODS

The OPTICARE trial is a multicentre, open, multidisciplinary randomised controlled trial with a 6-month follow-up. The PRospective Open, Blinded Endpoint (PROBE) design will be applied, and an independent Clinical Event Committee will verify all cardiac events. [22] The protocol and procedures of OPTICARE were approved by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands.

Each patient will receive oral and written information on the trial objectives, study design, and advantages and disadvantages of study participation. A signed informed consent form by the patient is a prerequisite for participation in the trial.

Patient selection

OPTICARE is designed for patients with a documented ACS who are referred for CR. ACS is defined as persistent (>20 min) chest pain suggestive of myocardial ischaemia, which is unresponsive to nitro-glycerine and which is accompanied by ST-T changes (electrocardiographic evidence) and/or cardiac troponin elevations (biochemical evidence), regardless of in-hospital treatment. A total of 10 hospitals in the broader region of Rotterdam—The Hague refer their ACS patients to the local Capri Centre, which offers a standard CR program that is consistent with the Dutch guidelines.[23,24]

Allocated treatment

Eligible patients who consent to participate in the trial will be randomly allocated to one of three treatment strategies (Table 9.1), following inclusion and exclusion criteria as mentioned in Table 9.2. Randomisation will be performed by using sequentially numbered, opaque, sealed envelopes with information on allocated treatment. The envelopes will be prepared by an independent statistician, who uses a random number generator to construct the treatment sequence. The allocation process will be monitored to preserve randomness and concealment.

1) CR-only

Standard care (or: CR-only) consists of standard CR according to the Dutch guidelines as is currently offered to all patients referred to Capri Cardiac Rehabilitation.

CR-only is a group exercise program of 1.5 h that is offered 2 times a week for 12 weeks under the supervision of a physiotherapist. Participation in multifactor lifestyle and cardiovascular risk factor group education sessions is offered to all patients, and comprises: information on cardiovascular diseases risk factors, medical information, dietary advice, and advice on coping with emotions. If indicated, there is an option to participate in a smoking cessation program, nutritional counselling sessions, stress management sessions or an individually based psychological program.

At the start of the program, each patient will undergo an intensive interview to determine his/her individual program. Only the physical training program is strictly obligatory; the counselling and group sessions will be attended upon motivation of each patient.

2) CR+T (CR+ Telephonic counselling)

The 2nd strategy is based on the COACH study that demonstrated favourable effects of personal coaching.[20] In the CR+T arm of the trial, standard CR is extended with five telephone coaching sessions with an interval of 5–6 weeks during the first 6 months after completion of standard CR. The coaching sessions intend to keep the patient aware of his or her cardiovascular risk factors, and on methods learned to improve cardiovascular health. The personal coaching is offered by specialised nurses, who are trained to stimulate patients to pursue the target levels for their particular coronary risk factors. This COACH based strategy consists of coaching the patient in a process of continuous improvement in coronary risk factors. Patients are stimulated to develop a personal plan of action in which they measure their coronary risk factors (e.g. at their general practitioner's office), define their targets, act upon, measure again, etc. Patients are also persuaded to adopt and adhere to appropriate lifestyle measures, including a healthy diet, persistent smoking cessation, and daily physical activities at moderate intensity.

3) CR+F (CR+ Face-to-face counselling)

The 3rd strategy, CR+F, is another extension of standard CR. Patients who are allocated to this strategy have a commitment during CR to participate in the multifactorial lifestyle and cardiovascular risk factor management group sessions (rather than participation on a voluntary basis). Besides, during standard CR patients will participate in three group counselling sessions under the supervision of a physiotherapist to promote an active lifestyle (aiming at regular exercise of moderate intensity for 30 min at least 5 times a week). The intrinsic motivation of the patient to change behaviour will be encouraged by the motivational interviewing technique which has shown to be effective in improving activity levels in daily life.[25,26] To provide feedback on the patient's home activity, pedometers (Yamax Digiwalker SW-200) will be provided.[27] Finally, at 4, 6 and 12 months after the start of the program the patients will again be required to participate in multifactor lifestyle and cardiovascular risk factor group sessions of 2 h each in which maintenance of healthy lifestyle behaviour (including physical activity) is discussed to increase long-term adherence. These group sessions are led by physiotherapists, social workers, dietician, nurses and physicians and are based on self-regulation. Finally, in patients randomised to CR+F, the cholesterol and blood pressure levels will be monitored and medication will be adjusted when needed. The target level will be: LDL ≤1.8 mmol/l and systolic blood pressure (SBP) <140 mmHg.

Table 9.1 Treatment arms

CR-only	• Standard CR
CR+T	• Standard CR • 5 Telephone calls after completion of standard CR for 6 months with an interval of 5 a 6 weeks
CR+F	• Standard CR with obligation to participate in the multifactorial lifestyle and cardiovascular risk factor management group sessions • 3 Counselling sessions during standard CR with an interval of 1 month to promote an active lifestyle • 3 Multifactorial lifestyle and risk factor group sessions after completion of standard CR (at 4/6/12 months post randomization) Titration of medication to LDL level<=1.8 mmol/l and SBP<=140 mmHg

CR-only= standard cardiac rehabilitation; CR+T= cardiac rehabilitation plus individual telephonic counselling; CR+F= cardiac rehabilitation plus face-to-face group counselling.

Table 9.2 Inclusion and exclusion criteria

Inclusion criteria	• Recent acute coronary syndrome • Age over 18 years • Proficient in the Dutch language • Providing written informed consent
Exclusion criteria	• Heart failure and/or impaired left ventricular function (left ventricular ejection fraction <40 %) • Angina NYHA Class II–IV • Psychological or cognitive impairments which may limit cardiac rehabilitation • Congenital heart disease • Chronic obstructive pulmonary disease Gold classification ≥II • Diabetes with organ damage • Locomotive disorders that will preclude participation in an exercise training program • Implantable cardio-defibrillator (ICD) • Renal failure needing follow-up by a nephrologist • Intermittent claudication impairing CR exercises

CR = cardiac rehabilitation.

Data collection

Apart from the baseline clinical characteristics, the following data will be collected by the OPTICARE team in all patients at baseline (i.e. prior to CR), at the end of standard CR, and at 1 year and 1.5 year after inclusion:

1) The 10-year CVD mortality risk according to the SCORE risk chart, which is based on the following factors[21]:

- Age
- Sex
- Total cholesterol and HDL cholesterol measured in blood samples after fasting for a minimum of 8h
- Systolic blood pressure as measured by a trained nurse
- Smoking status determined during an interview by one of the social workers of the Capri cardiac rehabilitation centre. The concentration of carbon monoxide in breath will be measured using a breath analyser (Smokerlyzer®).

2) The level of everyday physical activity:

The level of everyday physical activity is objectively measured with a validated accelerometry-based activity monitor (Actigraph GT3X, Fort Walton Beach, Florida), for 7 consecutive days in the home situation. The Actigraph is a small device worn on a belt around the waist that measures and records movement, movement intensity and duration. The Actigraph is the most widely used (commercially available) accelerometer and different studies report acceptable to good validity.[28]

3) A broad spectrum of characteristics and risk factors that determine cardiovascular health:

- Medication
- Blood glucose, blood lipids, and glomerular filtration rate. All blood samples are taken after a minimum of 8 h of fasting
- Body mass index (BMI) and waist circumference
- Physical fitness assessed by a 6-minute walk test and a 5 times sit-to-stand test
- Working, marital, and educational status
- Information on return-to-work, quality of life, anxiety and depression, health care consumption, illness perception, medication adherence, perceived physical activity, fatigue, self-efficacy, type D personality, social participation and movement fear. We will use validated questionnaires to obtain these data (Table 9.3).

Study endpoints and sample size

The primary study endpoint is the SCORE Risk Score that is measured 1.5 years post randomisation. The RESPONSE trial[29] studied the effectiveness of a nurse-coordinated outpatient risk management program in cardiac patients. That strategy was associated with a 17% reduction in SCORE Risk Score as compared with standard care.[21] Based on these data,

and taking into account the more intensive interventions that we will perform, we expect in both the CR+F and in the CR+T arm at least a 20% reduction in the SCORE Risk Score at 1.5 years: from 5.40 to 4.32 points with an estimated standard deviation (SD) of 4.5. With 274 patients in each treatment arm, the study has 80% power (beta-error=0.02) to detect this difference with an alpha-error of 0.05 (2-sided test). We will enrol a total of 300 patients in each treatment arm, taking into account a 10% drop-out rate.

Secondary endpoints include all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, rehospitalisation for heart failure, re-hospitalisation for angina, admission to the emergency room, non-fatal stroke, and coronary intervention. All clinical endpoints will be monitored and verified by an independent Clinical Event Committee.

Table 9.3 Questionnaires

KVL H: Quality of Life Questionnaire[38]
HADS: Hospital Anxiety and Depression Scale[39]
IPQ: Illness Perception Questionnaire[40]
IPAQ: Self-perceived level of daily physical activity: International Physical Activity Questionnaire[41]
FSS: Fatigue Severity Scale[42]
DS14: Type-D personality[43]
USER P: User-Participation[44]
AVI scale: “Angst Voor Inspanning”(i.e. fear of movement: self-designed questionnaire)
Smoking behaviour, self-designed questionnaire
EQ5D[45]
GSE: General Self-Efficacy[46]

Cost effectiveness analysis

A cost-effectiveness analysis will be performed in accordance with the current Dutch guidelines (Guidelines for Pharmaco-economic Evaluations).[30] Costs will therefore be calculated from both the health care sector and the societal perspective (where all costs are included in the analysis regardless of who incurs them). Costs will include direct medical costs, patient costs, and productivity losses. Unit prices for the most important cost items will be determined using the micro-costing method, which is based on a detailed inventory and measurement of all resources used. The primary health outcome will be quality-adjusted life-years. Short-term costs and effectiveness will be based on observed outcomes measured in this trial. Lifetime costs and health outcomes will be calculated with a Markov model using data from this trial in combination with literature data. Future costs and life-years will be discounted at 4% and 1.5% respectively. Extensive (probabilistic) sensitivity analyses and value of information analysis will be performed. Cost-effectiveness will be assessed by calculating the incremental cost-effectiveness ratio, which is the difference between the mean costs of two treatment strategies divided by the difference in their mean effects (e.g. life years).[31]

DISCUSSION

Over the past years it has been demonstrated that standard CR reduces morbidity and mortality in patients with CAD.[7,8,14,15] An extended CR program consisting of supervised 30 min aerobic exercise, comprehensive lifestyle and risk factor counselling sessions may even further benefit patients in the long term, as shown in the GOSPEL trial.[16] However, it should be realised that in this trial multiple (11 sessions in 3 years) and thus costly interventions were done. In the COACH trial a limited number of telephone interventions also had beneficial effects.[20] However, in that trial only approximately half of the patients underwent CR and the beneficial effect of the COACH intervention in the CR subgroup is unknown. This is an important limitation of the COACH trial since standard CR is recommended in the Dutch guidelines.[24] In the OPTICARE study we will investigate in a separate study arm whether the COACH approach (CR+T arm) still has beneficial effects in patients who suffered from an ACS and who subsequently underwent standard CR. In addition, the effects of a more time-consuming CR+F arm, including a limited number of extra sessions to promote a healthy lifestyle with a focus on physical activity, will be studied.

Secondary prevention after an ACS has several components. Preventive medication should be started and titrated to optimal doses by the physician according to current guidelines.[11] In addition, modifiable risk factors (diabetes, hypertension, cholesterol, smoking, overweight, sedentary lifestyle) should be inventoried and appropriate action should be taken in a combined effort of the patient and physician. In most studies the pharmacological components of the program showed benefits[11,16,20], but strategies to promote smoking cessation and in particular physical activity and weight loss are needed. Therefore, in this study, we will focus on reaching long-term lifestyle changes, with a special focus on increasing the level of physical activity. Lifestyle inactivity is an important cardiovascular risk factor and related to several cardiac risk factors such as lipid profile, blood pressure and body composition.[32] Despite the well-known beneficial effects of CR on physical fitness, mortality and quality of life[31,33], only little is known about the effects of CR programs on the level of daily physical activity after CR. In some studies positive effects on daily physical activity after CR have been shown[9,34], but it has also been reported that physical activity tends to decline 6 to 12 months after completion of standard CR.[9,35] Furthermore, results from a study in patients with chronic heart failure suggest that improved physical fitness does not automatically result in a more active lifestyle.[36] The CR+F arm aims to incorporate daily physical activity in one's life and thus promotes long-term adherence by maintenance programs and booster sessions at 4, 6 and 12 months post randomisation.

In this era of financial constrains it is essential to not only show beneficial effects of an intervention but also the cost-effectiveness of the intervention. This may be particularly true for comparing the less intensive CR+T arm, involving just some telephone contacts, with the more extensive CR+F arm. Therefore, a full ex-post economic evaluation of both extended CR programs and standard CR will be performed.[37]

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Chapter 10

RANDOMISED CONTROLLED TRIAL OF TWO ADVANCED AND EXTENDED CARDIAC REHABILITATION PROGRAMMES

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ABSTRACT

Objective

The OPTICARE (OPTImal CArdiac REhabilitation) randomised controlled trial compared two advanced and extended cardiac rehabilitation (CR) programmes to standard CR for patients with acute coronary syndrome (ACS). These programmes were designed to stimulate permanent adoption of a heart-healthy lifestyle. The primary outcome was the SCORE (Systematic COronary Risk Evaluation) 10-year cardiovascular mortality risk function at 18 months follow-up.

Methods

In total, 914 patients with ACS (age, 57 years; 81% men) were randomised to: (1) 3 months standard CR (CR-only); (2) standard CR including three additional face-to-face active lifestyle counselling sessions and extended with three group fitness training and general lifestyle counselling sessions in the first 9 months after standard CR (CR+F); or (3) standard CR extended for 9 months with five to six telephone general lifestyle counselling sessions (CR+T).

Results

In an intention-to-treat analysis, we found no difference in the SCORE risk function at 18 months between CR+F and CR-only (3.30% vs 3.47%; p=0.48), or CR+T and CR-only (3.02% vs 3.47%; p=0.39). In a per-protocol analysis, two of three modifiable SCORE parameters favoured CR+F over CR-only: current smoking (13.4% vs 21.3%; p<0.001) and total cholesterol (3.9 vs 4.3 mmol/L; p<0.01). The smoking rate was also lower in CR+T compared with CR-only (12.9% vs 21.3%; p<0.05).

Conclusions

Extending CR with extra behavioural counselling (group sessions or individual telephone sessions) does not confer additional benefits with respect to SCORE parameters. Patients largely reach target levels for modifiable risk factors with few hospital readmissions already following standard CR.

INTRODUCTION

Most cardiac rehabilitation (CR) referrals are for patients with acute coronary syndrome (ACS). Although major changes have been implemented in ACS treatment during recent decades, CR programmes have changed little since the 1980s, and little data are available about optimal CR format. Most patients with ACS undergo percutaneous coronary intervention acutely and receive cardio protective medication during long-term follow-up. As a result, the prognosis for these patients has improved significantly[1], and hospital stays have been reduced to 3–4 days. Consequently, healthcare professionals have limited time to increase patient awareness of important lifestyle changes, and CR has become even more important. Although current CR has been shown to reduce mortality and non-fatal myocardial infarction (MI)[2,3], these benefits do not persist over long term follow-up.[4] Patients with ACS likely would benefit from more guidance during the subacute phase.

The OPTICARE (OPTImal CArdiac REhabilitation) randomised controlled trial (RCT) compared two extended CR programmes with standard CR in patients with ACS. One programme included face-to-face group counselling sessions, whereas the other was based on individual telephone contact between patients and a personal coach. Both novel programmes focused on incorporating lifestyle changes into daily life and included behavioural techniques such as goal setting and relapse prevention, which have previous evidence of effectiveness.[5,6] We designed OPTICARE to evaluate the long-term effects of extended CR on the SCORE (Systematic COronary Risk Evaluation) function and its modifiable components of systolic blood pressure (SBP), total cholesterol and smoking behaviour.[7] The novel interventions may provide additional emotional support, and consequently, improve quality of life, anxiety and depression.

METHODS

The OPTICARE trial was an open, randomised controlled superiority trial; the full study design has been published previously.[8] The trial, which was registered at ClinicalTrials.gov (NCT01395095), used the PROBE (PRospective Open, Blinded Endpoint) design.[9] The protocol was approved by the Medical Ethics Committee of Erasmus Medical Center, Rotterdam, the Netherlands (MEC-2010391). All patients provided written informed consent prior to enrolment.

Patients

OPTICARE was designed for patients with documented ACS who were referred for CR (see cardiovascular event definition in Appendix 10A). A total of 10 hospitals in the greater region of Rotterdam-The Hague referred patients with ACS to the local Capri Cardiac Rehabilitation Center. Exclusion criteria are provided in Appendix 10A.

Treatment allocation

For a complete explanation of interventions, please see Appendix 10A.

Standard CR (CR-only)

Standard care consisted of CR based on the Dutch, European Society of Cardiology, and American College of Cardiology/ American Heart Association guidelines (Figure 10.1).[10,11] This CR programme consisted of a group exercise programme with 1.5-hour training sessions offered twice weekly for 12 weeks, under the supervision of a physiotherapist. Participation in multifactor lifestyle and cardiovascular risk factor group education sessions was offered to all patients.

Standard CR extended with group counselling sessions (CR+F)

During the 12-week period of standard CR, three additional face-to-face physical activity group counselling sessions were organised (Figure 10.1). Additionally, patients were required to participate in face-to-face group sessions at 4, 6 and 12 months, which each lasted 2 hours and consisted of a 1-hour exercise programme and a 1-hour behavioural counselling session on a heart-healthy lifestyle (eg, physical activity and healthy diet).

Standard CR extended with individual telephone counselling sessions (CR+T)

In the CR+T arm, standard CR was extended with five to six individual telephone coaching sessions at 5 to 6-week intervals following completion of standard CR (Figure 10.1). Patients were coached to develop a personal plan for a heart-healthy lifestyle. The personal coaching was offered by the Medical Service Center of the health insurance company 'Zilveren Kruis', which consisted of specialised nurses.

Randomisation

Patients were randomly allocated to one of the three groups in a 1:1:1 ratio. Randomisation was performed using sequentially numbered, opaque, sealed envelopes, which were prepared by an independent statistician using a computer random number generator. Allocation was monitored throughout recruitment by a contract research associate to preserve randomness and concealment. Randomisation was performed at the start of CR, which was, on average, 6 weeks after ACS and 1–2 weeks after the first outpatient clinic visit after ACS diagnosis.

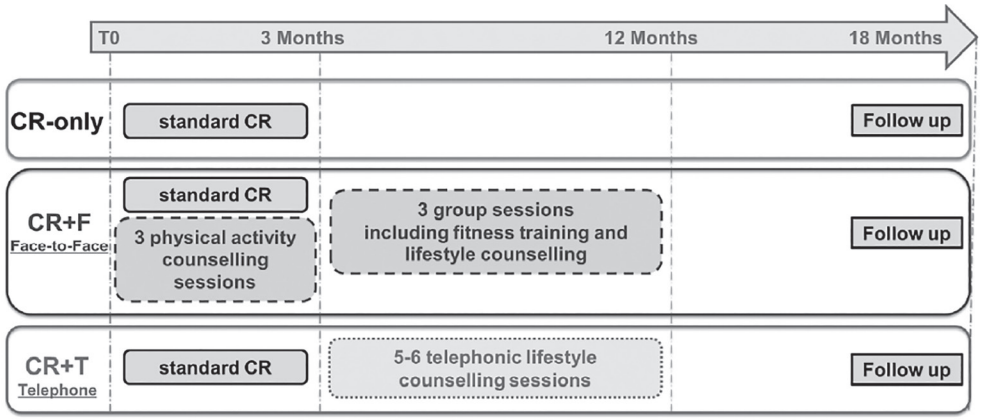

Figure 10.1 Study design and treatment allocation
CR= cardiac rehabilitation

Outcome measures

The primary endpoint was the SCORE risk function at 18-month follow-up (ie, 6 months after completion of interventions) to assess improvements in long-term adherence. SCORE has been validated to estimate 10-year risk of cardiovascular death based on age, sex, total cholesterol, SBP and smoking behaviour.[7,12] For all SCORE calculations, baseline age was used. SCORE was not computed until after the last patient completed the study. Secondary endpoints included modifiable factors comprising the SCORE, number of modifiable risk factors on target (ie, SBP≤140 mm Hg, diastolic blood pressure ≤90 mm Hg, body mass index (BMI) ≤25, waist circumference ≤94 cm for men and ≤80 cm for women, low-density lipoprotein (LDL) <1.8 mmol/L, total cholesterol ≤4.5 mmol/L, smoking cessation, no anxiety, no depression), quality of life (MacNew Questionnaire)[13] and the presence of anxiety and depression (Hospital Anxiety and Depression Scale (HADS)).[14] Cut-off values for depression and anxiety were scores of 8 or higher on respective subscales of the HADS (see Appendix 10A). During each visit, weight, waist circumference, SBP, BMI, total cholesterol, high-density lipoprotein cholesterol, LDL cholesterol and triglycerides were assessed. Clinical events were

verified by an independent committee. All measurements were performed at baseline (start of standard CR), at 3 months (end of standard CR) and at 18 months after randomisation.

Sample size calculation

An earlier study found a 17% reduction in SCORE for patients participating in a nurse-coordinated intervention programme compared with patients receiving standard care.[15] Based on those data and considering that more intensive interventions were used in the present study, at least a 20% reduction in SCORE at 18 months was expected for both CR+F and CR+T groups (decrease from 5.40 to 4.32 points, with an estimated SD of 4.5 (superiority design)) (Cohen's effect size d=0.24). With 274 patients in each treatment arm, the study had 80% power (beta=0.20) to detect this difference with a two-sided alpha of 0.05. In total, 914 patients were enrolled to account for a 10% expected dropout rate.[18] In all analyses, CR+F was compared with CR-only, and CR+T was compared with CR-only.

Statistical analysis

Primary analysis: intention-to-treat

All randomised patients' data were included in the intention-to-treat (ITT) analysis. The continuous, non-normally distributed, SCORE risk function was reported as median and IQR, and groups were compared using Wilcoxon's rank-sum test. The difference in SCORE risk function delta (Δ) scores between 18 months and baseline was compared between CR+F and CR-only and between CR+T and CR-only, using a Student's t-test. Secondary continuous outcome variables were presented as mean, SD, and 95% CIs, and 18-month outcomes and Δ (18 months to baseline) were compared using Student's t-tests. Normality was checked with the Kolmogorov-Smirnov tests. Categorical variables were compared using $\chi 2$ tests or Fisher's exact tests where appropriate. There was no need to correct for multiple testing. SPSS software (V.24.0, SPSS) was used for the statistical analyses.

Secondary analyses: per-protocol

Patient completion of 75% of standard CR (at least 18 training sessions) and 75% of the extended programmes (at least four of six group counselling sessions and at least three of five telephone sessions) was required to be included in the per-protocol analyses. The same analyses described for the ITT analyses were performed for the per-protocol analyses. Results from these two statistical strategies were compared.

RESULTS

Between November 2011 and August 2014, a total of 914 patients with ACS were randomised and included in the ITT analysis (CR+F: n=309; CR+T: n=299; CR-only: n=306; Figure 10.2). Main reasons to decline participation in this trial were transportation issues, motivation and lack of time. Randomly allocated treatment was completed by 60.5% of patients in the CR+F group, 56.8% in the CR+T group and 82.3% in the CR-only group. The three groups were well balanced with respect to baseline characteristics (Table 10.1). The mean patient age was 57 years, and 81% were male. The pre-ACS smoking rate of 43% had decreased to 15% by randomisation. At baseline, more than 75% of patients met blood pressure targets, and nearly 70% met total cholesterol targets. At that time, 97% of patients were taking aspirin and statins, 84% beta blockers and 70% ACE inhibitors.

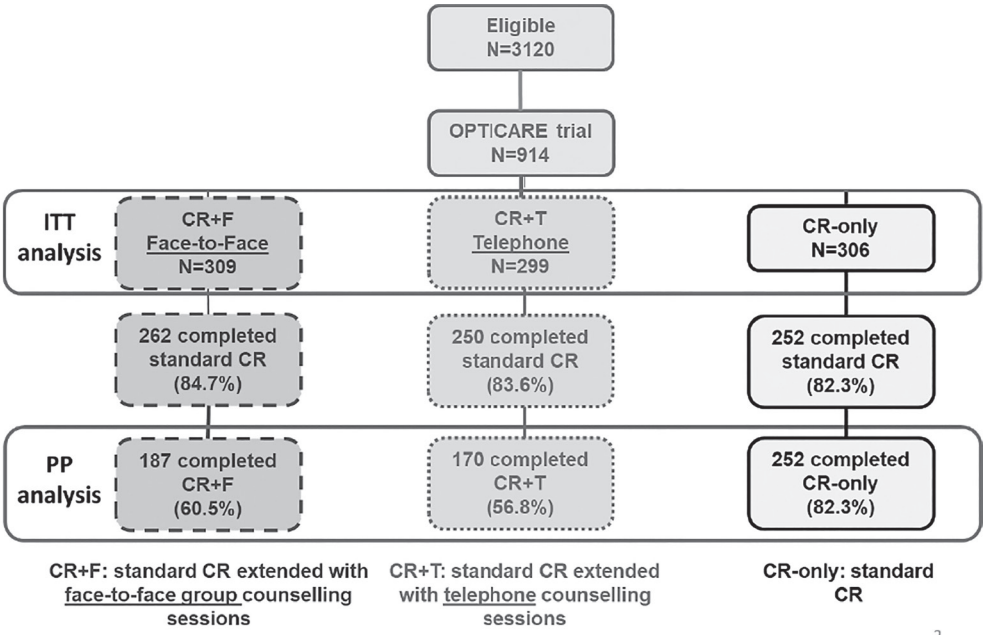

Figure 10.2 CONSORT (CONsolidated Standards Of Reporting Trials) flow diagram
CR= cardiac rehabilitation; CR+F = standard CR extended with face-to-face group counselling sessions; CR+T= standard CR extended with telephone counselling sessions; CR-only= standard CR; ITT= intention-to-treat; OPTICARE= OPTImal CArdiac Rehabilitation; PP= per-protocol.

Table 10.1 Patients characteristics by treatment group

	CR+F	CR+T	CR-only	p
	N=309	N=299	N=306	
Age (years), mean (±SD)	57.5 (±9.2)	57.1 (±9.7)	57.4 (± 9.3)	0.91
Male	245 (79.3%)	246 (82.9%)	246 (80.4%)	0.52
Therapeutic intervention at index event				0.37
No revascularization	22 (7.1%)	29 (9.7%)	25 (8.2%)	
PCI	250 (80.9%)	224 (74.9%)	239 (78.1%)	
CABG	37 (12.0%)	46 (15.4%)	42 (13.7%)	
Cardiac history				
Myocardial infarction	22 (7.1%)	31 (10.4%)	27 (8.8%)	0.37
PCI	25 (8.1%)	29 (9.7%)	35 (11.4%)	0.32
CABG	4 (1.3%)	2 (0.7%)	7 (2.3%)	0.23
Angina	14 (4.5%)	18 (6.0%)	20 (6.5%)	0.54
Stroke/TIA	12 (3.9%)	4 (1.3%)	8 (2.7%)	0.26
Risk Factors				
Diabetes	44 (14.2%)	34 (11.4%)	43 (14.1%)	0.51
Dyslipidaemia	90 (29.1%)	100 (33.4%)	122 (39.9%)	0.018
Family history	165 (53.4%)	148 (49.5%)	167 (54.6%)	0.43
Current Smoking (pre-ACS)	138 (44.7%)	127 (42.9%)	129 (42.2%)	0.79
Hypertensions	135 (43.7%)	119 (39.8%)	120 (39.2%)	0.47
Renal Impairment[*]	11 (3.7%)	13 (4.2%)	6 (2.0%)	0.28
Cardiac medication				
Acetylsalicyllic acids	293 (94.8%)	291 (97.3%)	297 (97.1%)	0.19
Thienopyridines	262 (84.8%)	244 (81.6%)	264 (86.3%)	0.27
Statins	289 (93.5%)	282 (94.3%)	298 (97.4%)	0.07
Beta blockers	251 (81.2%)	240 (80.3%)	257 (84.0%)	0.47
ACE inhibitors	215 (69.6%)	203 (67.9%)	214 (69.9%)	0.84
Education[‡]				0.51
High	70 (28.8%)	75 (32.6%)	69 (28.3%)	
Intermediate	156 (64.2%)	147 (63.9%)	163 (66.8%)	
Low	17 (7.0%)	8 (3.5%)	12 (4.9%)	
Marital status[‡]				0.45
Married/partnered	198 (81.1%)	192 (83.5%)	196 (80.3%)	
Single	17 (7.0%)	22 (9.6%)	19 (7.8%)	
Widower	9 (3.7%)	4 (1.7%)	13 (5.3%)	
Divorced	20 (8.2%)	12 (5.2%)	16 (6.6%)	
Working status[‡]				0.54
Full time	122 (50.0%)	110 (47.6%	109 (44.5%)	
Part time	29 (11.7%)	19 (8.0%)	21 (8.8%)	
Unemployed	15 (6.3%)	17 (7.5%)	14 (5.7%)	
Retired	57 (23.4%)	56 (24.5%)	74 (30.4%)	
Other	21 (8.6%)	28 (12.3%)	26 (10.6%)	

*ACS= acute coronary syndrome; CABG= coronary artery bypass graft; CR= cardiac rehabilitation; CR+F= CR extended with face-to-face counselling sessions; CR+T= CR extended with telephone counselling sessions; CR-only= standard CR; PCI= percutaneous coronary intervention; TIA= transient ischemic attack. *Renal impairment: eGRF<60 ml/min; ‡Educational, Marital status and Working status were available in 230 (CR+F), 244 (CR+T) and 244 (CR-only) patients.*

CR+F versus CR-only

ITT analyses

The median SCORE at 18 months was 3.30% (25%–75% IQR, 1.01–5.59) in the CR+F group and 3.47% (25%–75% IQR, 0.86– 6.28) in the CR-only group (p=0.48; Figure 10.3). The between-group difference in SCORE between baseline and 18 months was not significant (p=0.19). Of the three modifiable SCORE parameters, only total cholesterol at 18 months (p<0.001) and a decrease in total cholesterol at 18 months differed between groups (p=0.013; Figure 10.4). Changes to health-related quality of life (HRQL), anxiety and depression did not differ between groups (Appendix 10H).

Per-protocol analyses

In the per-protocol analyses (CR+F: n=187; CR-only: n=252; Figure 10.2), the median SCORE results were similar to those from the ITT analyses (Figure 10.3). However, two of three individual SCORE parameters favoured CR+F. Current smoking increased from randomisation to 18 months by 2.9% in the CR+F group and 10.4% in the CR-only group (p<0.001). The smoking rate at 18 months was also lower in the CR+F group compared with the CR-only group (13.4% vs 21.3%; p<0.05; Figure 10.4). Furthermore, total cholesterol at 18 months and Δ (18 months to baseline) favoured CR+F (both p<0.01).

In contrast to the ITT results, per-protocol analysis showed that CR+F patients had higher HRQL on emotional and physical subscales at 18 months compared with CR-only patients (emotional subscale, p=0.004; physical subscale, p=0.015; Appendix 10H). Furthermore, CR+F patients had lower anxiety scores compared with CR-only patients at 18 months (p=0.036). However, the Δ scores (18 months to baseline) were similar between groups.

CR+T versus CR-only

ITT analyses

The median SCORE at 18 months was 3.02% (25%–75% IQR, 0.36–5.68) in the CR+T group and 3.47% (25%–75% IQR, 0.86–6.28) in the CR-only group (p=0.39; Figure 10.3). The difference in SCORE between baseline and 18 months did not differ between both groups (p=0.25). At 18 months, all three modifiable parameters of SCORE were similar for the CR+T and CR-only groups. Anxiety, depression and HRQL did not differ at 18 months or from baseline to 18 months (Appendix 10I).

Per-protocol analyses

In the per-protocol analyses (CR+T: n=170; CR-only: n=252; Figure 10.2), the median SCORE results were similar to those from the ITT analyses (Figure 10.3). Although smoking rates increased from randomisation to 18 months for both groups, the increase was greater in the CR-only group compared with the CR+T group (10.4% vs 4.6%; p<0.05; Figure 10.4). At 18 months, the CR+T group smoking rate was lower than that of the CR-only group (12.9% vs 21.3%; p<0.05).

In contrast to the ITT analysis, per-protocol analysis showed that CR+T patients had higher HRQL on emotional subscales at 18 months compared with CR-only patients (p=0.04; Appendix 10I). In contrast, anxiety and depression did not differ between groups. The Δ (18 months to baseline) scores were similar between groups.

Cardiovascular risk factors on target

Of nine modifiable risk factors in the ITT analysis, a mean of 4.50 was on target in the CR+F group compared with 4.39 in the CR-only group (p=0.58), and 4.35 was on target in the CR+T group (p=0.82 vs CR-only). In contrast, the per-protocol analysis showed that 5.35 risk factors of the CR+F patients were on target versus only 4.78 of the CR-only patients (p=0.002) and 5.04 of the CR+T patients (p=0.18 vs CR-only). ITT analyses showed that, at 18 months, more patients in the CR+F versus CR-only group were on target for LDL cholesterol (31% vs 21%; p=0.012) and total cholesterol (77% vs 64%; p=0.002; Appendix 10B). There were no differences in the percentage of patients on target for any of the outcome measures between the CR+T and CR-only groups (Appendix 10C).

Appendix 10D and 10E (ITT), Appendix 8F and 8G (per-protocol) and Figure 10.5 show mean values for the measured cardiovascular risk factors at all time points.

Adverse cardiac events

Eighteen months after randomisation, 83 rehospitalisations occurred in the CR+F group and 79 in the CR+T group, compared with 70 in the CR-only group (p=0.25 and p=0.44, respectively; Table 10.2). Two patients died from causes unrelated to the CR interventions, eight experienced ST-elevation myocardial infarction and 11 experienced non-ST-elevation myocardial infarction. There were no between-group differences.

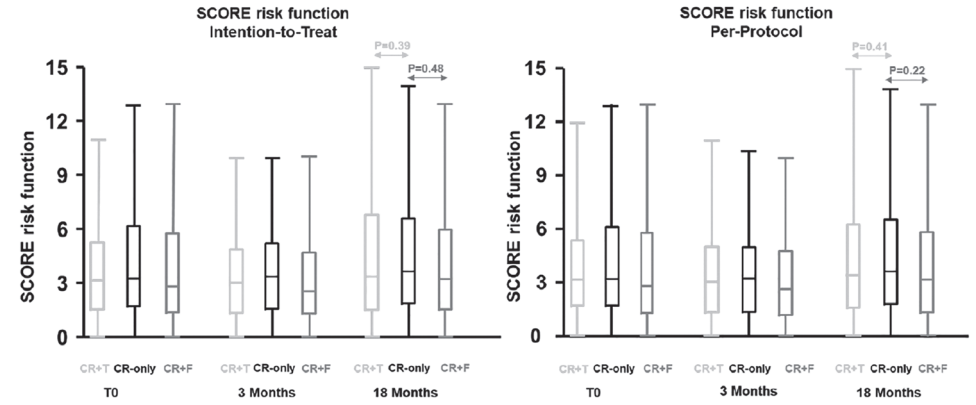

Figure 10.3 SCORE (Sytematic COronary Risk Evaluation) risk function (median, 25th-75th percentiles and minimum and maximum)
CR= cardiac rehabilitation; CR+T= standard CR extended with telephone counselling sessions; CR-only= standard CR; CR+F = standard CR extended with face-to-face group counselling sessions.

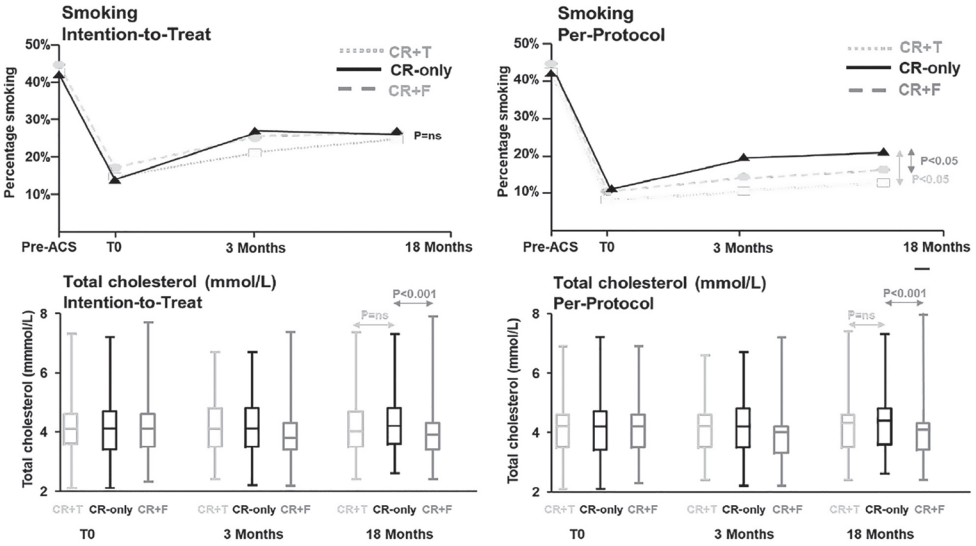

Figure 10.4 Smoking behaviour (percentages) and total cholesterol (median, 25th-75th percentiles and minimum and maximum)
CR= cardiac rehabilitation; CR+T= standard CR extended with telephone counselling sessions; CR-only= standard CR; CR+F = standard CR extended with face-to-face group counselling sessions; ns= not significant

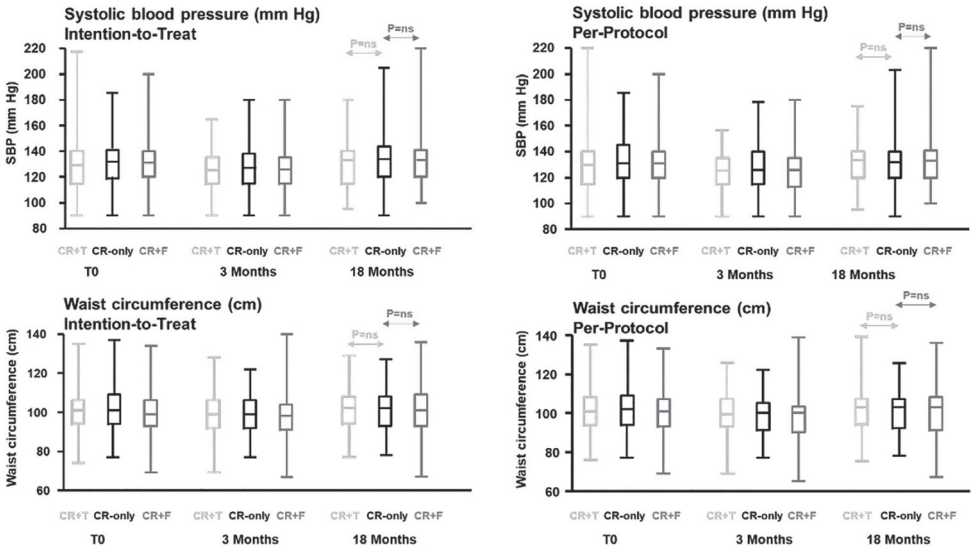

Figure 10.5 Systolic blood pressure and waist circumference (median, 25th-75th percentiles and minimum and maximum) *CR= cardiac rehabilitation; CR+T= standard CR extended with telephone counselling sessions; CR-only= standard CR; CR+F = standard CR extended with face-to-face group counselling sessions; ns= not significant; SBP= systolic blood pressure*

Table 10.2 Adverse cardiac events at 18 months: intention-to-treat analysis

				P-values	
	CR+F (n=309)	**CR+T (n=299)**	**CR-only (n=306)**	**CR+F vs CR-only**	**CR+T vs CR-only**
Total number of events	83 (26.8%)	79 (26.4%)	70 (22.3%)	0.25	0.44
Mortality	1 (0.3%)	1 (0.3%)	0 (0.0%)	0.56	0.56
Readmissions for ACS					
STEMI	1 (0.3%)	5 (1.7%)	2 (0.7%)	0.56	0.24
NSTEMI	5 (1.6%)	3 (1.0%)	3 (1.0%)	0.49	0.98
Unstable angina	4 (1.2%)	3 (1.0%)	2 (0.7%)	0.40	0.64
Other CVD admissions					
Stable angina	14 (4.5%)	13 (4.3%)	9 (3.0%)	0.65	0.64
Chest pain	16 (5.2%)	12 (4.0%)	11 (3.6%)	0.58	0.53
Ventricular fibrillation	6 (1.9%)	2 (0.7%)	2 (0.7%)	0.16	0.98
Atrial Fibrillation	0 (0%)	1 (0.3%)	0 (0%)	Na	0.31
Arrhythmias	0 (0%)	1 (0.3%)	0 (0%)	Na	0.31
CVA	0 (0%)	0 (0%)	0 (0%)	Na	Na
Interventions					
CAG	8 (2.6%)	5 (1.7%)	7 (2.3%)	0.81	0.59
PCI	9 (2.9%)	9 (3.0%)	12 (3.9%)	0.98	0.85
CABG	1 (0.3%)	0 (0%)	2 (0.7%)	0.56	0.16
Cardiac ER	18 (5.8%)	24 (8.0%)	20 (6.5%)	0.55	0.90

ACS= acute coronary syndrome; CABG= coronary artery bypass graft; CAG= coronary angiography; CR= cardiac rehabilitation; CR+F= CR extended with face-to-face counselling sessions; CR+T= CR extended with telephone counselling sessions; CR-only= standard CR; CVA= cerebrovascular accident; CVD= cardiovascular disease; ER= emergency room; Na= not available; NSTEMI= non-ST-elevation myocardial infarction; PCI= percutaneous coronary intervention; STEMI= ST-elevation myocardial infarction.

DISCUSSION

Extending CR with either face-to-face group counselling or individual telephone counselling did not improve SCORE risk function. Standard CR was associated with similar health outcomes compared with extended CR. Nevertheless, total cholesterol did improve slightly when CR was extended to include group counselling sessions. Likewise, adherent patients who completed extended interventions were less likely to smoke after either novel intervention. Adherent patients in the extended group counselling arm also showed increased numbers of modifiable risk factors on target, decreased anxiety and improved HRQL.

Our hypothesis that intensified and extended CR would improve SCORE risk function was not supported. One possible explanation for this lack of effect may be a need for longer follow-up. Second, standard CR control intervention was associated with very low SCORE outcomes, so detecting a difference for novel interventions would be difficult. Our study power calculation was based on the RESPONSE study intervention effect,[15] which resulted in a SCORE of 4.4% after a nurse-coordinated intervention. In comparison, our study showed a SCORE of 3.5% after standard CR alone. Thus, standard CR was already successful in achieving targeted health outcomes and no additional resources are needed. Patients in our standard CR group reached optimal targets for ACS risk factors at high rates: 75% for SBP, 64% for total cholesterol and 27% still smoked. These low-risk factor levels corresponded to low 18-month event rates of 3% death from MI and 25% non-fatal cardiovascular events. A comparable patient population in the RESPONSE study had a higher event rate of 31%.[15]

One could hypothesise that longer lasting or more intense programmes could have led to better outcomes in our study. Recently, successful CR maintenance programmes that differed in organisation, meeting intensity and frequency, and content have been studied in comparable patient samples.[15,17-19] However, these studies all compared their intervention programme to usual care, which does not usually include CR. The difference in study design explains why we failed to find a difference between control and experimental groups in our study. Individual risk factor outcomes were comparable for patients in all three study arms; thus, different CR structure does not appear to be related to results. A recent RCT that also compared extended behavioural CR to standard CR showed similar improvements in SBP, smoking cessation and total cholesterol.[20]

Consistent with our results, the EuroAspire study showed that blood pressure and lipid management have improved during recent years.[21,22] In that study, however, lifestyle habits had deteriorated.[22] Our extended programmes were designed to stimulate permanent adoption of a heart-healthy lifestyle in patients with ACS to improve coronary disease risk factors. Although extended CR was not shown to benefit SCORE results, future research should focus on potential impact of such programmes on healthy lifestyle components such as physical activity and fitness. Adoption of a healthy lifestyle remains important because of its direct effect on cardiovascular mortality and several chronic diseases. We will focus on those factors in forthcoming research.

Psychosocial parameters such as HRQL, anxiety and depression are additional important outcome parameters. The CR goal in patients with ACS to improve emotional health may be reached through extended interventions that provide additional emotional support.[17] Indeed, per-protocol analysis showed lower anxiety scores for patients in the CR+F group compared with the CR-only group and quality of life improvement in the CR+F group compared with the CR-only group. However, these differences seem to result mainly from baseline differences. Patients with higher anxiety scores and lower HRQL were more likely to drop out during the extended programme and not be included in the per-protocol analysis. Future studies should focus on developing programmes to support this group.

Our results suggest that no additional resources are needed because standard CR is already successful in helping patients achieve target health outcomes. Because referral for CR is very low worldwide,[23] and our results show a high dropout rate, it seems important that future studies focus on finding interventions that appeal to CR non-attenders and determine actual reasons for non-referral prospectively. Because our study showed that adherence was already low for an intervention consisting of only a few telephone calls, creating more appealing interventions may be challenging.

Limitations

Adherence with extended programmes was very low in our study. We anticipated a premature dropout rate of 10%; however, 15%–20% of patients quit standard CR, and an additional 25% did not complete extended counselling. This high dropout rate may have resulted in bias. Because intervention effects were most pronounced for patients completing 75% or more of the additional sessions, our results are probably valid mainly for more adherent patients. There may be an additional bias from patients' willingness to participate in this trial, which is a general issue found in RCTs. Our study mainly enrolled young patients with relatively few risk factors. Future studies should focus on older patients with more complicated health status.

The SCORE risk function was originally developed for primary prevention.[7] Because of the lack of a validated risk function assessment for secondary prevention, we selected the SCORE risk function for 10-year cardiovascular risk as the primary outcome for our secondary prevention trial. The SCORE risk function has been used to quantify the effectiveness of secondary prevention in two previous CR RCTs.[15,24] Although the absolute SCORE function estimates are inaccurate for secondary prevention, the SCORE difference between groups provides an estimate of the relative overall impact of a risk factor intervention.

CONCLUSIONS

Extending CR with extra behavioural counselling sessions, either face-to-face in groups or individual telephone counselling, did not confer additional benefit with respect to SCORE. Patients largely reached target levels of modifiable risk factors following standard CR, with few hospital readmissions.

ACKNOWLEDGEMENT

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APPENDIXES

Appendix 10A

Exclusion criteria

Patient's ≥ 18 years with a recent acute coronary syndrome (ACS) and proficient in the Dutch language were eligible for the study. Exclusion criteria were heart failure and/or impaired left ventricular function (left ventricular ejection fraction <40 %), angina NYHA Class II–IV, psychological or cognitive impairments which may limit cardiac rehabilitation, congenital heart disease, chronic obstructive pulmonary disease Gold classification ≥II, diabetes with organ damage, locomotive disorders that will preclude participation in an exercise training program, implantable cardio-defibrillator (ICD), renal failure needing follow-up by a nephrologist and intermittent claudication impairing cardiac rehabilitation (CR) exercises.

Allocated treatment

1) Standard CR (CR-only; Figure 10.1) Standard care consisted of CR according to the Dutch and European Society of Cardiology (ESC) guidelines.[10-11] This was a group exercise program with training sessions of 1.5 hours offered 2 times a week for 12 weeks under supervision of a physiotherapist. The training sessions were performed in groups of circa 15-20 patients and consisted of strength exercises, an aerobic program (running/brisk walking, aiming for an intensity of 13 points at the BORG scale) and relaxation. In addition, participation in multifactor lifestyle and cardiovascular risk factor group education sessions was offered to all patients, and comprised: information on cardiovascular risk factors, medical information, dietary advice, and advice on coping with emotions. If indicated, there was an option to participate in a smoking cessation program, nutritional counseling sessions, stress management sessions or an individually based psychological program. Only the training program was strictly obligatory; the counseling and group sessions were attended upon motivation of each patient.

2) Standard CR extended with group counseling sessions (CR+F; Figure 10.1). During the 12-week period of standard CR (as described above), three extra face-to-face (F) physical activity group counseling sessions were organized. These 75 minute sessions with 6-8 patients were under supervision of a physiotherapist and aimed at regular physical activities of moderate intensity for 30 min at least 5 days a week.

In addition, at 4, 6 and 12 months after the start of the program the patients were again required to participate in face-to-face multifactor lifestyle and cardiovascular risk factor group sessions of 2 hours each, comprising a 1-hour exercise program (comparable to the exercise program described for standard CR) and a 1-hour counseling session in which long-term maintenance of healthy lifestyle behavior (e.g. healthy diet, smoking cessation, physical activity) and psychosocial problems were discussed. These group sessions were led alternating by a physiotherapist, social worker, dietician, nurse and physician trained in

motivational interviewing. All additional group sessions were performed in small groups of 6-8 patients and were based on self-regulation techniques (e.g. goal-setting, self-monitoring, and developing plans for relapse) that were proven successful to change lifestyle.[5,6] Finally, in patients randomized to CR+F the cholesterol and blood pressure levels were monitored and medication was adjusted when needed. The target level was: LDL ≤1.8 mmol/l and systolic blood pressure <140 mmHg.

3) Standard CR extended with telephone counseling sessions (CR+T; Figure 10.1). The third strategy was based on The COACH Program© that demonstrated favorable effects in Australia.[25] In the CR+T arm of the trial, standard CR (as described above) was extended with 5-6 telephone coaching sessions with an interval of 5–6 weeks during the first months after completion of standard CR. In line with the group sessions, the telephone coaching sessions were also based on successful self-regulation techniques, such as goal setting and relapse prevention.[5,6] Patients were stimulated to develop a personal action plan in which they defined and self-monitored their lifestyle (e.g. smoking cessation, healthy diet, and active lifestyle) and coronary risk factor (e.g. blood pressure, cholesterol, BMI) targets, acted upon, measured again, etc. The coaching program was terminated when patient and coach felt that personal goals were met, with a maximum of 6 phone calls. The personal coaching was offered by the Medical Service Center of the health insurance company "Zilveren Kruis", which consisted of specialized nurses, trained in the motivational interviewing technique.[26]

Definition cardiovascular events

ACS was defined as persistent (>20 min) chest pain suggestive of myocardial ischemia, which is unresponsive to nitroglycerin and which was accompanied by ST-T changes (electrocardiographic evidence) and/or cardiac troponin elevations (biochemical evidence), regardless of in-hospital treatment. Myocardial infarction (MI) was diagnosed by elevated creatine kinase-MB greater and elevated troponin. (N)STEMI was defined (no) ST-elevation myocardial infarction. Unstable angina was defined as NSTEMI without elevated troponin. Cerebrovascular accident (CVA) was defined as a focal, central neurological deficit lasting >72 hours which resulted in irreversible brain damage or body impairment. Repeat revascularization was defined as any repeat percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Stable angina was diagnosed as short-lasting (5-10 minutes) chest discomfort provoked by exercise and released by rest or nitroglycerine. Chest pain was defined as chest discomfort with non-angina characteristics. Ventricular Fibrillation (VF) was diagnosed as disorganized electrical activity in the ventricles. Atrial Fibrillation (AF) was diagnosed as disorganized electrical activity in the atria. Arrhythmias was diagnosed as any electrical disturbance other than VF/AF.

Study parameters

Assessments were made at Capri rehabilitation center at baseline (i.e. prior to CR), at the end of standard CR (at 12 weeks), and at 18 months (Figure 10.1). During the assessment patients underwent extensive cardiac and psychological examination.

The following demographic parameters were collected: sex, age and smoking status before the index event. Collected clinical variables included diabetes, hypertension, dyslipidemia, renal impairment (eGFR), cardiovascular history, BMI, waist circumference, cardiac medication. Blood pressure was measured by using a validated sphygmomanometer. Blood samples were analyzed by the local laboratories for total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and creatinine clearance. Smoking status was determined during an interview and by measuring the concentration of carbon monoxide in breath using a breath analyzer (piCO Smokelyzer). Educational level was measured with a questionnaire at baseline. Educational level was divided into low, intermediate and high. Low educational level was considered when the patient's highest achieved education level was primary school. Intermediate level was considered when the highest level was secondary school or secondary vocational. High educational level was considered when patients completed a higher professional education or university.

The MacNew Heart Disease Health-related Quality of Life (HRQL) instrument

The MacNew Heart Disease HRQL questionnaire [MacNew] is a self-administered modification of the original HRQL instrument.[13] The MacNew consists of 27 items which fall into three domains (a physical limitations domain scale, an emotional function domain scale, and a social function domain scale). The time frame for the MacNew is the previous two weeks. The maximum possible score in any domain is 7 (high HRQL) and the minimum is 1 (poor HRQL). With an internal consistency and intraclass correlation coefficients ≥0.73, reliability was high.

Anxiety and depression

The Dutch version of the HADS was completed by patients at baseline. The HADS has a subscale for depression (HADS-D) and a subscale for anxiety (HADS-A). Each subscale consists of seven items (score range: 0–3). Levels of depression and anxiety were considered clinically relevant at a cut-off score of 8 on each subscale.[14] The Dutch HADS has been proven to be a valid and reliable instrument to detect symptoms of anxiety and depression.[14]

Appendix 10B Cardiovascular risk factors on target. CR+F *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		12 weeks (T1)		18 months (T2)		P-values		
	CR+F	CR-only	CR+F	CR-only	CR+F	CR-only	CR+F vs CR-only		
	n=309	n=306	n=251	n=235	n=257	n=252	T0	T1	T2
Systolic blood pressure ≤ 140 mmHg, %	77	76	86	86	75	75	0.60	0.92	0.86
Diastolic blood pressure ≤ 90 mmHg, %	89	92	95	94	91	93	0.28	0.56	0.54
Waist circumference, men ≤ 102cm, females ≤ 88 cm, %	23	24	23	22	22	24	0.76	0.93	0.55
LDL cholesterol ≤ 1.8 mmol/L, %	46	46	56	55	52	44	0.96	0.81	0.15
Total cholesterol ≤4.5 mmol/L, %	27	26	31	26	31	21	0.87	0.23	0.012
HDL cholesterol ≥1.0 mmol/L, %	70	67	81	68	77	64	0.45	0.002	0.002
Triglyceride, mmol/L ≤ 1.7, %	60	58	66	57	69	67	0.67	0.05	0.71
Triglyceride, mmol/L ≤ 1.7, %	68	64	75	64	72	67	0.30	0.019	0.19
Current smoking, %	17.1	14.0	25.2	27.1	26.9	27.5	0.29	0.60	0.87

Data are percentages; p-values are Chi-squared tests. CR+F= CR extended with face-to-face counselling sessions; CR-only= standard CR.

Appendix 10C Cardiovascular risk factors on target. CR+T *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		12 weeks (T1)		18 months (T2)		P-values		
	CR+T	CR-only	CR+T	CR-only	CR+T	CR-only	CR+T vs CR-only		
	n=299	n=306	n=251	n=235	n=257	n=252	T0	T1	T2
Systolic blood pressure ≤ 140 mmHg, %	78	76	90	86	74	75	0.38	0.22	0.76
Diastolic blood pressure ≤ 90 mmHg, %	92	92	95	94	90	93	0.92	0.58	0.31
Body mass index ≤25 kg/m^2, %	26	24	27	22	23	24	0.64	0.26	0.67
Waist circumference, men ≤ 102cm, females ≤ 88 cm, %	49	46	54	55	45	44	0.58	0.81	0.92
LDL cholesterol ≤1.8 mmol/L, %	25	26	27	26	24	21	0.79	0.71	0.50
Total cholesterol ≤4.5 mmol/L, %	68	67	66	68	69	64	0.78	0.74	0.27
HDL cholesterol ≥1.0 mmol/L, %	65	58	65	57	70	67	0.10	0.06	0.47
Triglyceride, mmol/L ≤1.7, %	66	64	67	64	71	67	0.59	0.55	0.37
Current smoking, %	14.7	14.0	21.1	27.1	25.8	27.5	0.81	0.08	0.51

Data are percentages; p-values are Chi-squared tests. CR+T= CR extended with telephone counselling sessions; CR-only= standard CR.

Appendix 10D Cardiovascular risk factors. CR+F *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months*:*
Intention-to-treat analysis

	Baseline (T0)		3 months		18 months		P-values	
	CR+F	CR-only	CR+F	CR-only	CR+F	CR-only	CR+F vs CR-only	
	n=309	n=306	n=251	n=235	n=257	n=252	T0-T1	T0-T2
Systolic blood pressure, mmHg (SD)	131.0 (19.7)	130.6 (18.9)	126.0	126.5	132.8	133.1	0.93	0.79
Diastolic blood pressure, mmHg (SD)	80.1 (10.5)	78.8 (10.6)	76.6	80.7	79.0	79.4	0.12	0.22
Weight, kg (SD)	86.4 (15.1)	86.7 (14.9)	86.3	85.9	87.1	87.0	0.09	0.39
Body mass index, kg/m^2 (SD)	28.0 (4.0)	28.0 (3.9)	28.0	27.8	28.2	28.1	0.11	0.48
Waist circumference, cm (SD)	101.2 (11.8)	101.9 (10.8)	99.8	99.7	102.6	102.6	0.14	0.27
Total cholesterol, mmol/L (SD)	4.2 (0.9)	4.2 (1.0)	4.0	4.2	4.1	4.3	0.002	0.013
HDL cholesterol, mmol/L (SD)	1.1 (0.3)	1.1 (0.3)	1.1	1.1	1.2	1.2	0.40	0.93
LDL cholesterol, mmol/L (SD)	2.4 (0.8)	2.4 (0.8)	2.3	2.5	2.3	2.5	0.001	0.009
Triglyceride, mmol/L (SD)	1.7 (1.3)	1.7 (1.0)	1.5	1.6	1.5	1.7	0.59	0.21
Current smoking (%)	17.1	14.0	25.2	27.1	26.9	27.5	<0.001	0.34

Data are mean (SD) or percentages; p-values are Student's t-tests or Chi-squared tests. CR+F= CR extended with face-to-face counselling sessions; CR-only= standard CR.

Appendix 10E Cardiovascular risk factors. CR+T *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months*:*
Intention-to-treat analysis

	Baseline (T0)		3 months		18 months		P-values	
	CR+T	CR-only	CR+T	CR-only	CR+T	CR-only	CR+T vs CR-only	
	n=299	n=306	n=249	n=235	n=248	n=252	T0-T1	T0-T2
Systolic blood pressure, mmHg (SD)	129.6 (19.6)	130.6 (18.9)	125.2	126.5	133.3	133.1	0.52	0.18
Diastolic blood pressure, mmHg (SD)	78.7 (10.6)	78.8 (10.6)	79.9	80.7	80.1	79.4	0.54	0.28
Weight, kg (SD)	86.9 (15.2)	86.7 (14.9)	86.5	85.9	87.2	87.0	0.29	0.93
Body mass index, kg/m^2 (SD)	27.9 (4.2)	28.0 (3.9)	27.8	27.8	28.0	28.1	0.24	0.90
Waist circumference, cm (SD)	101.4 (11.3)	101.9 (10.8)	100.0	99.7	102.5	102.6	0.12	0.57
Total cholesterol, mmol/L (SD)	4.2 (0.9)	4.2 (1.0)	4.2	4.2	4.3	4.3	0.57	0.29
HDL cholesterol, mmol/L (SD)	1.2 (0.3)	1.1 (0.3)	1.2	1.1	1.3	1.2	0.22	0.91
LDL cholesterol, mmol/L (SD)	2.4 (0.8)	2.4 (0.8)	2.5	2.5	2.4	2.5	0.86	0.29
Triglyceride, mmol/L (SD)	1.6 (1.0)	1.7 (1.0)	1.7	1.6	1.7	1.7	0.04	0.25
Current smoking (%)	14.7	14.0	21.1	27.1	25.8	27.5	<0.001	0.31

Data are mean (SD) or percentages; p-values are Student's t-tests or Chi-squared tests. CR+T= CR extended with telephone counselling sessions; CR-only= standard CR.

Appendix 10F Cardiovascular risk factors. CR+F *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months*:*
Per-protocol analysis

	Baseline (T0)		3 months		18 months		P-values	
	CR+F	CR-only	CR+F	CR-only	CR+F	CR-only	CR+F vs CR-only	
	n=187	n=252	n=176	n=234	n=176	n=226	T0-T1	T0-T2
Systolic blood pressure, mm Hg (SD)	131.2 (20.4)	132.0 (18.9)	125.7	126.6	132.4	133.9	0.88	0.88
Diastolic blood pressure, mm Hg (SD)	80.4 (10.7)	79.1 (12.0)	76.8	77.1	78.9	79.6	0.09	0.22
Weight, kg (SD)	86.0 (14.9)	86.8 (15.2)	86.0	86.0	86.1	87.1	0.12	0.93
Body mass index, kg/m^2 (SD)	27.7 (3.9)	28.0 (3.9)	27.8	27.7	27.8	28.1	0.12	0.98
Waist circumference, cm (SD)	100.5 (11.8)	101.8 (10.8)	98.7	99.7	100.9	101.7	0.27	0.37
Total cholesterol, mmol/L (SD)	4.0 (0.8)	4.2 (1.0)	3.9	4.2	3.9	4.3	0.007	0.009
HDL cholesterol, mmol/L (SD)	1.2 (0.3)	1.1 (0.3)	1.2	1.1	1.2	1.2	0.68	0.96
LDL cholesterol, mmol/L (SD)	2.3 (0.7)	2.4 (0.8)	2.2	2.4	2.2	2.5	0.002	0.001
Triglyceride, mmol/L (SD)	1.6 (1.5)	1.7 (1.0)	1.4	1.6	1.4	1.6	0.49	0.36
Current smoking (%)	10.5	10.9	14.4	19.8	13.4	21.3	<0.001	<0.001

Data are mean (SD) or percentages; p-values are Student's t-tests or Chi-squared tests. CR+F= CR extended with face-to-face counselling sessions; CR-only= standard CR.

Appendix 10G Cardiovascular risk factors. CR+T *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months*:*
Per-protocol analysis

	Baseline (T0)		3 months		18 months		P-values	
	CR+T	CR-only	CR+T	CR-only	CR+T	CR-only	CR+T vs CR-only	
	n=170	n=252	n=168	n=234	n=153	n=226	T0-T1	T0-T2
Systolic blood pressure, mm Hg (SD)	129.5 (0.5)	132.0 (18.9)	124.3	126.6	132.9	133.9	0.87	0.21
Diastolic blood pressure, mm Hg (SD)	78.5 (10.6)	79.1 (10.2)	76.5	77.1	79.2	79.6	0.92	0.54
Weight, kg (SD)	86.8 (13.8)	86.8 (15.2)	86.2	86.0	86.5	87.1	0.53	0.55
Body mass index, kg/m^2 (SD)	27.7 (3.7)	28.0 (3.9)	27.6	27.7	27.6	28.1	0.47	0.55
Waist circumference, cm (SD)	101.1 (10.3)	101.8 (10.8)	99.5	99.7	101.9	101.7	0.39	0.63
Total cholesterol, mmol/L (SD)	4.1 (0.9)	4.2 (1.0)	4.1	4.2	4.2	4.3	0.97	0.55
HDL cholesterol, mmol/L (SD)	1.2 (0.3)	1.1 (0.3)	1.2	1.1	1.3	1.2	0.43	0.31
LDL cholesterol, mmol/L (SD)	2.3 (0.7)	2.4 (0.8)	2.5	2.4	2.4	2.5	0.83	0.29
Triglyceride, mmol/L (SD)	1.5 (0.9)	1.7 (1.0)	1.6	1.6	1.4	1.6	0.026	0.75
Current smoking (%)	8.3	10.9	10.6	19.8	12.9	21.3	<0.001	0.031

Data are mean (SD) or percentages; p-values are Student's t-tests or Chi-squared tests. CR+T= CR extended with telephone counselling sessions; CR-only= standard CR.

Appendix 10H Health related quality of life, anxiety and depression. CR+F *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months

	Baseline (T0)		3 months		18 months		Δ (T2-T0)		p-values	
	CR+F	CR-only	CR+F	CR-only	CR+F	CR-only	CR+F	CR-only	CR+F vs CR-only	
Intention-to-treat	**n=309**	**n=306**	**n=251**	**n=235**	**n=257**	**n=252**			**Δ (T2-T0)**	**T2**
McNew HRQL										
Emotional, mean score (SD)/	5.17 (1.23)	5.05 (1.25)	5.48 (1.12)	5.38 (1.20)	5.64 (1.01)	5.51 (1.05)	0.47	0.46	0.39	0.25
mean difference [95%CI]							[0.19, 0.54]	[0.31, 0.64]		
Physical, mean score (SD)/	5.12 (1.23)	4.99 (1.25)	5.74 (1.09)	5.62 (1.18)	5.99 (1.01)	5.85 (1.05)	0.87	0.86	0.84	0.19
mean difference [95%CI]							[0.62, 0.98]	[0.65, 1.00]		
Social, mean score (SD) /	5.50 (1.21)	5.53 (1.21)	6.11 (1.10)	5.92 (1.18)	6.37 (0.78)	6.33 (0.89)	0.87	0.80	0.72	0.65
mean difference [95%CI]							[0.68, 1.02]	[0.63, 0.98]		
HADS										
Depression, %	13.9	13.1	6.1	9.2	7.3	9.0				0.56
Anxiety, %	11.3	14.2	7.1	7.7	6.2	8.9				0.32
Per-protocol	**n=187**	**n=252**	**n=143**	**n=234**	**n=149**	**n=226**				
McNew HRQL										
Emotional, mean score (SD)/	5.33 (1.20)	5.07 (1.23)	5.59 (1.11)	5.38 (1.20)	5.85 (0.90)	5.52 (1.05)	0.46	0.47	0.97	0.004
mean difference [95%CI]							[0.27, 0.65]	[0.30, 0.65]		
Physical, mean score (SD)/	5.23 (1.12)	5.03 (1.25)	5.84 (0.99)	5.63 (1.18)	6.14 (0.78)	5.87 (1.09)	0.85	0.83	0.92	0.015
mean difference [95%CI]							[0.64, 1.04]	[0.65, 1.01]		
Social, mean score (SD) /	5.58 (1.12)	5.52 (1.23)	6.17 (1.04)	5.93 (1.17)	6.49 (0.71)	6.35 (0.89)	0.91	0.82	0.72	0.65
mean difference [95%CI]							[0.71, 1.11]	[0.64, 0.99]		
HADS										
Depression, %	13.1	11.4	4.6	9.2	6.2	9.2				0.35
Anxiety, %	9.5	13.7	5.4	7.7	3.1	9.1				0.036

Data are mean (SD: standard deviation) or mean difference [95%CI: 95% confidence interval]. HRQL: health related quality of life. p-values are Student's t-tests or Chi-squared tests. CR+F= CR extended with face-to-face counselling sessions; CR-only= standard CR.

Appendix 10I Health related quality of life, anxiety and depression. CR+T *vs* CR-only pre CR (T0), post-CR (3 months) and at 18 months

	Baseline (T0)		3 months		18 months		Δ (T2-T0)		p-values	
	CR+T	CR-only	CR+T	CR-only	CR+T	CR-only	CR+T	CR-only	CR+T vs CR-only	
Intention-to-treat	**n=299**	**n=306**	**n=249**	**n=235**	**n=248**	**n=252**			**Δ (T2-T0)**	**T2**
McNew HRQL										
Emotional, mean score (SD)/	5.14 (1.16)	5.05 (1.25)	5.57 (1.01)	5.38 (1.20)	5.76 (0.96)	5.51 (1.05)	0.62	0.46	0.98	0.56
mean difference [95%CI]							[0.31, 0.83]	[0.31, 0.64]		
Physical, mean score (SD)/	5.11 (1.26)	4.99 (1.25)	5.75 (1.07)	5.62 (1.18)	6.01 (0.98)	5.85 (1.05)	0.77	0.86	0.65	0.15
mean difference [95%CI]							[0.63, 0.92]	[0.65, 1.00]		
Social, mean score (SD) /	5.64 (1.10)	5.53 (1.21)	6.15 (0.98)	5.92 (1.18)	6.41 (0.80)	6.33 (0.89)	0.77	0.81	0.79	0.33
mean difference [95%CI]							[0.68, 1.02]	[0.63, 0.98]		
HADS										
Depression, %	11.2	13.1	8.9	9.2	6.6	9.0				0.40
Anxiety, %	8.9	14.2	6.8	7.7	6.6	8.9				0.42
Per-protocol	**n=170**	**n=252**	**n=156**	**n=234**	**n=143**	**n=226**				
McNew HRQL										
Emotional, mean score (SD)/	5.29 (1.08)	5.07 (1.23)	5.59 (0.99)	5.38 (1.20)	5.77 (0.96)	5.52 (1.05)	0.41	0.47	0.63	0.04
mean difference [95%CI]							[0.23, 0.58]	[0.30, 0.63]		
Physical, mean score (SD)/	5.27 (1.20)	5.03 (1.25)	5.77 (1.07)	5.63 (1.18)	6.00 (1.01)	5.87 (1.09)	0.71	0.83	0.36	0.31
mean difference [95%CI]							[0.54, 0.88]	[0.65, 1.01]		
Social, mean score (SD) /	5.75 (1.05)	5.52 (1.23)	6.15 (0.98)	5.93 (1.17)	6.40 (0.84)	6.35 (0.89)	0.68	0.82	0.31	0.60
mean difference [95%CI]							[0.50, 0.86]	[0.64, 0.99]		
HADS										
Depression, %	6.8	11.4	8.3	9.2	6.0	9.2				0.32
Anxiety, %	3.0	13.7	5.3	7.7	7.7	9.1				0.67

Data are mean (SD: standard deviation) or mean difference [95%CI: 95% confidence interval]. HRQL: health related quality of life. p-values are Student's t-tests or Chi-squared tests. CR+T= CR extended with telephone counselling sessions; CR-only= standard CR.

Chapter 11

EFFECTS OF TWO BEHAVIORAL CARDIAC REHABILITATION INTERVENTIONS ON PHYSICAL ACTIVITY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background

Standard cardiac rehabilitation (CR) is insufficient to help patients achieve an active lifestyle. The effects of two advanced and extended behavioral CR interventions on physical activity (PA) and sedentary behavior (SB) were assessed.

Methods

In total, 731 patients with ACS were randomized to 1) 3 months of standard CR (CR-only); 2) 3 months of standard CR with three pedometer-based, face-to-face PA group counseling sessions followed by 9 months of aftercare with three general lifestyle, face-to-face group counseling sessions (CR+F); or 3) 3 months of standard CR, followed by 9 months of aftercare with five to six general lifestyle, telephonic counseling sessions (CR+T). An accelerometer recorded PA and SB at randomization, 3 months, 12 months, and 18 months.

Results

The CR+F group did not improve their moderate-to-vigorous intensity PA (MVPA) or SB time compared to CR-only (between-group difference= 0.24% MVPA, *P*=.349; and 0.39% SB, *P*=.529). However, step count (between-group difference= 513 steps/day, *P*=.021) and time in prolonged MVPA (OR=2.14, *P*=.054) improved at 3 months as compared to CR-only. The improvement in prolonged MVPA was maintained at 18 months (OR=1.91, *P*=.033). The CR+T group did not improve PA or SB compared to CR-only.

Conclusions

Adding three pedometer-based, face-to-face group PA counseling sessions to standard CR increased daily step count and time in prolonged MVPA. The latter persisted at 18 months. A telephonic after-care program did not improve PA or SB. Although after-care should be optimized to improve long-term adherence, face-to-face group counseling with objective PA feedback should be added to standard CR.

INTRODUCTION

Physical behavior comprises both physical activity (PA) and sedentary behavior (SB).[1] Patients with acute coronary syndrome (ACS) who have higher levels of moderate-to-vigorous intensity PA (MVPA; e.g., brisk walking or biking) have more favorable cardiovascular risk profiles and lower cardiac mortality.[2,3] Independent of PA time, SB time is also related to health outcomes such as Body Mass Index (BMI) and mortality.[4,5] In addition to the total time (volume) of physical behavior, the way physical behavior is distributed (accumulated in shorter or longer periods) might be important. For example, it has been suggested that MVPA yields greater health benefits when accumulated in periods lasting at least 10 min.[6-8] With regard to SB, regular active breaks may counteract the harmful effects of prolonged sedentary periods.[9]

An important goal of cardiac rehabilitation (CR) for patients with ACS is the adoption of a healthy lifestyle. Although CR reduces cardiovascular risk factors, improves quality of life, and improves physical fitness[10,11], standard CR seems insufficient to improve the amount of PA performed outside the supervised CR settings.[12,13] Furthermore, standard CR generally does not target SB, and although some SB improvements do occur, patients with ACS remain sedentary following program completion.[13]

We hypothesized that patients with ACS need more guidance to improve physical behavior. Adding behavioral interventions with self-regulation techniques, such as self-monitoring and goal-setting, seems the most promising approach.[14,15] Findings from previous studies that investigated the effectiveness of adding behavioral interventions aiming to improve daily PA to CR[16-18] are limited because they rely largely on self-reported measures of PA that have poor validity and reliability.[19] Additionally, most protocols were designed to evaluate short-term effectiveness only and the investigated novel behavioral interventions often were not integrated into existing CR programs. To successfully implement behavioral components into daily clinical practice, pragmatic trials are needed that use existing infrastructure.

In the OPTImal CArdiac REhabilitation (OPTICARE) RCT, standard CR and two advanced and extended behavioral CR interventions (one using face-to-face group counseling and one using individual telephonic counseling) were evaluated in patients with ACS. The OPTICARE trial was designed as a pragmatic trial in an outpatient rehabilitation setting. The primary objective described in this paper was to evaluate the short-term and long-term effectiveness of the novel behavioral CR interventions on PA volume. The secondary aim was to evaluate SB volume as well as PA and SB distribution over time.

METHODS

Study design

The OPTICARE study is an RCT that has been described in detail elsewhere.[20] OPTICARE is registered at ClinicalTrials.gov (NCT01395095).

Setting and participants

Patients referred to Capri Cardiac Rehabilitation (an outpatient rehabilitation center with several locations in the Netherlands) between November 2011 and August 2014 were invited to participate. Inclusion criteria were ACS diagnosis, age >18 years, and proficiency in Dutch. Exclusion criteria were the presence of severe physical and/or cognitive impairments that could limit CR participation.[20] The OPTICARE protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam, the Netherlands (MEC-2010-391). All patients provided written informed consent.

Randomization and intervention

Patients were randomized by trained research assistants using sequentially numbered, opaque and sealed envelopes that were prepared by an independent statistician who used a computer random number generator. Patients were randomized (1:1:1) to one of the following groups (see for the timeline of the interventions also Appendix 11A):

1) CR-only: Standard CR was in line with the guidelines[2,21] and comprised two 75 min group exercise sessions per week for 3 months consisting of gymnastic exercises, running/brisk walking, sports activities and relaxation exercises. Additionally, patients were invited to participate in educational sessions addressing healthy diet, emotional coping, and cardiovascular disease risk factors. When indicated, patients could participate in group counseling sessions addressing diet, stress management, and smoking cessation, or an individual psychologic program. Only general information was given on health benefits of PA. SB was not addressed. There was no aftercare at the end of the 3 month CR program (initial phase).

2) CR+F: During the initial phase patients participated in standard CR as described above with the addition of three face-to-face, group PA counseling sessions (four to eight patients per session) lasting 75 min each. The sessions were facilitated by a physical therapist trained in motivational interviewing.[22] The content of the sessions was based on the following evidence-based behavioral change techniques: information about health behavior, self-monitoring, goal setting, feedback, barrier identification, and relapse prevention.[14,23,24] Pedometers (Yamax Digiwalker SW-200) were used to provide daily PA feedback and to facilitate goal-setting. The physical therapist coached the patient to set specific and realistic personal PA goals. In addition, a booklet with assignments focusing on goal setting, barrier

identification and relapse prevention was used. Information was provided about the health benefits of breaking up SB time.

After the initial 3 month period, a 9 month after-care program was offered that consisted of three face-to-face group sessions (six to eight patients per session). Every session consisted of a 1 hour exercise program followed by a 1 hour behavioral counseling program. The exercise program served as self-monitoring of aerobic capacity and also intended to stimulate interaction between patients in the group. The counseling sessions focused on permanent adoption of a healthy lifestyle (healthy diet, optimal PA, smoking cessation, medication adherence and stress management), but also on psychosocial problems. During the sessions information on health consequences of health behaviors was repeated and there was a focus on relapse prevention. The behavioral counseling sessions were led alternatingly by a physical therapist, a social worker, and a dietician who were all trained in motivational interviewing.

3) CR+T: Patients participated in the initial phase only in standard CR (see CR-only). After the initial 3 month period, a 9 month telephonic after-care program was offered that was based on the COACH program.[25] This program consisted of five to six individual telephone coaching sessions with specialized nurses who were trained in motivational interviewing.[22] Patients received information on risk factors and were encouraged to measure their coronary risk factors (cholesterol, blood pressure, glucose, weight) and define personal goals. Furthermore, psychosocial problems were discussed and patients were coached to develop a personal plan for a heart-healthy lifestyle (diet, PA, smoking cessation, medication adherence). During follow-up calls, progress was discussed. At the end of every phone call patients received a written overview of the topics that were discussed and the agreements made. SB was not addressed.

Measurements

Physical behavior measurement and processing

Measurements were performed directly after randomization (T0), at completion of standard CR (T3m, 3 months after randomization), completion of after-care (T12m, 12 months after randomization), and 6 months after completion of after-care (T18m, 18 months after randomization) (Appendix 11A). Measurements were performed by trained research assistants. Both patients and testers were not blinded to group allocation.

Patients were asked to wear a tri-axial accelerometer for 8 consecutive days during waking hours. Because consensus is lacking for how to process accelerometer data (e.g., determination of epoch length and cut-off points), the existing literature was consulted to determine data processing procedures, which have been described previously.[13] In short;

data were sampled at 30 Hz. The ActiGraph converts accelerations on three axes (vertical, horizontal and perpendicular axes) into activity counts and steps. Steps were processed using Actilife software. Counts were summed over a sampling interval (epoch) of 15 seconds using Actilife software and further processed using Matlab version R2011b. The vector magnitude (a composite measure of counts on the three axes) was used for analysis. Data were only included in the analysis when the accelerometer was worn for at least 4 days with a minimum of 660 min per day. In our data, a minimum of 660 min/day proved to be the most optimal threshold, which is a threshold that minimizes excluding measurements of patients that spend a long time in bed and maximizes excluding measurements of patients that did not wear the Actigraph a full valid[13] Non-wear time was defined as a minimum of 60 min of consecutive zeros. After subtracting the non-wear from the data, each 15 sec epoch was categorized as:

- MVPA: activities of ≥672.5 counts[26]
- Light activity: activities of >37.5 and <672.5 counts[26]
- SB: activities of ≤37.5 counts[27]

Physical behavior outcomes

After data processing, the following outcome measures were obtained:

Volume of physical behavior

- Duration of time spent in MVPA and SB, expressed as a percentage of wear time
- Step count, expressed as average steps per minute of wear time

Distribution of physical behavior over time

- Prolonged MVPA was defined as periods of at least 10 min, in accordance with recommendations.[2,8] In daily life, short MVPA interruptions seem reasonable (e.g., waiting for a traffic light). Therefore, a maximum of four (*not necessarily consecutive*) non-MVPA epochs were allowed during a prolonged MVPA period. Total time spent in prolonged MVPA was expressed as a percentage of wear time.
- Prolonged SB was defined as periods lasting at least 30 min. Although clear recommendations for SB are lacking, this time was chosen because interrupting SB every 30 min seems to be a feasible target for interventions. A sedentary period could include multiple short interruptions with a maximal duration of three *consecutive* 15 sec epochs of non-SB time. Thus, we defined a prolonged SB period as ending after at least 1 min of continuous non-SB. Total time spent in prolonged SB periods was expressed as percentage of wear time.

Attaining physical behavior recommendations

We investigated whether patients were meeting physical behavior recommendations. We calculated the number of patients that walked at least 6500 steps/day, which has been previously recommended for prevention of cardiac disease progression.[28,29] We also calculated whether participants met a target of ≥150 min of prolonged MVPA bouts

per week.[30] This guideline is consistent with those addressing secondary prevention of cardiovascular disease.[3,31,32] Because not all participants wore an accelerometer for a full week, we calculated the number of participants achieving a mean of 21.4 min of prolonged MVPA/day (150 min/7 days). For SB, currently no guidelines are available.

Sample size calculation

This RCT was designed to evaluate effects on cardiovascular risk profile (described in a separate paper) and physical behavior (current paper). A sample size calculation was performed for both outcome measures. Based on previous studies[33,34], it was hypothesized that patients randomized to CR+T or CR+F would reach a mean of 25 (+/-20) and 32 (+/-23) MVPA min/day at T18m, respectively, compared with a mean of 16 (+/-13) MVPA min/day in patients randomized to CR-only. To show differences between the newly developed interventions and CR-only with 80% power (based on a two-sided test with alpha = 0.05), 202 patients were needed per treatment arm. A drop-out rate of 20% was anticipated, thus the recruitment was targeted to enroll 245 patients per arm, or 735 total patients. This study size was sufficient to enable a post-hoc comparison between CR+F and CR+T, depending on actual findings, with adjustment for multiple testing. The required sample size was smaller than the number needed to evaluate cardiovascular risk profile differences. For logistic reasons, patient inclusion was restricted to the Rotterdam site of Capri for this part of the study.

Statistical analysis

Descriptive statistics were used to present baseline characteristics. Data on relative time in prolonged MVPA violated the normality assumptions, even after transformation. A large group of patients did not spend any time in prolonged MVPA, leading to a severe positive skew. Therefore, this outcome was dichotomized, and a value of '0' was given to those patients with no periods of prolonged MVPA and '1' to those patients with at least one period of prolonged MVPA.

Intention-to-treat (ITT) analysis with full datasets is preferred to avoid bias in RCTs.[35] However, patients who quit CR before T3m had no post-baseline accelerometry measurements; thus, a full ITT analysis was not possible. Only patients with at least one valid post-baseline physical behavior measurement were included in the analysis. A priori, it was decided to impute only missing baseline values and not post-baseline outcomes (study endpoints). We used generalized estimating equations (GEE) with exchangeable correlation structures to evaluate study endpoints. A GEE model was chosen because it corrects for missing values and because corrections are made for the dependency of observations within one individual.[36] GEE models use all available data of the dependent outcome and not only complete cases. Imputation of endpoints (in our case T3m, T12m, T18m) is therefore not needed.[36] First, overall models were made for each outcome measure, including group allocation, and baseline values of the outcome measure to correct for baseline differences

between patients. Next, the factor time and an interaction term between group and time were added to the overall model to compare between-group differences at the different time points. For continuous variables, the regression coefficient (B) of the group variable (representing between-group differences) is displayed. For dichotomous variables, between-group differences are displayed as odds ratios (ORs). All models were adjusted for age and sex. Missing values at baseline were imputed five times (multiple imputation) by predictive mean matching, using all available baseline characteristics and physical behavior outcomes at all time points as predictors. For all analyses, pooled results are reported.

To evaluate possible bias, baseline values (using *t*-tests and Chi-square tests) were compared for patients included and excluded from the main analysis. Additionally, two sensitivity analyses were performed: (1) ITT analysis: identical GEEs on all randomized patients after multiple imputation (five times) of missing data on all time points; and (2) per-protocol (PP) analysis: identical GEEs on patients that attended at least 75% of all sessions.

A *P* value <.05 was considered significant. All analyses were performed using SPSS version 20 (IBM Corp, Armonk, USA).

RESULTS

Patients

A total of 731 patients with ACS were randomized (Figure 11.1), 130 patients quit CR prematurely, and 112 additional patients did not have a post-baseline measurement. The 242 patients who did not complete the study were, on average, 4.5 years younger (P<.001), more likely to have had a past MI (13% vs 7%, P=.011), and more likely to smoke (65% vs 34%, P<.001). The remaining 489 patients who were included in the main analysis had a mean age of 59 years, and most were treated with percutaneous coronary intervention (Table 11.1).

Outcomes

At each time point, 69% to 86% of patients provided usable physical behavior measurements (Appendix 11B). Unsuccessful measurements resulted from technical problems, failure of measurements to meet the minimum required duration, or patient inability to visit the rehabilitation center for application of the accelerometer due to lack of time or motivation. At T0, 86 (17.5%) missing physical behavior outcomes were imputed. At other measurement times, missing data was not imputed.

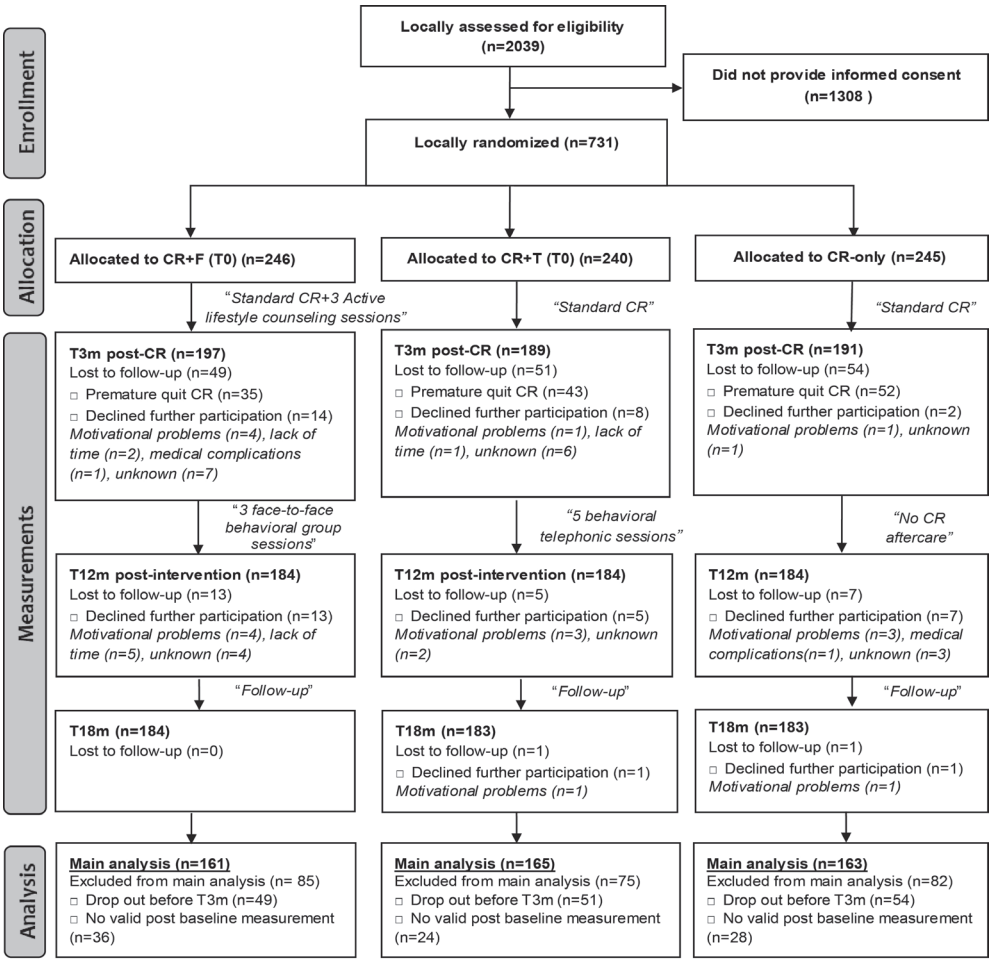

Figure 11.1 Consort flow diagram.
CR= cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m=month.

Table 11.1 Baseline participant characteristics (n=489)

Characteristics	CR+F (n=161)	CR+T (n=165)	CR-only (n=163)
Demographics			
Male, n (%)	129 (80)	141 (86)	131 (80)
Age in years, mean (SD)	58.8 (9)	58.2 (9)	59.1 (8)
Partnered, n (%)[†]	116 (81)	116 (87)	125 (84)
Employed, n (%)[‡]	78 (61)	75 (62)	72 (53)
Education, n (%)[§]			
High	38 (27)	44 (33)	40 (27)
Intermediate	97 (67)	83 (62)	101 (68)
Low	9 (6)	6 (5)	7 (5)
Therapeutic intervention at index event, n (%)			
No revascularization	12 (7)	15 (9)	14 (8)
PCI	130 (81)	124 (75)	129 (79)
CABG	20 (12)	27 (16)	21 (13)
Cardiac History, n (%)			
Myocardial infarction	9 (6)	15 (9)	11 (7)
Angina	8 (5)	10 (6)	11 (7)
PCI	12 (8)	15 (9)	16 (10)
CABG	2 (1)	1 (1)	4 (3)
Stroke/TIA	9 (6)	3 (2)	4 (3)
Risk Factors, n (%)			
Diabetes	19 (12)	18 (11)	21 (13)
Dyslipidemia	45 (28)	64 (39)	75 (46)
Family history	87 (54)	80 (49)	93 (57)
Smoking (pre-ACS)	62 (39)	61 (37)	49 (30)
Hypertension	70 (44)	68 (41)	68 (42)
Overweight	126 (79)	127 (77)	124 (76)
Medication, n (%)			
Acetylsalicylic acid	157 (98)	161 (98)	160 (98)
Oral anticoagulant	8 (5)	11 (7)	6 (4)
Thienopyridine	137 (86)	131 (79)	142 (87)
Cholesterol lowering medication	157 (98)	159 (96)	160 (98)
Beta-blocker	136 (85)	141 (86)	136 (83)
ACE inhibitor	116 (73)	115 (70)	116 (71)
Angiotensin II receptor blocker	19 (12)	22 (13)	21 (13)
Calcium blocker	19 (12)	24 (15)	19 (12)
Nitrate	70 (44)	50 (30)	57 (35)
Diuretic	17 (11)	23 (14)	19 (12)
Psychotropic	6 (4)	13 (8)	11 (7)

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; PCI= percutaneous coronary intervention; CABG= coronary artery bypass graft; TIA= transient ischemic attack; ACS= acute coronary syndrome.

[†]Data missing for n=17 (CR+G), n=31 (CR+T), and n=14 (CR-only).

[‡]Data missing for n=33 (CR+G), n=44 (CR+T), and n=28 (CR-only).

[§]Data missing for n=17 (CR+G), n=32 (CR+T), and n=15 (CR-only).

Intervention effects of CR+F compared to CR-only

Figure 11.2 displays observed study endpoints over time (for exact values see Appendix 11C). With respect to volume of physical behavior, there were no overall intervention effects for MVPA time (between-group difference=0.24%; 95% CI=-0.27 to 0.76; *P*=.349) and SB time (between-group difference= 0.39%; 95% CI=0.82 to 1.59; *P*=.529). However, we did find overall intervention effects for step count (between-group difference= 0.45 steps/min of wear time; 95% CI=0.03 to 0.86; *P*=.035) and for prolonged MVPA (OR=2.01; 95% CI=1.30 to 3.14; *P*=.002; Table 11.2). Overall effects were also noted for achieving ≥6500 steps/day (OR=1.77; 95% CI=1.20 to 2.60; *P*=.004; Table 11.2).

Those patients randomized to CR+F participated in extra PA counseling sessions between T0 and T3m. Compared to CR-only patients, CR+F patients at T3m improved their step count with 0.59 steps per min of wear time more (95% CI=0.09 to 1.09; *P* =.021). This difference corresponds to an additional 513 steps per 14.5 hours of daytime waking hours. Furthermore, the odds of having prolonged MVPA periods ≥10 min were 2.14 times higher in the CR+F group compared to CR-only (95% CI=0.99 to 4.62; *P*=.054). Those patients randomized to CR+F also participated in a face-to-face, after-care program between T3m and T12m. Although between-group differences in increases in step count were not maintained long-term, the odds of spending time in prolonged MVPA were still 1.86 times higher at T12m (95% CI=1.04 to 3.32; *P*=.037) and 1.91 times higher at T18m (95% CI=1.05 to 3.44; *P*=.033) compared to CR-only.

At T3m and T12m, patients in the CR+F group were more likely to meet ≥6500 steps/day compared to those in the CR-only group (OR=2.00; 95% CI=1.19 to 3.35; *P*=.009; and OR=1.81; 95% CI=1.07 to 3.09; *P*=.028, respectively). This difference was no longer significant at T18m.

Intervention effects of CR+T compared to CR-only

There were no overall intervention effects for MVPA time (B=-0.15%; 95% CI=-0.65 to 0.34; *P*=.544) or step count (B=-0.14 steps/min of wear time; 95% CI=-0.58 to 0.30; *P*=.536). There were also no intervention effects noted with respect to SB time, PA distribution, and SB distribution (Table 11.2).

Outcome sensitivity analyses

For the sensitivity ITT analysis, all 731 randomized patients were analyzed after imputation at all time points. This analysis showed smaller intervention effects compared to the main analysis. The 428 patients who did participate in at least 75% of scheduled sessions were analyzed in the sensitivity PP analysis. That analysis showed slightly larger effects (Appendix 11D and 11E).

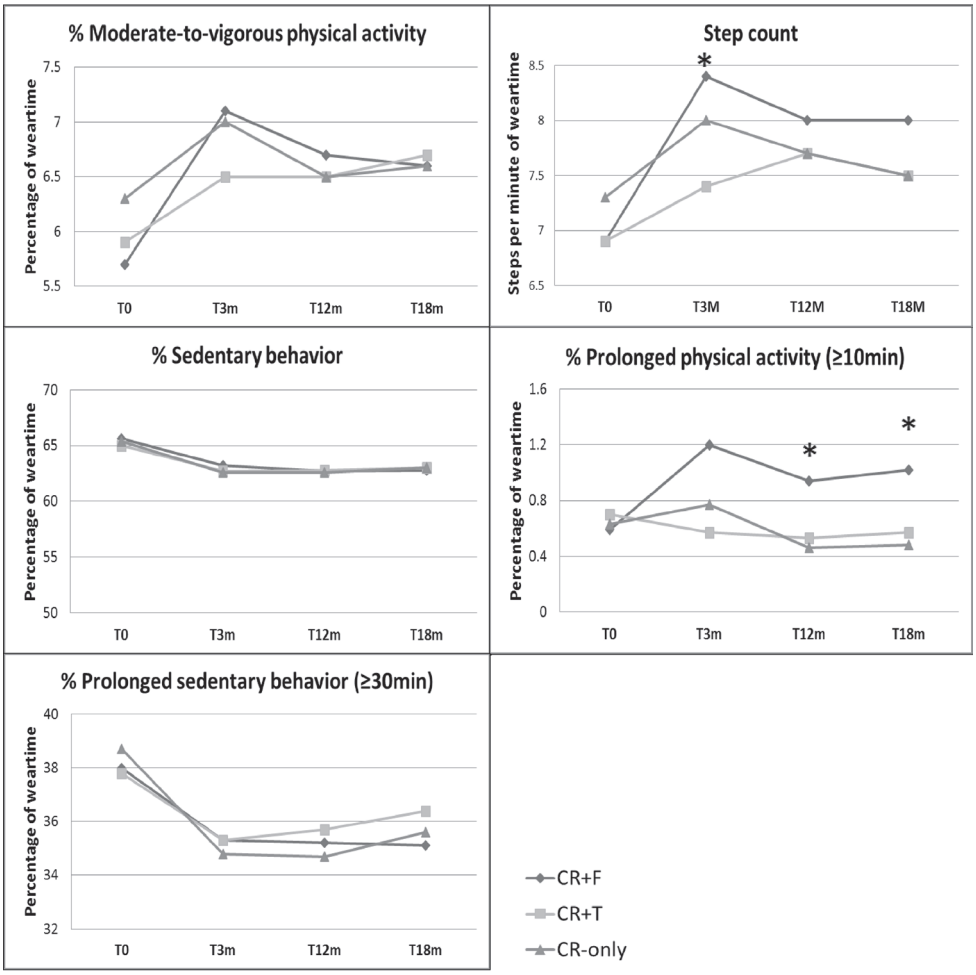

Figure 11.2 Volume of physical behavior and distribution over time.
*Abbreviations as in Figure 11.1. *Significant intervention effect for CR+F compared to CR-only.*

Table 11.2 Main analysis: generalized estimating equation models[†] of intervention effects

Physical behavior		CR+F (n=161) vs CR-only (n=163)			CR+T (n=165) vs CR-only (n=163)		
		B[‡]	CI	P	B[‡]	CI	P
Volume							
MVPA	overall	0.24	-0.27:0.76	0.349	-0.15	-0.65:0.34	0.544
(% of wear time)	ΔT0-T3m	0.34	-0.24:0.92	0.245	-0.48	-1.01:0.04	0.073
	ΔT0-T12m	0.22	-0.42:0.85	0.502	-0.11	-0.78:0.55	0.736
	ΔT0-T18m	0.08	-0.62:0.77	0.832	0.17	-0.52:0.86	0.621
Step count	overall	**0.45**	**0.03:0.86**	**0.035***	-0.14	-0.58:0.30	0.536
(nr of steps per min of	ΔT0-T3m	**0.59**	**0.09:1.09**	**0.021***	-0.44	-0.91:0.03	0.067
wear time)	ΔT0-T12m	0.22	-0.30:0.74	0.408	-0.06	-0.66:0.53	0.835
	ΔT0-T18m	0.44	-0.16:1.03	0.150	0.12	-0.48:0.72	0.692
SB	overall	0.39	-0.82:1.59	0.529	0.35	-1.07:1.77	0.632
(% of wear time)	ΔT0-T3m	0.59	-0.80:1.98	0.404	0.51	-0.98:1.99	0.505
	ΔT0-T12m	0.44	-1.12:2.00	0.583	0.40	-1.49:2.29	0.679
	ΔT0-T18m	0.10	-1.62:1.83	0.905	0.10	-1.86:2.06	0.918
Distribution							
MVPA bout >10min	overall	**2.01**[§]	**1.30:3.14**	**0.002***	1.02[§]	0.69:1.50	0.935
(% of wear time)[§]	ΔT0-T3m	2.14[§]	0.99:4.62	0.054	0.77[§]	0.42:1.45	0.425
	ΔT0-T12m	**1.86**[§]	**1.04:3.32**	**0.037***	1.30[§]	0.76:2.25	0.341
	ΔT0-T18m	**1.91**[§]	**1.05:3.44**	**0.033***	0.83[§]	0.48:1.44	0.505
Prolonged SB (≥30min)	overall	0.76	-1.02:2.53	0.403	1.08	-0.98:3.14	0.303
(% of wear time)	ΔT0-T3m	0.57	-1.56:2.69	0.602	0.80	-1.52:3.12	0.499
	ΔT0-T12m	1.42	-0.79:3.63	0.208	1.36	-1.09:3.81	0.277
	ΔT0-T18m	0.29	-2.15:2.73	0.815	1.14	-1.56:3.85	0.408
Achieving guidelines, %							
150 min prolonged	overall	1.60[§]	0.97:2.64	0.069	1.02[§]	0.58:1.77	0.957
MVPA/week[§]	ΔT0-T3m	1.75[§]	0.89:3.47	0.107	0.81[§]	0.37:1.75	0.590
	ΔT0-T12m	1.60[§]	0.80:3.17	0.184	1.00[§]	0.47:2.12	0.995
	ΔT0-T18m	1.45[§]	0.71:2.98	0.306	1.32[§]	0.65:2.66	0.409
6500 steps/day[§]	overall	**1.77**[§]	**1.20:2.60**	**0.004***	0.90[§]	0.60:1.34	0.594
	ΔT0-T3m	**2.00**[§]	**1.19:3.35**	**0.009***	0.90[§]	0.54:1.51	0.700
	ΔT0-T12m	**1.81**[§]	**1.07:3.09**	**0.028***	0.87[§]	0.51:1.47	0.606
	ΔT0-T18m	1.45[§]	0.83:2.52	0.190	0.92[§]	0.53:1.59	0.768

*CR+F = cardiac rehabilitation plus face-to-face group counseling; CR+T = cardiac rehabilitation plus telephonic counseling; CR-only = standard cardiac rehabilitation; MVPA = moderate-to-vigorous physical activity; SB = sedentary behavior; m=months. [†]All analyses were adjusted for baseline values, sex, and age. The CR-only group is the referent group for all analyses. [‡]The regression coefficient (B) represents the between-group difference and thus the intervention effect relative to CR-only at the specified time point. [§]For dichotomous variables odds ratios are displayed. *P < .05*

DISCUSSION

Neither the novel behavioral CR interventions improved MVPA time (eg, brisk walking or sports activities) compared to standard CR. However, results from the CR+F group showed that integrating pedometer-based face-to-face group PA counseling into the initial phase of CR improved PA by an additional 500 steps/day, which is an encouraging result. PA distribution over time also improved, with MVPA accumulating more often in prolonged periods of at least 10 minutes, which is recommended for optimal health. As patients in the CR+F group progressed through the face-to-face after-care program, improvements in step count partly diminished. However, improvements in prolonged PA were maintained. The CR+T group experienced no benefit compared to CR-only.

Consistent with previous intervention studies in healthy subjects[37], our results show that achieving lasting PA change is a challenge. Nevertheless, we were encouraged by improvements in the CR+F group daily step count. A previous study showed that 6500 steps per day corresponds to the minimum energy expenditure (1500 kcal/week) needed to prevent disease progression in patients with ACS.[28] After the initial phase of CR and after completion of the after-care program, more patients in the CR+F group met this step count goal compared to those in the CR-only group (62% vs 49% at T3m; 60% vs 47% at T12m). In addition to step volume improvement, there were long-lasting improvements in time in prolonged MVPA compared to CR-only. Nevertheless, this improvement did not translate to differences in achievement of 150 min/week of exercise in prolonged MVPA. Adherence rates with this last guideline may be underestimated, however, because the guideline is based on self-report, whereas our data were objectively measured.[38]

In a previous publication, we concluded that the novel interventions do not result in relevant improvements in cardiovascular risk factors such as lipid profile, blood pressure, BMI and waist circumference.[39] This could suggest that the improvements we found with regard to PA were insufficient to yield improvements in cardiovascular health. An alternative explanation is that the association between PA and cardiovascular health is masked by the effects of cardio protective medication. The majority of patients were taking aspirins, statins, beta-blockers, and ACE-inhibitors which resulted in already well-controlled lipids and blood pressure at baseline ('ceiling effect'). Regardless of the correct explanation, adoption of an active lifestyle remains important since PA can influence cardiovascular mortality through other pathways (e.g. by improving coronary blood flow, augmenting cardiac function or enhancing endothelial function).[40] In addition, PA was previously found to be associated to other health outcomes such as fitness and several chronic diseases.[40,41]

Time spent sedentary remained high for all groups. Although general advice was given to CR+F participants about the health benefits of regularly breaking up SB time, the focus of these sessions concerned PA; this focus might explain the lack of effects. Likewise, the CR+T group did not improve their time in SB after PA counseling. Previous studies support the finding that PA interventions do not affect sedentary time.[15]

To our knowledge, this is the first study investigating the effects of a physical behavior

counseling program integrated into the initial phase of multidisciplinary CR. A large meta-analysis summarizing the effect of PA interventions among healthy subjects found improvements in step count of the same magnitude as seen in CR+F participants in our study.[37]

After the initial phase of CR, the CR+F group participated in a face-to-face after-care program focused on multiple lifestyle components. Previous studies investigating the effectiveness of such interventions have mainly relied on less well-validated self-reported PA.[17-19] A previous study that used objective pedometry to measure intervention effectiveness showed larger and longer-lasting effects in daily step count compared to our study.[42] However, patients in that study were measured using the same (non-blinded) pedometers as used during the investigated intervention for feedback, which may have biased their findings. Our study adds the finding that increased step count does not necessarily translate to increased MVPA time. A possible explanation is that a part of the walking activities was classified as light intensity. Another explanation is that the extra walking activities were compensated for by decreasing other MVPA activities. Future research is needed to determine whether increasing total stepping activities (independent of intensity) or increasing total MVPA time is more important for health.

In contrast to our study, two previous studies investigating the effects of the COACH program on which our telephonic after-care program (CR+T) was based, did show PA improvements.[25,43] These outcomes were also self-reported, which may explain the discrepancy between those studies and our present study.

Although the increases in step count achieved by the CR+F group are encouraging, optimization of the intervention is needed. Results of our study suggest future directions. Firstly, our finding that patients responded to objective feedback on walking activities (in our study provided by pedometers) by increasing their daily step count is consistent with a previous review that emphasized the importance of self-monitoring for PA change.[14] Possibly, our counseling sessions could be improved by not only providing feedback on walking activities, but also on volume and distribution of total MVPA and SB, which is possible with new technologies. Secondly, our after-care programs that focused on several heart-healthy lifestyle components simultaneously were ineffective in improving PA compared to the pedometer-based counseling sessions during the initial phase of CR. Like Conn et al[37,44], we hypothesize that for successful improvements in physical behavior, sessions may need to focus exclusively on PA and SB. Studies investigating the effects of CR after-care programs focusing solely on PA have provided inconsistent results thus far, suggesting that further research is needed to determine the optimal format.[45,46] Patients probably require ongoing attention, which could be feasible using E-health solutions.[47]

Although after-care optimization is needed, we recommend that face-to-face group counseling sessions, including objective PA feedback, be added to standard CR. The CR+F intervention was imbedded in an existing and reimbursed CR program and consisted

of a small number of additional sessions performed in groups. Therefore, costs of the intervention are estimated to be relatively low. However, for successful implementation and reimbursement, a detailed economic evaluation of our intervention is needed.

Limitations

We included only patients who had at least one follow-up measurement. This method may have biased our results. To test for bias, we performed two sensitivity analyses. Because between-group differences were more pronounced in patients attending at least 75% of sessions and less pronounced when we performed a stricter ITT analysis that included all randomized patients, our results are probably valid primarily in more adherent patients.

Objective PA measurement is the method of choice, as it is more valid than self-reported measures.[19] However, accelerometry also has limitations. Firstly, cut-off points used for PA intensity categories were developed for a healthy population. Consequently, PA intensity may be underestimated for patients with lower fitness levels. Secondly, incorrect categorizing of "standing still" as "SB" in our study cannot be ruled out. Finally, participants were aware that their PA was being measured, which may have influenced their behavior. Because our measurement period lasted at least 4 days, we expect this effect to be minimal and equal between groups.

CONCLUSIONS

None of the investigated novel CR programs were successful in increasing total MVPA. However, adding three pedometer-based, face-to-face group counseling sessions that focused exclusively on changing physical behavior during the initial phase of CR was effective in improving daily step count and increasing time spent in prolonged MVPA. After the face-to-face after-care program focusing on several healthy lifestyle components ended, only improvement in prolonged MVPA was maintained. The intervention was not successful in changing SB. The telephonic after-care program that focused on several healthy lifestyle components did not improve PA or SB. Although after-care optimization is needed to improve long-term adherence, we recommend that face-to-face group counseling sessions including objective PA feedback be added to standard CR.

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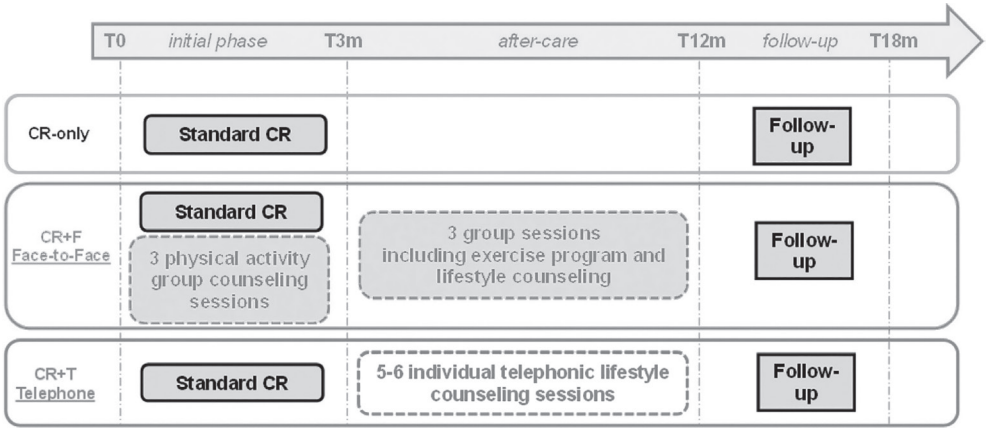
APPENDIXES

Appendix 11A Treatment allocation



CR= cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m=month.

Appendix 11B Usable physical behavior measurements, failed measurements, no-shows, and drop-outs at each time point

Measurement time	Group (n)	Successful measurements n (%)	Failed measurements† n (%)	Measurement not performed n (%)	Drop-out n (%)
T0	**CR+F** (161)	128 (79)	8 (5)	25 (16)	0
	CR+T (165)	135 (82)	9 (5)	21 (13)	0
	CR-only (163)	140 (86)	12 (7)	11 (7)	0
T3m	**CR+F** (161)	134 (83)	10 (6)	17 (11)	0
	CR+T (165)	139 (84)	11 (7)	15 (9)	0
	CR-only (163)	126 (77)	20 (12)	17 (11)	0
T12m	**CR+F** (161)	121 (75)	10 (6)	24 (15)	6 (4)
	CR+T (165)	119 (72)	10 (6)	34 (21)	2 (1)
	CR-only (163)	134 (82)	9 (5)	19 (12)	1 (1)
T18m	**CR+F** (161)	112 (69)	16 (10)	27 (17)	6 (4)
	CR+T (165)	117 (71)	18 (11)	27 (16)	3 (2)
	CR-only (163)	130 (80)	12 (7)	19 (12)	2 (1)

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m= months.
†Failure to obtain measurements resulted from technical problems or because the measurement did not meet the minimum required duration of 4 days.

Appendix 11C Physical behavior at each time point, per allocation group

Physical behavior	CR+F (n=161)				CR+T (n=165)				CR-only (n=163)			
	T0 (n=128)	T3m (n=134)	T12m (n=121)	T18m (n=112)	T0 (n=135)	T3m (n=139)	T12m (n=119)	T18m (n=117)	T0 (n=140)	T3m (n=126)	T12m (n=133)	T18m (n=130)
Volume, mean (SD)												
MVPA (% of wear time)	5.7	7.1	6.7	6.6	5.9	6.5	6.5	6.7	6.3	7.0	6.5	6.6
	(2.5)	(2.8)	(3.0)	(3.1)	(2.8)	(2.7)	(3.3)	(3.3)	(2.9)	(2.7)	(3.0)	(3.1)
Step count (nr of steps per min of wear time)	6.9	8.4	8.0	8.0	6.9	7.4	7.7	7.5	7.3	8.0	7.7	7.5
	(2.2)	(2.6)	(2.6)	(2.8)	(2.6)	(2.7)	(3.3)	(2.8)	(2.9)	(2.5)	(2.8)	(2.9)
SB (% of wear time)	65.6	63.2	62.7	62.8	65.0	62.7	62.8	63.0	65.4	62.6	62.6	63.0
	(8.3)	(7.4)	(8.1)	(7.7)	(8.3)	(8.4)	(10.0)	(8.5)	(8.2)	(7.3)	(8.2)	(9.0)
Distribution, mean (SD)												
Prolonged MVPA (≥ 10 min; % of wear time)	0.59†	1.20†	0.94†	1.02†	0.7†	0.57†	0.53†	0.57†	0.63†	0.77†	0.46†	0.48†
	(0:5.2)	(0:7.1)	(0:6.6)	(0:10.3)	(0:8.3)	(0:8.9)	(0:5.6)	(0:10.8)	(0:8.3)	(0:7.8)	(0:6.9)	(0:8.2)
Prolonged SB (≥ 30 min; % of wear time)	38.0	35.3	35.2	35.1	37.8	35.3	35.7	36.4	38.7	34.8	34.7	35.6
	(12.5)	(10.8)	(11.9)	(11.8)	(13.1)	(12.7)	(13.8)	(12.8)	(11.9)	(11.1)	(11.1)	(12.3)
Achieving guidelines, %												
6500 steps	36.7	61.9	60.3	58.6	38.5	46.8	46.2	47.9	39.3	49.2	46.6	49.2
150 min prolonged MVPA/wk	17.2	19.4	21.5	22.3	14.8	10.8	14.3	17.1	17.1	12.7	13.5	14.6

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; MVPA= moderate-to-vigorous physical activity; SB= sedentary behavior; m=months.

†Because outcomes violated the normality assumptions, medians (ranges) are displayed.

Appendix 11D Sensitivity analysis Intention-to-treat: generalized estimating equation models[†] of intervention effects

Physical behavior		CR+F (n=246) vs CR-only (n=245)			CR+T (n=240) vs CR-only (n=245)		
		B[‡]	CI	P	B[‡]	CI	P
Volume							
MVPA	overall	-0.002	-0.44:0.44	0.993	-0.17	-0.62:0.27	0.439
(% of wear time)	ΔT0-T3m	0.12	-0.48:0.71	0.703	-0.28	-1.12:0.56	0.489
	ΔT0-T12m	-0.11	-0.75:0.54	0.746	-0.31	-0.97:0.35	0.351
	ΔT0-T18m	-0.02	-0.86:0.83	0.971	0.07	-0.58:0.72	0.827
Step count (nr of steps per	overall	0.27	-0.01:0.55	0.056	-0.01	-0.30:0.28	0.957
min of wear time)	ΔT0-T3m	0.27	-0.09:0.63	0.136	-0.24	-0.60:0.12	0.188
	ΔT0-T12m	0.15	-0.23:0.53	0.429	0.04	-0.38:0.47	0.841
	ΔT0-T18m	0.39	-0.04:0.83	0.077	0.17	-0.23:0.58	0.399
SB	overall	0.22	-0.54:0.99	0.571	0.15	-0.68:0.99	0.723
(% of wear time)	ΔT0-T3m	0.38	-0.55:1.31	0.420	0.15	-0.90:1.20	0.776
	ΔT0-T12m	0.31	-0.78:1.39	0.577	0.29	-0.90:1.49	0.628
	ΔT0-T18m	-0.03	-1.36:1.30	0.966	0.01	-1.17:1.19	0.985
Distribution							
Prolonged MVPA (≥10min)	overall	1.25[§]	0.81:1.91	0.283	1.05[§]	0.72:1.53	0.785
(% of wear time)	ΔT0-T3m	1.23[§]	0.73:2.07	0.433	1.04[§]	0.54:1.99	0.898
	ΔT0-T12m	1.25[§]	0.70:2.23	0.425	1.24[§]	0.77:1.99	0.361
	ΔT0-T18m	1.27[§]	0.54:2.95	0.534	0.90[§]	0.56:1.43	0.640
Prolonged SB (≥30min)	overall	0.32	-1.65:2.29	0.731	0.44	-1.04:1.91	0.560
(% of wear time)	ΔT0-T3m	-0.06	-1.97:1.84	0.947	-0.42	-3.06:2.23	0.743
	ΔT0-T12m	0.75	-1.62:3.12	0.517	1.04	-0.87:2.95	0.285
	ΔT0-T18m	0.28	-2.92:3.47	0.851	0.68	-1.50:2.87	0.534

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; MVPA= moderate-to-vigorous physical activity; SB= sedentary behavior; m= months.

[†]All analyses were adjusted for baseline values, sex, and age. The CR-only group is the referent group for all analyses.

[‡]The regression coefficient (B) represents the between-group difference and thus the intervention effect relative to CR-only at the specified time point.

[§]Because outcomes violated normality assumptions, prevalence of prolonged MVPA was dichotomized, with '0' indicating no periods and '1' indicating at least one period. Instead of regression coefficients, odds ratios are displayed to indicate the odds (relative risk) of having any MVPA period greater than 10 min, relative to CR-only at the specified time point.

Appendix 11E Sensitivity analysis per-protocol: generalized estimating equation models[†] of intervention effects

Physical behavior		CR+F (n=138) vs CR-only (n=163)			CR+T (n=127) vs CR-only (n=163)		
		B[‡]	CI	P	B[‡]	CI	P
Volume							
MVPA	overall	0.37	-0.15:0.89	0.165	-0.26	-0.78:0.27	0.331
(% of wear time)	ΔT0-T3m	0.52	-0.08:1.13	0.089	-0.53	-1.07: -0.03	0.051
	ΔT0-T12m	0.36	-0.29:1.0	0.276	-0.30	-1.01:0.40	0.399
	ΔT0-T18m	0.18	-0.51:0.88	0.607	0.07	-0.67:0.82	0.847
Step count (nr of steps	overall	**0.55**	**0.13:0.98**	**0.010***	-0.24	-0.70:0.22	0.307
per min of wear time)	ΔT0-T3m	**0.79**	**0.26:1.32**	**0.003***	-0.44	-0.93:0.05	0.078
	ΔT0-T12m	0.33	-0.20:0.86	0.227	-0.29	-0.89:0.31	0.347
	ΔT0-T18m	0.52	-0.07:1.11	0.085	0.01	-0.63:0.65	0.980
SB	overall	0.11	-1.10:1.33	0.855	0.75	-0.73:2.24	0.321
(% of wear time)	ΔT0-T3m	0.19	-1.24:1.62	0.797	0.76	-0.78:2.31	0.334
	ΔT0-T12m	0.26	-1.32:1.84	0.749	0.97	-0.95:2.90	0.321
	ΔT0-T18m	-0.10	-1.80:1.61	0.911	0.53	-1.52:2.58	0.614
Distribution							
Prolonged MVPA	overall	**0.73**[‡]	**0.28:1.19**	**0.002***	1.02[‡]	0.67:1.54	0.941
(≥10min)	ΔT0-T3m	0.73[‡]	-0.08:1.54	0.079	0.76[‡]	0.39:1.48	0.411
(% of wear time)	ΔT0-T12m	**0.76**[‡]	**0.15:1.37**	**0.014***	1.39[‡]	0.77:1.10	0.237
	ΔT0-T18m	**0.68**[‡]	**0.07:1.29**	**0.028***	0.80[‡]	0.44:1.45	0.460
Prolonged SB (≥30min)	overall	0.35	-1.47:2.17	0.706	1.819	-0.38:4.02	0.105
(% of wear time)	ΔT0-T3m	-0.01	-2.23:2.21	0.995	1.33	-1.13:3.80	0.291
	ΔT0-T12m	1.07	-1.18:3.33	0.351	2.29	-0.34:4.91	0.088
	ΔT0-T18m	-0.024	-2.43:2.38	0.985	1.95	-0.93:4.83	0.184

CR+F = cardiac rehabilitation plus face-to-face group counseling; CR+T = cardiac rehabilitation plus telephonic counseling; CR-only = standard cardiac rehabilitation; MVPA = moderate-to-vigorous physical activity; SB = sedentary behavior; m=months.

[†]All analyses were adjusted for baseline values, sex, and age. The CR-only group is the referent group for all analyses.

[‡]The regression coefficient (B) represents the between-group difference and thus the intervention effect relative to CR-only at the specified time point. [§]Because outcomes violated normality assumptions, prevalence of prolonged MVPA was dichotomized, with '0' indicating no periods and '1' indicating at least one period. Instead of regression coefficients, odds ratios are displayed to indicate the odds (relative risk) of having any MVPA period greater than 10 min, relative to CR-only at the specified time point. * *P*< .05.

Chapter 12

PATIENTS WHO DO NOT COMPLETE CARDIAC REHABILITATION HAVE INCREASED RISK OF CARDIOVASCULAR EVENTS DURING LONG-TERM FOLLOW-UP: LESSONS LEARNED FROM OPTICARE

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Submitted.

ABSTRACT

Background

Cardiac rehabilitation (CR) has favourable effects on cardiovascular mortality and morbidity. Therefore, it might reasonable to expect that incomplete CR participation will result in suboptimal patient outcomes.

Methods

We studied the 914 post-Acute Coronary Syndrome patients (mean age 57 years, 19 % woman) who participated in the OPTImal CArdiac REhabilitation (OPTICARE) trial. They all started a 'standard' CR program, with physical exercises (group sessions) twice a week during 12 weeks. Incomplete CR was defined as participation in <75% of the scheduled physical activities. Patients were followed-up for 2.7 years, and the incidence of cardiac events was recorded. Major adverse cardiac events (MACE) included all-cause mortality, non-fatal MI and coronary revascularization. We studied differences in cardiac events and MACE between patients with incomplete and complete CR by Cox regression, with adjustment for age, gender, prior cardiovascular event, diabetes, hypertension, familiar history, smoking, hypercholesterolemia and study treatment. Determinants of incomplete CR were studied with logistic regression.

Results

A total of 142 (16 %) patients had incomplete CR. They had higher incidence of MACE than their counterparts who completed CR (11.3% versus 3.8%, adjusted hazard ratio [aHR] 2.86 and 95% confidence interval [CI] 1.47-5.26). Also the incidence of any cardiac event, including MACE and coronary revascularisation, was higher (20.4% versus 11.0%, aHR 1.54; 95% CI 0.98-2.44). Patients with incomplete CR were more often persistent smokers than those who completed CR (31.7% versus 11.5%), but clinical characteristics were similar otherwise.

Conclusion

Post-ACS patients who did not complete a 'standard' 12-week CR program had higher incidence of adverse cardiac events during long-term follow-up than those who completed the program. Since CR is proven beneficial, further research is needed to understand the reasons why patients terminate prematurely.

INTRODUCTION

Cardiac Rehabilitation (CR) is a class I recommended intervention in coronary artery disease (CAD) patients (1,2) and has beneficial effects on physical fitness, quality of life, cardiovascular risk factors and clinical outcome, including mortality (3-5). Despite the evidence of these beneficial effects, CR programs are still largely underutilized (6). Importantly, also a substantial number of patients that do participate in CR attend only a few sessions and then drop out prematurely. It might reasonably be expected that such suboptimal CR participation results also in less favorable results. Suaya (7) and Beauchamp (8) were the first to describe a possible relation between the number of sessions attended and mortality. In more recent studies such a relation was also found in specific populations, including diabetic patients and women with CAD (9,10). However, contradictory findings of CR results were also reported (11), which may be caused by the lack of an unanimous definition of CR 'participation' and 'completion'. For example, in several studies the attendance of at least one session was already regarded as CR participation (12,13), whereas others use a more stringent definition (7,8).

Recently, we presented the OPTImal CArdiac REhabilitation (OPTICARE) a randomized controlled CR trial that enrolled 914 post-Acute Coronary Syndrome (ACS) patients (14,15). All patients started a 'standard' 12-week CR program, and we studied whether or not completing the program was associated with the incidence of adverse cardiac events during prolonged follow-up.

METHODS

Patients

OPTICARE was an open, randomized, controlled trial that studied the effects of intensified and prolonged CR on cardiac risk profile, levels of daily physical activity, quality of life and health care consumption in patients after an ACS. Details on in- and exclusion criteria and study procedures are described in the OPTICARE design paper (14). Briefly, 914 patients who were discharged alive after ACS admission were scheduled to receive 'standard' CR (see below) for 12 weeks according to the European Society of Cardiology (ESC) guidelines (16). A total of 608 patients were randomized to receive extended CR with extra behavioral counselling in individual telephone sessions or group sessions until 9 months after completion of standard CR. The primary outcome was the SCORE (Systematic COronary Risk Evaluation) 10-year cardiovascular mortality risk function at 18 months after the index ACS. Results of OPTICARE showed no additional benefits with respect to SCORE in patients randomized to extended CR (15). Patients largely reached target levels of modifiable risk factors already following standard CR. Therefore, for the purpose of the current analysis, all OPTICARE patients were analyzed as an homogeneous cohort.

Cardiac Rehabilitation according to the Capri program

Cardiac rehabilitation was offered by Capri Cardiac Rehabilitation (Capri CR) at eight different locations in the cities of Rotterdam and The Hague (www.caprihr.nl), with referrals from 10 hospitals in the broader Rotterdam/The Hague region. The core of the Capri CR program consists of twice a week 1.5 hours group exercise sessions. Besides the exercise program, verbal and written instructions are given on how to deal with exercise, diet, smoking cessation and stress management. The aim of the program is to improve adherence to lifestyle modification, and to help patients to adopt a positive role in the care of their own health. If necessary, individual consultations with psychiatrist, psychologist, social workers and dieticians are provided. The exact length of a CR program is determined together with the patient by a multidisciplinary team led by a physician, specialized physiotherapists, nurses and social workers with an average duration of 12 weeks. Upon completion of the CR program, a maximum (symptom-limited) bicycle stress test is performed.

For the current analysis, CR is defined as 'complete' if the participant attended at least 75% of the physical program, and 'incomplete' otherwise (8).

Data collection

Data were collected on demographic variables, cardiovascular risk factors and cardiovascular history. Data on cardiovascular risk factors were measured, as these were part of the OPTICARE study endpoint (SCORE). Systemic arterial hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, or treatment for hypertension. Hypercholesterolemia was defined as a total cholesterol >6.0 mmol/l or treatment for hypercholesterolemia before index event. Diabetes was diagnosed as a fasting

plasma glucose >7.0 mmol/L or the use of glucose-lowering therapy medication. Smoking was defined as self-reported smoking at the index ACS. At randomization, self-reported smoking cessation was verified by using a Smokerlyzer, which measures the concentration of carbon monoxide in breath. Family history of premature CAD was defined as a self-reported history of any first-degree family member with a history of myocardial infarction (MI), PCI, or coronary artery bypass grafting (CABG) before the age of 60 years.

Clinical endpoints

For the current analysis, clinical endpoint were collected until DATE, which resulted in a median (IQR) follow-up of 2.7 (range 2 years to 5 years) after the index ACS. We defined the incidence of major adverse cardiovascular events (MACE) as our primary endpoint, which includes all-cause mortality, non-fatal MI and coronary revascularization. We also collected data on other cardiovascular events, including hospitalization for unstable angina (chest pain in rest with negative biomarkers but positive stress testing), stable angina (chest pain on exertion with negative biomarkers), nonspecific chest pain (chest pain in rest with negative biomarkers and negative or absent stress testing), cardiac arrhythmia's and heart failure. We also counted cardiac emergency room visits without hospitalization. All clinical endpoints were verified by an independent Clinical Event Committee.

Statistical analysis

Continuous variables were presented as mean (standard deviation), whereas categorical variables are expressed as numbers and percentages. Comparisons between patients with and without completed CR were performed by the Student's t-test for continuous variables, and Pearson's chi-square test or Fishers exact tests, for categorical variables.

The cumulative incidence of the clinical endpoints over time was studied by the Kaplan-Meier method, whilst log-rank tests were applied to evaluate differences between patients with and without completed CR. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Cox regression analyses were performed to further study whether or not completing the program was associated with the incidence of study endpoints. We ran univariable models, and multivariable models with adjustment for outcome determinants and potential confounders. In view of the number of MACE events (N=45, see Results section), in the corresponding MACE-model we decided to only adjust for age, gender, diabetes, prior history of cardiovascular events, and randomly allocated study treatment, in order to avoid model overfitting (17). With respect to any cardiovascular events, we adjusted for age, gender, prior cardiovascular event, diabetes, hypertension, familiar history, smoking, hypercholesterolemia and study treatment. Findings are presented as crude hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI).

Logistic regression analyses were performed to identify factors that were associated with CR incompletion. We considered the following factors: age, sex, prior cardiovascular event, diabetes, hypertension, family history of premature CAD, smoking and hypercholesterolemia. Findings are presented as odds ratios (OR) with 95% confidence intervals (CI).

All statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 24 for Windows (SPSS Inc., Chicago, Il, USA).

RESULTS

Patient characteristics

In total, 770 (84%) patients completed CR, and 142 patients (16 %) did not. Patients who completed CR had on average 23 exercise sessions, as compared with 6 sessions in those who did not complete CR (p-value <0.001). Patients with and without CR completion had similar baseline characteristics, except for smoking, and the use of statins and ACE inhibitors: those who did not complete CR were more often persistent smokers (31.7% versus 11.5 %, p-value <0.001) (Table 12.1).

CR incompletion and clinical endpoints

Fourty-five patients (4.9%) had at least one MACE (Table 12.1). The incidence of MACE was higher in the patients who had incomplete CR than in their counterparts who completed the program (11.3 % versus 3.8%; HR 2.94 and 95% CI 1.59-5.55). After adjustment for multiple factors (see Methods), this relation remained significant (aHR 2.86 and 95% CI 1.47-5.26).

In total, 114 patients (12.5%) suffered from one or more cardiovascular event (Table 12.2). The cumulative incidence of any cardiovascular event at 4 years in complete CR versus incomplete CR was 18% and 25% according to the Kaplan-Meier method , respectively (log-rank p=0.006) (Figure 12.1). Incomplete CR was associated with higher incidence of cardiovascular events (HR 1.69; 95% CI 1.11-2.56). Again, after adjustment for multiple factors, this relation remained, although our criterion for statistical significance was not met (HR 1.54; 95% CI 0.98-2.44).

Predictors of incomplete CR

Persistent smokers had 2.78 times higher odds of incomplete CR than those who quitted smoking since the ACS admission (OR 2.78 and 95% CI 1.70-4.55, p-value <0.001) (Table 12.1). Never smokers tended to have a lower odds of incomplete CR than quitters, but this difference was statistically non-significant. We could not identify any other characteristic that (independent of smoking behaviour) related with higher or lower odds of incomplete CR. The C-index of the logistic regression model that related smoking behaviour with completing the CR program was 0.63. Thus, patients could not satisfactorily be identified as (non)completers on the basis of their smoking behaviour alone.

DISCUSSION

We found that post-ACS patients who did not complete CR - defined as participation of at least 75% of the sessions - had almost threefold higher incidence of MACE during prolonged follow-up. We further found that smoking behavior was associated with the degree of CR completion - stop smoking was a success factor. Still, the reasons why patients did not complete the 12-week 'standard' CR program remained largely unknown.

Duration and intensity of CR programs are highly variable (18). In a systematic review of Rauch *et al* (19) no comparison could be made between beneficial effects and the type of CR offered, given the wide heterogeneity of CR programs which varied both in duration (3 weeks to 12 months) and intensity (2 to 5 sessions per week). Not surprisingly therefore, a definition of "complete CR" is absent in the guidelines of the European Association for Cardiovascular Prevention & Rehabilitation (20), both in terms of length of a standard program and in particular in terms of the number of attended sessions. Unfortunately, in most studies completion is not defined at all (12), whereas in other studies it ranged from minimal attendance of one session (13), to 50% in EUROASPIRE IV (21), and to 75% in the study of Beauchamp *et al.* (8). We used the most stringent Beauchamp criterion, because in our opinion CR will only be effective if the absenteeism is minimal. This position is supported by our data, as incomplete CR according to Beauchamp was a strong and independent predictor of increased risk for cardiovascular events. It should be noticed that the majority of patients in the incomplete CR group quitted CR very early in the program, resulting in an important difference in attended sessions: on average 6 versus 23 session. In contrast to what one may expect, the occurrence of MACE during CR was not the reason of incomplete CR, as all 5 patients with MACE during CR ultimately completed CR after a new coronary intervention.

Benefits of complete versus incomplete CR were shown in a few retrospective studies. In 2009 Suaya *et al* (7) was the first to show a relation between mortality and less than 25 attended CR sessions in elderly with CAD. Subsequently, these results were confirmed by a study of Beauchamp *et al* (8) in which patients who suffered from an acute myocardial infarction or underwent a PCI and attended less than 25% of the CR sessions had a more than twice increased mortality risk during 14-year follow-up, compared to those attended >75% of the sessions. More recently, Armstrong *et al* (9) reported in a large study in almost 3,000 diabetic patients, included between 1996 to 2010, that diabetic patients were less likely to start and to complete CR. Although complete CR was not well defined, patients who fully participated in the 12-week CR program had reduced mortality and hospitalization in comparison to CR participants who did not complete CR. Finally, in a large study by Colbert *et al* (10) in over 6,000 women with at least one-vessel CAD who participated in CR in 1996 complete CR, defined as at least 12 of 24 CR sessions (50%), including a 12 week post CR assessment had the lowest mortality during long-term follow-up.

In a recent retrospective study of our group we already demonstrated a reduction in 10-year mortality in ACS patients. We studied 1159 ACS patients who had a pPCI. We found

that patients who attended a CR program had significantly lower 10-year mortality than their no-CR counterparts (14.7 % versus 23.5 %), and that patients who completed CR had a lower 10-year mortality compared to patients who started CR but did not complete the program (13.6 % versus 18.9 %) (22). The current study differs from the ones mentioned because 1) our patients constituted a more homogeneous population with ACS, in the large majority treated with pPCI, 2) medical therapy was more intense and 3) medical therapy did not differ between the patients with complete and incomplete CR.

Since incompleteness of CR is associated with clinical outcome, it seems important to identify patients at risk for drop-out. The single most important predictor for incompleteness of CR was persistence of smoking. Other authors have also shown that smoking is an important predictor for incompletion of CR (23). Much can be speculated why smoking is such a strong predictor. Patients not motivated to quit smoking may also be not motivated to work on a healthier lifestyle in general either. It could also be that smoking is a part of other patient characteristics, such as a certain type of personality, limited education, and lower socio economic status (24). Since patients not always see the relevance of stop smoking suggests that our efforts to educate society about the negative influence of smoking is still not optimal. Another explanation might be that smokers feel stigmatized and isolated during CR as suggested by Beauchamp *et al* (8). Importantly, many authors warn to interpret studies on smoking with caution, since in most studies "smoking" was poorly defined (24). Studies often relied on hospital records or self-reporting, without biochemically verification as we did in our current study. Since stop smoking rates are even lower by objective biochemically verification we plea to continue this measurement in the future.

Since these were patients included in the OPTICARE trial, a potential bias from patients' willingness to participate in a trial may exist. Certainly, the number of patients that drop-out may be higher in routine clinical care settings. Whether these patients have a different profile and /or different cardiac outcome is not known. Also, our study population was at relatively "low risk" for drop-out, with relatively young patients, without heart failure or renal impairment. Another limitation is that we do not know the reasons for incomplete CR. From our own daily experience we know that this could be a wide variety of reasons: both medical and non-medical.

Finally, it is difficult to define what exactly is "complete CR" since it consists of a multidisciplinary program, including exercise sessions and diet, smoking cessation and stress management courses. Each individual patient has different needs of attention, for instance for an obese diabetic patient dietary advise sessions may be more important to attend than for a non-obese non-diabetic patient. All studies until now focus on the number of exercise sessions: the effects of the other multidisciplinary sessions is still unknown and were therefore not incorporated in the current definition of complete CR. Future studies should address the importance of attending the non-exercise sessions.

CONCLUSION

Post-ACS patients who did not complete a 'standard' 12-week CR program had higher incidence of adverse cardiac events during long-term follow-up than their counterparts who completed the program. Persistent smokers are at risk of non-completion, which is an (indirect) extra argument to motivate patients stop smoking. Still, patients could not satisfactorily be identified as potential non-completers on the basis of their smoking behaviour alone. Because CR is proven beneficial, further research is needed to understand the reasons why patients terminate prematurely.

Table 12.1 - Patient characteristics in relation to the (in)completion of the cardiac rehabilitation program

	Complete CR	Incomplete CR	Odds ratio †	(95% CI)	P-value
No. of patients	770	142			
Age, years	57.6 (9.1)	55.5 (10.8)	0.98	(0.96-0.99)	0.11
Man	623 (80.9)	114 (80.3)	0.96	(0.61-1.50)	0.86
Initial revascularisation treatment					
PCI	600 (77.9)	112 (78.9)	1.06	0.68-1.63	0.80
CABG	3 (0.4)	2 (1.4)	3.65	0.60-22.05	0.13
No Revascularization	167 (21.7)	28 (19.7)	1.10	0.71-1.72	0.74
Cardiovascular risk factors					
Family history	409 (53.1)	71 (50.0)	0.88	(0.62-1.26)	0.50
Diabetes	102 (13.2)	19 (13.4)	1.01	(0.60-1.71)	0.96
Hypertension	319 (41.4)	55 (38.7)	0.89	(0.62-1.29)	0.55
Smoking					
Persistent	89 (11.5)	45 (31.7)	2.78	(1.70-4.55)	<0.001
Never	461 (59.9)	57 (40.1)	0.68	(0.44-1.05)	0.082
Quit (reference)	220 (28.5)	40 (28.1)	1		
Hypercholesterolemia	268 (34.8)	44 (31.0)	0.84	(0.57-1.23)	0.38
Cardiovascular history	129 (16.8)	33 (23.2)	1.50	0.97-2.31	0.14
MI	63 (8.2)	17 (12.0)	1.53	0.86-2.69	0.14
PCI	72 (9.4)	17 (12.0)	1.32	0.75-2.31	0.33
CABG	9 (1.2)	4 (2.8)	2.45	0.74-8.07	0.13
CVA	3 (0.4)	2 (1.4)	3.65	0.60-21.05	0.13
TIA	15 (1.9)	4 (2.8)	145	0.48-4.46	0.50
Cardiac medication					
Anticoagulants	766 (99.4)	139 (97.9)	NA		0.68
Statins	740 (96.1)	128 (90.1)	0.42	0.20-0.88	0.017
ACE inhibitors	545 (70.8)	87 (61.3)	0.68	0.46-0.99	0.046
Beta-blockers	634 (82.3)	113 (79.6)	0.91	0.57-1.45	0.69

Continuous data are presented as mean (standard deviation) values, and categorical data are presented as numbers (percentages)

ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CI: confidence interval; CR: cardiac rehabilitation; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischemic attack

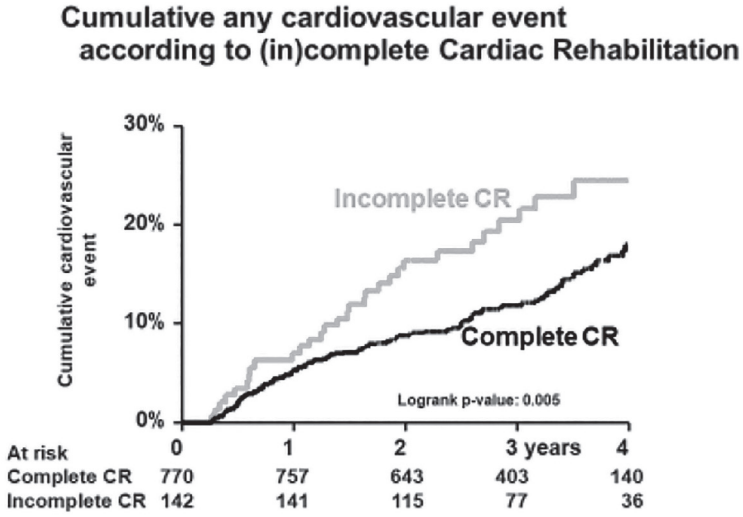
† Odds ratio related with the characteristic for incompletion of the cardiac rehabilitation program

Table 12.2 - Cardiovascular events after cardiac rehabilitation

	Complete CR	Incomplete CR	P-Value
No. of patients	770	142	
Any MACE	29 (3.8)	16 (11.3)	
Mortality	8 (1.0)	4 (2.8)	0.089
ST-elevation MI	7 (0.9)	2 (1.4)	0.58
Non-ST-elevation MI	10 (1.3)	4 (2.8)	0.17
CABG	4 (0.5)	2 (1.4)	0.23
PCI	9 (1.1)	9 (6.3)	0.003
Any non-major cardiovascular events	85 (11.0)	29 (20.4)	
Hospitalization because of			
Unstable angina	4 (0.5)	2 (1.4)	0.23
Stable angina	19 (2.5)	8 (5.6)	0.039
Nonspecific chest pain	17 (2.2)	6 (4.2)	0.16
Arrhythmias	12 (1.5)	1 (0.7)	0.48
Heart failure	0 (0.0)	0 (0.0)	--
Cardiac emergency room visit without hospitalization	38 (4.9)	11 (7.7)	0.17

Data are presented as numbers (percentages)
CABG: coronary artery bypass grafting; CR: cardiac rehabilitation; CVA: cerebrovascular accident; MACE: major adverse cardiac event; MI: myocardial infarction; PCI: percutaneous coronary intervention

Figure 12.1 Cumulative incidence of any cardiovascular event



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Chapter 13

EXTENDED CARDIAC REHABILITATION IMPROVES AEROBIC CAPACITY AND FATIGUE: A RANDOMIZED CONTROLLED TRIAL

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Submitted.

ABSTRACT

Purpose

To investigate secondary effects of two novel behavioral lifestyle interventions integrated into cardiac rehabilitation on aerobic capacity, fatigue, and participation in society and to explore mediating effects of physical activity and sedentary behavior.

Methods

In the OPTICARE trial, 914 patients with acute coronary syndrome (ACS) were randomized to 1) 3 months of standard cardiac rehabilitation (CR-only); 2) CR-only with additional face-to-face physical activity group counseling sessions plus 9 months of after-care with general lifestyle group counseling (CR+F); or 3) CR-only plus 9 months of after-care with individual, general lifestyle telephone counseling sessions (CR+T). Aerobic capacity (6-minute walk test), fatigue (Fatigue Severity Scale), and participation in society (Utrecht Scale for Evaluation of Rehabilitation-Participation) were measured at randomization, 3 months, 12 months, and 18 months.

Results

Generalized estimating equation analysis revealed favorable intervention effects for CR+F (compared to CR-only) in aerobic capacity up to 12 months (B= 12.49 m; 95% confidence interval [CI], 0.53 to 24.46; *P*= .041) and in prevalence of fatigue until at least 18 months (odds ratio [OR]= 0.47; 95% CI =0.26 to 0.84; *P*= .010). No additional improvements were seen for participation in society. No intervention effects were found for CR+T. Exploratory analysis showed that improvements in aerobic capacity in CR+F were mediated by improvements in physical activity. No mediating effects were found for improvements in fatigue.

Conclusions

Extending cardiac rehabilitation with a face-to-face behavioral group intervention was successful in sustaining aerobic capacity gains for up to 12 months and for reaching long-term goals for improvements in fatigue. The benefits in aerobic capacity seem to be mediated by improvements in daily physical activity. A telephonic behavioral intervention provided no additional benefits.

INTRODUCTION

Cardiac rehabilitation (CR) programs focus on the adoption of a healthy lifestyle and optimization of cardiovascular risk factors.[1-3] CR is an essential component of treatment for patients with acute coronary syndrome (ACS), as it decreases the risks of death and re-hospitalization.[4,5] Other important gauges of CR success are improvements in aerobic capacity, fatigue, and participation in society. To date, CR results for these outcomes have been suboptimal.[6,7] Although aerobic capacity has been shown to increase during CR[7,8], these gains decline after program completion. [7,9] Maintenance of improvements is important because aerobic capacity is related to re-hospitalization and mortality. [10,11] Fatigue and participation in society also improve during CR[6,7], but perceived levels of fatigue and restrictions and dissatisfaction with participation in society remain high after CR completion.[6,7] Further improvements to fatigue and participation in society are important, as both outcomes affect quality of life.[6,12]

In the OPTICARE randomized controlled trial (RCT), two novel CR interventions based on behavioral techniques (one offered face-to-face in groups and one offered individually by phone) were evaluated in patients with ACS.[13] The primary aim of these interventions was to further improve cardiovascular health and physical activity.[13] Although the novel interventions did not lead to additional improvements in cardiovascular health[14], additional improvements in physical activity were observed.[15] Because the novel interventions addressed a wide range of health behaviors and psychosocial problems, the interventions may more broadly affect aerobic capacity, fatigue, and participation in society. Previous studies have shown that behavioral lifestyle interventions can lead to improvements in these outcomes.[16-18] In addition to direct effects of the novel interventions, improvements may be mediated by improvements in physical activity and sedentary behavior. Previous studies show that physical activity and sedentary behavior are independently associated with aerobic capacity[19,20] and that they can influence fatigue.[21] With respect to participation in society, patients undergoing CR have reported being most dissatisfied with participation in exercise, outdoor activities, and domestic activities.[6] Because the novel interventions aimed to increase daily physical activity, improvements could also lead to improved participation in society.

The objective of the current study was to evaluate the effects of the two novel behavioral lifestyle interventions in comparison to standard CR on the secondary outcomes of aerobic capacity, fatigue, and participation in society. Additionally, in case significant intervention effects were found, we explored whether these effects were mediated by changes in physical activity and sedentary behavior.

METHODS

Study design

This study is part of the OPTICARE randomized controlled trial. The study, which has been described in detail previously,[13] was prospectively registered at ClinicalTrials.gov: NCT01395095.

Setting and participants

Patients referred for CR were invited to participate in the OPTICARE trial. Inclusion criteria were ACS diagnosis, age greater than 18 years, and Dutch language proficiency. The exclusion criterion was the presence of severe physical or cognitive impairment that could limit CR participation.[13] The Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam, the Netherlands approved this study (MEC-2010-391). All patients provided written informed consent.

Randomization and intervention

Randomization was performed using sealed envelopes that had been prepared by an independent statistician using randomly generated numbers. Patients were randomized to CR-only or to one of the two novel interventions: CR+F or CR+T (Figure 13.1).

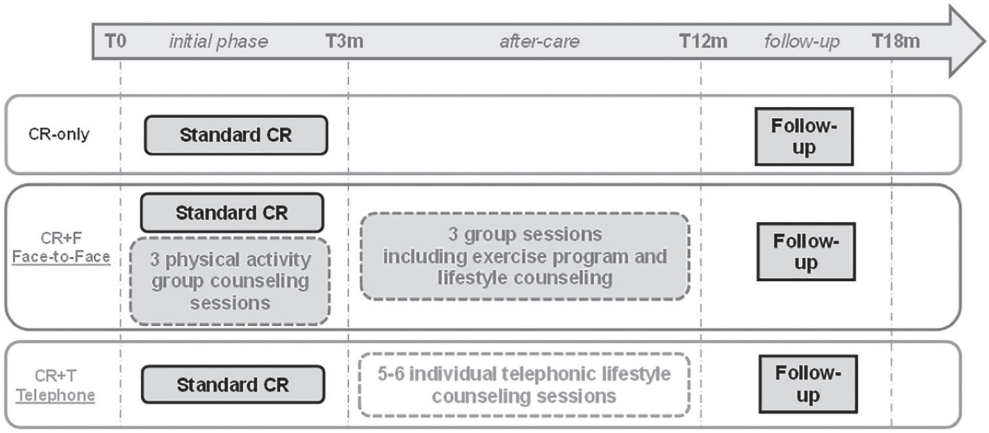

Figure 13.1 Treatment allocation and measurement time points
CR-only= standard cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus individual telephonic counseling; m= months.

1) CR-only: Standard CR[1,2] lasted 3 months. In this period, patients completed two 75-min exercise sessions per week that consisted of strengthening exercises, brisk walking or jogging, and relaxation exercises. Additionally, patients could participated in a three-session educational program about a heart-healthy diet, coping with emotions, and cardiovascular risk factors. Based on motivation and indication, patients could also participate in group

counseling sessions addressing stress management, healthy diet, or smoking cessation. If clinically indicated, patients were referred to a dietician, psychiatrist, psychologist, or social worker for individual treatment. At the end of the 3-month CR program (initial phase), no after-care was offered.

2) CR+F: During the initial phase, patients participated in the standard 3-month CR program plus three 75-minute counseling sessions designed to increase physical activity level. All sessions were conducted face-to-face in small groups of four to eight patients. During the sessions, patients were coached by a physical therapist trained in motivational interviewing.[22] The content of this intervention was based on evidence-based behavioral change techniques: information about health behavior, self-monitoring, goal setting, feedback, barrier identification, and relapse prevention.[23,24] Pedometers (Yamax Digiwalker SW-200; Yamax, Inc., Tokyo, Japan) were used to provide the patients with continuous objective feedback about daily physical activity level. During these sessions, information was also provided about the benefits of frequently interrupting sedentary time.

After the initial 3-month CR program, a 9-month after-care program was offered. This program consisted of three 2-hour group sessions with four to eight patients. Each session comprised 1 hour of exercise and 1 hour of healthy lifestyle counseling. The exercise sessions, which were similar to those offered during CR, served to help patients self-monitor aerobic capacity and stimulate interaction between patients in the group. The counseling sessions focused on permanent adoption of a healthy lifestyle (ie, healthy diet and optimal physical activity), but also on psychosocial problems. During these sessions, patients were coached alternatingly by a dietician, social worker, and physical therapist, all of whom were trained in motivational interviewing.

3) CR+T: This intervention was based on the existing Coaching Patients on Achieving Cardiovascular Health (COACH) program.[25] During the initial phase, patients participated only in standard CR. After the initial phase, patients participated in a 9-month individual after-care program comprised of five to six telephone coaching sessions. The coaching was performed by specialized nurses who were trained in motivational interviewing.[22] During the coaching sessions, patients were encouraged to self-monitor their coronary risk factors (eg, weight, blood pressure, or cholesterol) and make an action plan. Additionally, patients developed a personal plan for permanent adoption of a heart-healthy lifestyle (ie, healthy diet and sufficient physical activity). Progress was discussed during each session.

OUTCOMES

Functional aerobic capacity

The 6-minute walk test (6MWT) was performed according to American Thoracic Society guidelines.[26] Patients were asked to walk back and forth along a 30-meter corridor, covering as many meters as they could during 6 minutes without running. Standardized encouragement was given every minute, and the distance walked was recorded in meters. The 6MWT has been found to be a suitable outcome measure for evaluating the effects of CR on (functional) aerobic capacity.[27] The 6MWT was performed at the start of the second CR exercise session to avoid a possible learning effect[27] and to accommodate patients who may fear exercise. During the first exercise session, patients were familiarized with a walking protocol.

Fatigue

Fatigue was measured using the 9-item Fatigue Severity Scale (FSS).[28-30] The outcome is a continuous score between 0 and 7, with higher scores indicating more severe fatigue. Fatigue prevalence was calculated in addition to the FSS score.[7,30,31] Being fatigued was defined as a score of one standard deviation above the mean score for healthy persons (score higher than 4) and being severe fatigued as a score of two standard deviations above the mean score for healthy persons (score higher than 5.2).[30]

Participation in society

Participation in society was assessed using the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P),[32] a 32-item questionnaire that addresses three subdomains of participation: frequency, perceived restrictions, and satisfaction. Questions within these subdomains concern domestic, occupational, and recreational activities. For each subdomain, a separate score from 0 to 100 was calculated, with higher scores indicating better participation.

Potential mediating factors

Physical activity and sedentary behavior were measured using a tri-axial accelerometer (ActiGraph GT3x, Actigraph, Pensacola, FL, USA). Patients were asked to wear the accelerometer for 8 consecutive days, except while sleeping and during bathing. Actigraph data were sampled at 30 Hz. The ActiGraph captures accelerations on three axes and converts this into activity counts that reflect the intensity of performed activities. Using Actilife Software (Actigraph, Pensacola, FL, USA), activity counts were summed over 15-second sampling epochs (time intervals) after subtracting non-wear time. Non-wear intervals were defined as at least 60 min of consecutive zero counts. A valid day was defined as a wear time of at least 11 hours, and measurements were included in the analysis only when the accelerometer was worn for at least 4 valid days. Using Matlab version R2011 (MathWorks,

Natick, MA, USA), the vector magnitude of the three axes ($x^2 + y^2 + z^2$) was calculated for valid measurements and used to calculate time in moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time. MVPA time was defined as time spent in activities with at least 672.5 counts per 15-second epoch (on the vector magnitude).[33] Sedentary time was defined as time spent in activities with 37.5 or fewer counts per 15-second epoch.[34] Steps per day were also captured by the accelerometer. To correct for differences in accelerometer wear time between patients, MVPA time and sedentary time were expressed as percentages of wear time and the number of steps as mean steps per minute of wear time.

Measurement occasions

All outcomes and mediating factors were measured at randomization (T0); at completion of standard CR (3 months after randomization [T3m]); at completion of after-care (12 months after randomization [T12m]); and 6 months after completion of after-care (18 months after randomization [T18m]) (Figure 13.1).

Data analysis

Patients were only included in the data analysis if at least one measurement after baseline was available. We compared baseline characteristics of patients included and excluded from analysis using Student's T-tests and chi-squared tests, to explore unintentional bias.

Scores on the subdomain experienced restrictions in participation in society showed severe negative skewness. Therefore, dichotomized scores (no restrictions experienced or restrictions experienced) were used in the analysis. Data for other measures were normally distributed.

Generalized estimating equations (GEEs) with exchangeable correlation structures were performed to determine intervention effects of the two novel interventions compared to CR-only. First, separate overall models were created for each outcome (aerobic capacity, fatigue and participation in society); group allocation was included as a categorical predictor and baseline values for outcome measures were used as covariates to correct for baseline differences between subjects. Second, time-dependent models were created by adding the variable time (measurement occasions) and an interaction variable of group allocation x time. By changing the order of the time variable, between-group differences (intervention effects) could be calculated for T3m, T12m, and T18m. In all models, CR-only served as a reference group, and age and gender were added as confounders. The regression coefficient B represented between-group differences over all measurements for the overall model. In the time-dependent models, B represented the between-group difference at different time points. For dichotomous variables, between-group differences are presented as odds ratios (OR).

In case of missing baseline data, values were imputed five times (multiple imputations), using baseline characteristics and all available follow-up outcomes of the particular outcome as predictors. Because GEE models correct for missing data, other time points (endpoints) did not require data imputation.[35] The GEEs were performed using the original dataset and all five datasets containing imputed baseline values. Pooled results are reported.

In case significant intervention effects were found for any of the novel interventions compared to CR-only, additional analyses were performed to explore the mediating effects of MVPA time, sedentary time, and daily step count. Mediation was expressed as the percentage change in the intervention effect (regression coefficient, B) after adding the potential mediator to the overall model. We considered mediating effects to be clinically relevant when the percentage change was 10% or higher.

We considered a *P* value smaller than .05 to be statistically significant. SPSS version 21.0 (IBM Corp, Armonk, NY, USA) was used for all analyses.

RESULTS

Participants

In total, 914 patients with ACS were enrolled between November 2011 and August 2014, of whom 141 patients quit CR prematurely due to reasons unrelated to the study. An additional 33 patients dropped out of the study before the second measurement due to logistic reasons or lack of motivation (Figure 13.2). The remaining 740 patients were included in the analysis. The mean patient age was 57 years and 81% were male (Table 13.1). The excluded patients were, on average, two years younger (P = .017) and more likely to have a history of smoking (58% vs 40%, P < .001). Physical activity and sedentary behavior (potential mediating factors) were measured in a subsample consisting of 589 of the 740 patients (80%) included in the analysis

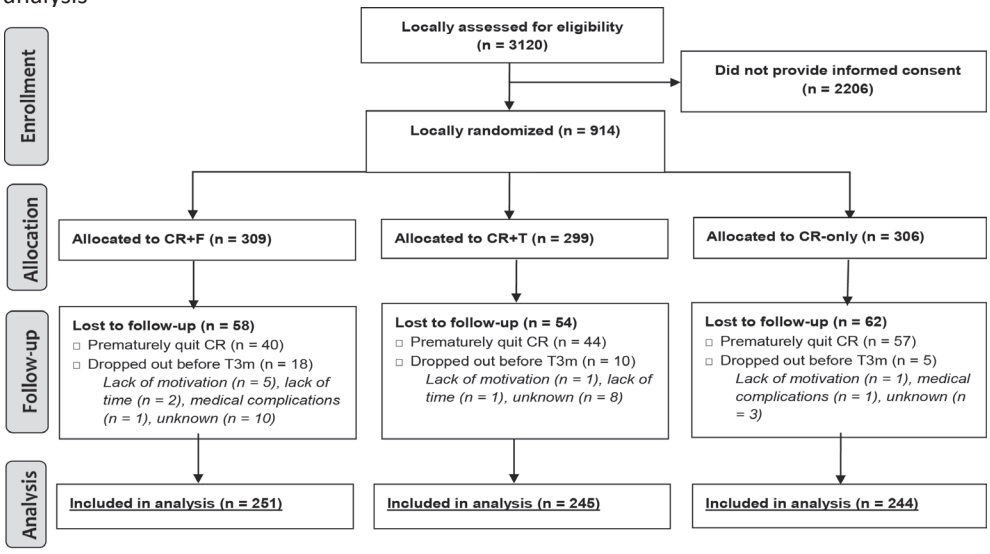

Figure 13.2 Consort Flow Diagram
CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus individual telephonic counseling; CR-only= standard cardiac rehabilitation; m= months

Table 13.1 Participant baseline characteristics (n = 740)

Characteristic	CR+F (n = 251)	CR+T (n = 245)	CR-only (n = 244)
Male, n (%)	80.5	82.4	80.3
Age, mean (SD), y	57.5 (8.8)	56.7 (9.2)	57.5 (9.2)
Therapeutic intervention at index event, n (%)			
No revascularization	6.8	9.8	7.4
Percutaneous coronary intervention	80.1	73.5	79.1
Coronary artery bypass graft	13.1	16.7	13.5
Risk factors, n (%)			
Diabetes	13.5	9.8	14.3
Dyslipidemia	27.9	35.5	41.4
Family history	53.4	52.2	55.7
Smoking history	43.4	38.8	36.5
Hypertension	43.4	39.2	40.2
Overweight	77.6	75.9	76.6
Partnered, n (%)[a]	80.5	84.0	83.4
Employed, n (%)[b]	64.7	60.5	56.0

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus individual telephonic counselling; CR-only= standard cardiac rehabilitation
[a] data missing for n = 41 (CR+G), n = 45 (CR+T), and n = 39 (CR-only); [b] data missing for n = 61 (CR+G), n = 60 (CR+T), and n = 53 (CR-only)

Intervention effects

Figure 13.3 shows the observed data for all outcomes measures. Outcomes of the GEE analyses are presented in Table 13.2.

Aerobic capacity

Significant intervention effects were found at T12m for CR+F. On average, participants in the CR+F grouped walked 12.49 m more on the 6MWT than patients in the CR-only group (95% confidence interval [CI], 0.53 to 24.46; *P* =.041; Table 13.2). This difference was no longer present at T18m. No intervention effects were found for CR+T (Table 13.2).

Fatigue

Patients randomized to CR+F had a greater improvement in FSS scores (3.29 at T0 to 2.56 at T18m) compared to patients randomized to CR-only (3.33 at T0 to 2.87 at T18m; between-group difference at T18m, -0.24; 95% CI, -0.49 to 0.03; *P* = .053; Table 13.2). Furthermore, prevalence of fatigue (including severe fatigue) decreased from 30.2% at T0 to 11.9% at T18m in the CR+F group compared to an improvement from 37.3% at T0 to 24.9% at T18m in the CR-only group (OR, 0.47; 95% CI, 0.26 to 0.84; *P* = .010). Prevalence of severe fatigue decreased from 13.8% at T0 to 4.2% at T18m for CR+F compared to an increase from 9.7% at T0 to 10.2% at T18m for CR-only (OR, 0.39; 95% CI, 0.17 to 0.95; *P* = .038; Table 13.2). No intervention effects were found for CR+T.

Participation in society

No interventions effects were found on any subdomain of participation in society for either novel intervention (Table 13.2).

Mediating effects

Exploratory analysis revealed that the intervention effects for CR+F on aerobic capacity were mediated by MVPA time (15.8%), sedentary time (5.3%), and daily step count (36.9%). None of the selected mediating variables explained the intervention effects observed for fatigue.

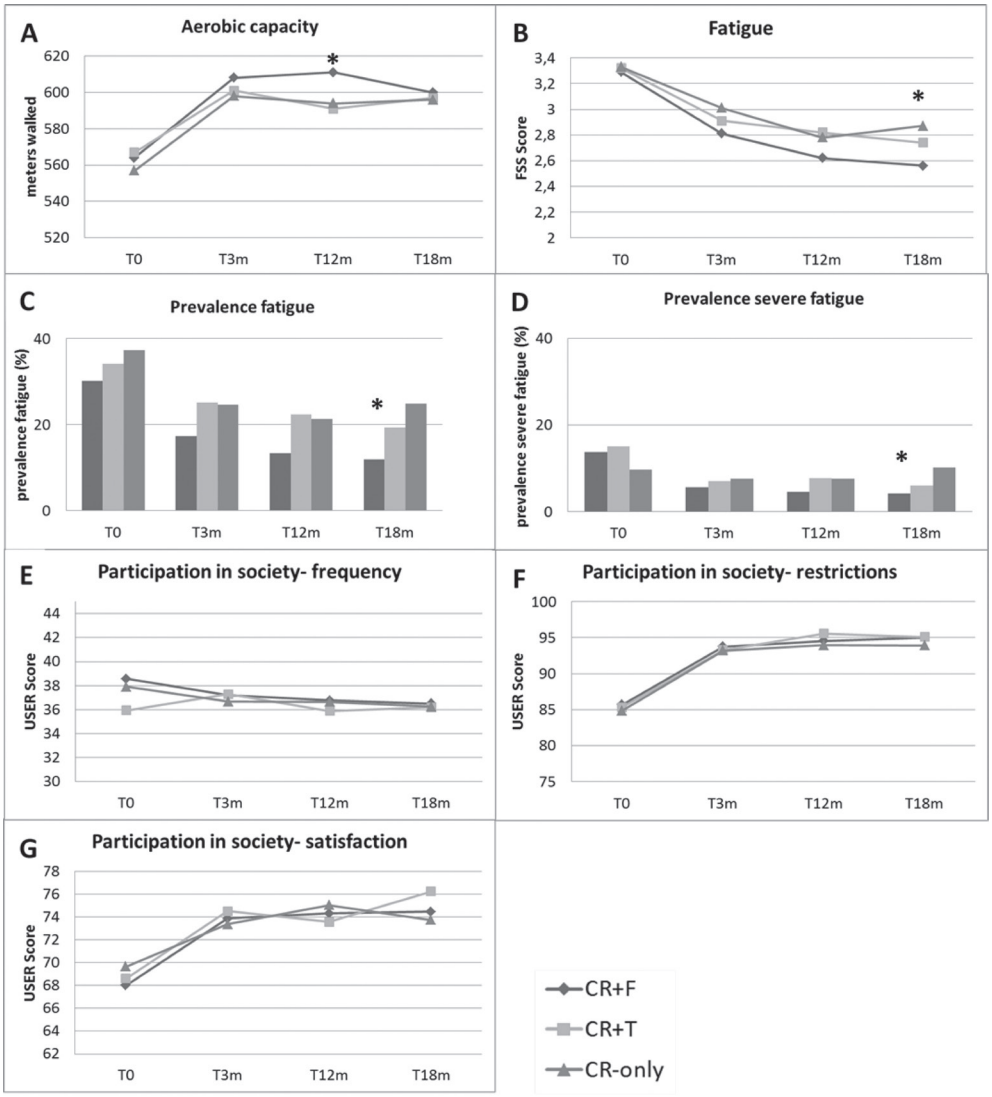

Figure 13.3 A) Aerobic capacity (meters walked on 6-minute walk test); **B)** FSS score, Fatigue severity scale score; **C)** Prevalence of fatigue (FSS > 4.0); **D)** Prevalence of severe fatigue (FSS > 5.2); **E)** Participation in society (frequency score of Utrecht Scale for Evaluation of Rehabilitation-Participation [USER-P] questionnaire); **F)** Participation in society (restrictions score of USER-P questionnaire); **G)** Participation in society (satisfaction score of USER-P questionnaire).

CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m= months

intervention effect present for CR+F compared to CR-only.

Table 13.2 General estimating equation model‡ intervention effects

		CR+F vs CR-only			CR+T vs CR-only		
		B†	CI	P	B†	CI	P
Aerobic capacity (n= 674)							
6MWT, m	overall	6.83	-3.45, 17.12	.192	3.82	-14.39, 6.74	.477
	ΔT0-T3m	6.84	-5.75, 19.43	.287	-0.14	-13.77, 13.48	.984
	ΔT0-T12m	**12.49**	**0.53, 24.46**	**.041**	-9.20	-20.89, 2.48	.122
	ΔT0-T18m	1.54	-11.86, 14.94	.822	-2.21	-15.66, 11.24	.747
Fatigue (n= 665)							
FSS score	overall	-0.16	-0.35, 0.03	.095	-0.05	-0.24, 0.14	.619
	ΔT0-T3m	-0.13	-0.35, 0.09	.235	-0.04	-0.26, 0.18	.708
	ΔT0-T12m	-0.13	-0.37, 0.11	.296	-0.02	-0.28, 0.23	.872
	ΔT0-T18m	-0.24	-0.49, 0.03	.053	-0.09	-0.34, 0.15	.453
Prevalence of fatigue (FSS > 4.0)	overall	**0.62**¥	**0.41, 0,94**	**.024**	0.95¥	0.63, 1.45	.832
	ΔT0-T3m	0.75¥	0.45, 1.23	.260	1.07¥	0.65, 1.77	.778
	ΔT0-T12m	0.63¥	0.35, 1.13	.119	1.01¥	0.57, 1.79	.969
	ΔT0-T18m	**0.47**¥	**0.26, 0.84**	**.010**	0.76¥	0.43, 1.35	.356
Prevalence of severe fatigue (FSS > 5.2)	overall	0.55¥	0.30, 1.01	.056	0.70¥	0.38, 1.28	.250
	ΔT0-T3m	0.72¥	0.31, 1.63	.428	0.83¥	0.37, 1.84	.644
	ΔT0-T12m	0.57¥	0.24, 1.35	.199	0.80¥	0.34, 1.92	.623
	ΔT0-T18m	**0.39**¥	**0.17, 0.95**	**.038**	0.53¥	0.24, 1.17	.117
Participation in society (n= 671)							
Frequency	overall	-0.46	-1.92, 1.01	.540	0.73	-0.71, 2.16	.320
	ΔT0-T3m	-0.18	-1.96, 1.60	.842	0.98	-0.79, 2.74	.277
	ΔT0-T12m	-1.06	-2.92, 0.80	.263	-0.03	-2.15, 2.08	.977
	ΔT0-T18m	-0.30	-2.26, 1.65	.760	1.10	-0.77, 2.98	.248
Perceived restrictions[a]	overall	1.03¥	0.73, 1.46	.858	0.93¥	0.66, 1.32	.698
	ΔT0-T3m	1.03¥	0.68, 1.55	.903	1.09¥	0.70, 1.67	.698
	ΔT0-T12m	0.95¥	0.60, 1.51	.824	0.82¥	0.51, 1.30	.386
	ΔT0-T18m	1.07¥	0.67, 1.70	.777	0.86¥	0.54, 1.36	.524
Satisfaction	overall	0.32	-1.93, 2.57	.778	1.08	-1.24, 3.39	.361
	ΔT0-T3m	0.67	-1.96, 3.31	.618	1.50	-1.13, 4.12	.264
	ΔT0-T12m	-0.76	-3.59, 2.06	.596	-0.72	-3.68, 2.24	.632
	ΔT0-T18m	1.40	-1.84, 3.65	.518	2.27	-0.49, 5.02	.107

6MWT= 6-minute walk test; CI= confidence interval; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR-only= standard cardiac rehabilitation; CR+T= cardiac rehabilitation plus individual telephonic counselling; m= months; FSS= Fatigue Severity Scale.

‡All analyses were adjusted for baseline differences between patients and corrected for confounding effects of gender and age. The CR-only group is the reference group for all analyses;

n=number of patients that had at least 1 outcome post-baseline and were included in the GEE analysis;

†B, regression coefficient; represents the between-group difference and the intervention effect relative to CR-only at the specified time point;

¥odds ratios are shown for dichotomous variables to indicate the odds (relative risk) relative to CR-only at the specified time point;

[a]scores violated normality assumption, dichotomized scores used for analysis

DISCUSSION

Extending CR with a face-to-face behavioral group intervention (CR+F) focused on permanent healthy lifestyle adoption resulted in improved maintenance of aerobic capacity gains up to 12 months and decreased prevalence of fatigue up to at least 18 months, compared to CR alone. The improvements in aerobic capacity seemed to be mediated by improvements in physical activity. Extending CR with a telephonic behavioral program (CR+T) did not lead to additional improvements in aerobic capacity or fatigue. Furthermore, neither the telephonic nor the face-to-face intervention improved participation in society compared to CR-only.

All three groups improved aerobic capacity during the initial 3-month CR period. As in previous studies[7,9], a decline in these benefits was seen after completion of CR (after T3m) in patients randomized to CR-only. The finding that CR+F prevented this decline is important, as aerobic capacity is associated with secondary cardiovascular events and mortality.[10,11] Because CR+T did not prevent this decline in aerobic capacity, we hypothesize that the stronger focus on physical activity during the face-to-face intervention was a crucial element in the successful maintenance. Indeed, an exploratory analysis showed that the CR+F intervention effects were mediated by both MVPA time (15.8%) and daily step count (36.9%). These mediating effects partly overlap, as some of the walking activities (step count) will be performed at a moderate-to-vigorous intensity. Another interesting finding is that the mediating effect of walking was twice as large as that of physical activity expressed as total MVPA time. This result is not completely surprising, as the 6MWT is a functional aerobic capacity test comprised of walking. A previous study showed a similar relationship between daily step count and functional aerobic capacity. [36] An alternative explanation for the positive effects of the CR+F intervention on maintenance of aerobic capacity gains is that the intervention included an exercise component during after-care. Although the frequency of this exercise program (three 1-hour sessions during a 9-month period) was insufficient to improve aerobic capacity, these sessions may have encouraged patients to pursue activities that improve aerobic capacity.

Our results suggest that ongoing attention might be needed for permanent maintenance of gains in aerobic capacity. As soon as the after-care program ended, aerobic capacity also declined in the CR+F group. Our results suggest that this ongoing attention can be low-frequency, an after-care program with only three group meetings during a 9 months periods was sufficient.

To our knowledge, this is the first study to assess secondary effects of a lifestyle intervention integrated into CR on fatigue. In addition to improving aerobic capacity, the CR+F intervention improved perceived fatigue (including severe fatigue). Patients who were randomized to CR+F reached fatigue levels even lower than those reported for healthy persons (11.9% vs 18%).[30] In contrast, those randomized to standard CR continued to have a high prevalence of fatigue (24.9%). With regard to prevalence of severe fatigue, the prevalence among those randomized to CR+F (4.2%) approached that of healthy persons

(3.5%) by study end.[30] As with previous results[7], the prevalence of severe fatigue in our study remained high following CR-only (10.2%). The improvements to fatigue are clinically important, as fatigue is known to influence quality of life.[12] In contrast to our hypothesis, additional improvements in fatigue were not mediated by changes in physical activity or sedentary behavior. Because the telephonic behavioral intervention (CR+T) did not confer additional benefits to fatigue, an element of the face-to-face group sessions must have been essential for these benefits. Unfortunately, the study design was not appropriate to detect the specific factor for the program's success. Perhaps the improvements in aerobic capacity seen in CR+F lowered the physical strain associated with activities of daily life, which consequently decreased feelings of fatigue.[7] In addition, the face-to-face coaching method (as opposed to individual telephone coaching) may have contributed. Another possibility is the mediating effect of depression, which is known to be associated with perceived fatigue.[37] However, a previous investigation showed that neither novel intervention conferred benefits to depressed mood[14], so we do not expect improvements in depression to have mediated the additional improvements in fatigue.

Adding behavioral interventions to standard CR (using face-to-face group or individual telephonic coaching) did not affect participation in society. As participation in society is associated with quality of life[6], future research should focus on finding effective interventions. A more individualized approach may be needed.

Study Limitations

Some study limitations deserve discussion. Firstly, patients who were lost to follow-up and excluded from analyses were, on average, younger and more likely to smoke. CR drop-out rates tend to be higher among younger patients and those with more risk factors.[38,39] Therefore, our results are probably most valid among the more adherent patients. Secondly, the power analysis for this RCT was performed using the primary outcomes **SCORE (Systematic COronary Risk Evaluation) risk function** and physical activity.[13] The study was not powered for the outcomes analyzed in this study; therefore, our results should be considered as exploratory. Lastly, we did not perform official mediation analyses. However, our exploratory analyses do offer insight into possible mediators of findings.

CONCLUSIONS

CR extended by a face-to-face behavioral group intervention focusing on permanent adoption of a healthy lifestyle was successful in maintaining aerobic capacity gains up to 12 months and improving perceived levels of fatigue up to 18 months. The benefits in aerobic capacity seemed to be mediated by improvements in physical activity. Extending CR with a telephonic behavioral program was not effective with respect to these outcome measures and none of the behavioral interventions improved participation in society.

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Chapter 14

SUMMARY AND CONCLUSIONS

SAMENVATTING EN CONCLUSIES

DISCUSSION AND FUTURE PERSPECTIVES

SUMMARY AND CONCLUSIONS

The aim of this thesis was to investigate the outcome after 'standard' Cardiac Rehabilitation (CR) which was developed in the late 1970s, in Acute Coronary Syndrome (ACS) patients **(Part 1)**, and to study if 'extended' CR will improve patient outcomes **(Part 2)**.

PART 1

In **Chapter 1** patient-related factors were sought that are associated with participation in and completion of a CR program in the Dutch setting. We studied 3871 patients in the Rotterdam-Rijnmond region who had undergone primary percutaneous coronary intervention (pPCI) for acute myocardial infarction (AMI). Only 39% of patients appeared to participate in a CR program, whereas 80% finally completed the program. Elderly (>70 years) patients, women, and patients with low socio-economic status had particular low participation- and completion rates. We concluded that targeted approaches are needed in order to enhance their uptake and adherence to CR.

In **Chapter 2** the effects of CR on long-term mortality were studied in 1159 ACS patients who were treated with pPCI. We found that patients who attended a CR program had significantly lower 10-year mortality than their non-CR counterparts (14.7% versus 23.5%), and that patients who completed CR had a lower 10-year mortality compared to patients who started CR but did not complete the program (13.6% versus 18.9%).

In **Chapter 3** we compared changes in subjective health status in 282 AMI patients who underwent pPCI, in relation to their age. Patients completed the SF-12 questionnaire before CR, immediate after CR (i.e. 3 months after CR start) and 12 months after CR start. Regardless of age, the mean PCS score improved over time, and reached the mean levels of the normative Dutch population. The MCS score also improved, but patients <60 years had larger improvement than their elderly counterparts (change at 1 year: 5.3 versus 2.1). Still, mean levels of the normative Dutch population were not reached by patients <60 years (47.6 <60 years and 49.3 ≥60 years versus the reference of normative Dutch population which is 50). We concluded that a tailored CR program with more focus on mental status, may be beneficial in younger patients.

In **Chapter 4** we studied longitudinal changes in physical activity and sedentary behaviour using objective accelerometers in 135 AMI patients who underwent pPCI. Sedentary behaviour is known to be an independent risk factor for lower health. Patients achieved a small improvement of 5 extra min/day in moderate-to-vigorous intensity physical activity (MVPA) during CR. More substantial improvements occurred for sedentary behaviour (22 fewer min/day). Regardless these improvements, by the end of CR, patients still spent relatively little time in MVPA (for example only half of the participants reached the recommended daily step target of 6500 steps) and had a long sedentary time (9 hours/day).

We concluded that standard CR was insufficient to change physical activity and sedentary behaviour.

In **Chapter 5** we studied whether participation in society (domestic, occupational and recreational activities) changed during and after CR in 121 AMI patients who underwent pPCI. We found no change in participation rates. However, the proportion of patients experiencing restrictions in participation decreased at one-year follow-up (from 69% to 29%), as did dissatisfaction (from 71% to 53%). Despite these improvements, the proportion of patients that experienced restrictions (29%) and dissatisfaction (53%) remained high at one-year. We concluded that an individualized approach during CR, focusing on activities in which restrictions and dissatisfaction are experienced, seems to be needed**.**

In **Chapter 6** we investigated fatigue during and after CR in 121 AMI patients who underwent pPCI, using the Fatigue Severity Scale (FSS). The prevalence of severe fatigue decreased during CR (from 17.7% to 10.6%) and at one year follow-up (to 8.1%). At one year follow-up, the prevalence of severely fatigued patients was still higher as compared to the general population (3.5%). Aerobic capacity (6-min walk test) was weakly associated with fatigue (p-value 0.030), while depressive symptoms (HADS questionnaire) were more strongly associated (p-value< 0.001). For patients with severe fatigue additional interventions seem necessary, especially focussing on the mental components of fatigue, instead of the physical components.

In **Chapter 7** the association between marital quality and loneliness and subjective health status in 223 pPCI patients who underwent CR was investigated. The Short Form 12 (SF-12) questionnaire was used to measure subjective health status, which was expressed as a physical component summary score (PCS) and a mental component summary score (MCS). The MCS level at one-year follow-up of patients with less optimal marital quality and lonely patients was lower than the average healthy Dutch population (respectively 47.3 versus 50, and 46.1 versus 50). We concluded that extra care and support should be given to these patients in a CR program.

In **Chapter 8** described the association between body mass index (BMI) and subjective health status based on the SF-12 questionnaire between patients who underwent CR compared to those who did not. We considered 3 BMI strata: normal weight (BMI <25, N=75), overweight (BMI 25 to 30, N=122) and obese (BMI >30, N=45) patients. In the overweight group, subjective health after CR was significantly improved after CR (OR = 3.4), and these improvements were sustained at 1-year follow-up (OR=5.1). Patients with normal weight did not improve, neither did obese patients.

PART 2

In **Chapter 9** the design of the OPTImal CArdiac REhabilitation (OPTICARE) trial was described. In OPTICARE, we studied the effects of two advanced and extended CR programs that were designed to stimulate permanent adaption of a heart-healthy lifestyle, compared

with current standard CR. The target population consisted of ACS patients who had pPCI. We aimed to evaluate effects in terms of cardiac risk profile, levels of daily physical activity, quality of life and health care consumption.

Chapter 10 describes the main findings of OPTICARE trial. A total of 914 patients were 1:1:1 randomised to: (1) 3 months standard CR (CR-only); (2) standard CR including three additional face-to-face active lifestyle counselling sessions and extended with three group fitness training and general lifestyle counselling sessions in the first 9 months after standard CR (CR+F); or (3) standard CR extended for 9 months with 5 to 6 telephone general lifestyle counselling sessions (CR+T). In the intention-to-treat analysis, we found no statistically significant difference in the SCORE risk function at 18 months between CR+F and CR-only (3.30% vs 3.47%; p=0.48), or CR+T and CR-only (3.02% vs 3.47%; p=0.39). In a per-protocol analysis, two of three modifiable SCORE parameters favoured CR+F over CR-only: current smoking (13.4% vs 21.3%; p<0.001) and total cholesterol (3.9 vs 4.3 mmol/L; p<0.001). The smoking rate was also lower in CR+T compared with CR-only (12.9% vs 21.3%; p<0.05). So extending CR with extra behavioural counselling (group sessions or individual telephone sessions) does not confer additional benefits with respect to SCORE risk. Patients largely reach target levels for modifiable risk factors with few hospital readmissions already following standard CR.

In **Chapter 11** we used the OPTICARE trial data to study whether non-completion of the standard CR program was associated with increased risk of major adverse cardiovascular events (MACE). During a median follow up of 2.7 years, patients who did not complete standard CR had a higher MACE incidence than their counterparts who did not complete CR (11.3% versus 3.8%). Smoking appeared a strong predictor for non-completion: 11.5% of smokers complete CR versus 58.9% of non-smokers.

In **Chapter 12** the results on physical activity of the extra behavioural interventions of the OPTICARE trial are described, based on 731 patients with corresponding measurements. Compared to standard CR, adding 3 pedometer-based physical activity counselling sessions (initial phase CR+F) significantly improved the daily step count (513 extra steps) and the time spent in prolonged MVPA periods (> 10 minutes, which is suggested for health benefit). There were no changes in total MVPA time or sedentary behaviour. After ending of the initial CR phase, improvements in step count partly diminished, irrespective of the extra-behavioural sessions (after care) that followed. However, the additional improvements in prolonged MVPA were maintained. No additional benefits were found for the CR+T intervention. Based on these results, we recommended that physical activity group counselling sessions including objective feedback (CR+F) be added to standard CR, although aftercare optimization is needed.

In **Chapter 13** the benefits of the extra behavioural interventions on aerobic capacity and fatigue were evaluated in all 914 OPTICARE patients. The CR+F intervention was successful in sustaining aerobic capacity gains up to 12 months (on average 12.49 m more on 6MWT)

and reaching long-term improvements in prevalence of severe fatigue (4.2% vs 10.2%). No additional improvements were seen for participation in society. No additional benefits were found for the CR+T intervention. The additional benefits in aerobic capacity and fatigue increase the clinical relevance of the CR+F intervention.

SAMENVATTING EN CONCLUSIES

Het doel van dit proefschrift is om de uitkomst van 'standaard' hartrevalidatie (CR) (**Deel 1**), een programma dat in de jaren 70 is ontwikkeld, te onderzoeken bij ACS-patiënten (patiënten met een acuut coronair syndroom) en om te onderzoeken of 'verlengde' CR de uitkomsten verbetert **(Deel 2).**

DEEL 1

In **Hoofdstuk 1** zijn patiënt gerelateerde factoren bekeken die samenhangen met deelname aan en afronding van een CR-programma in Nederland. We bestudeerden 3871 patiënten in de regio Rotterdam-Rijnmond die met een primaire percutane coronaire interventie (pPCI) werden behandeld voor een acuut myocardiaal infarct (AMI). Slechts 39% van de patiënten bleek deel te nemen aan een CR-programma, waarvan 80% het programma uiteindelijk voltooide. Oudere (> 70 jaar) patiënten, vrouwen en patiënten met een lage sociaaleconomische status hadden in het bijzonder lage participatie- en voltooiingspercentages. We concludeerden dat gerichte benaderingen nodig zijn om deelname aan en voltooiing van CR te verbeteren.

In **Hoofdstuk 2** zijn de effecten van CR op de mortaliteit op lange termijn bestudeerd bij 1159 ACS patiënten met pPCI. We ontdekten dat patiënten die aan een CR-programma deelnamen een significant lagere 10-jaars mortaliteit hadden dan hun niet-CR-"tegenhangers" (14.7% versus 23.5%). We ontdekten ook dat patiënten die CR voltooiden een lagere 10-jaars mortaliteit hadden in vergelijking met patiënten die met CR begonnen, maar het programma niet voltooiden (13.6% versus 18.9%).

In **Hoofdstuk 3** vergeleken we veranderingen in de subjectieve gezondheidsstatus bij 282 AMI-patiënten die pPCI ondergingen, in verhouding tot hun leeftijd. Patiënten voltooiden de SF-12 vragenlijst voor CR, onmiddellijk na CR (dat wil zeggen 3 maanden na start CR) en 12 maanden na start CR. Ongeacht de leeftijd verbeterde de gemiddelde PCS-score (= fysieke status) in de loop van de tijd en bereikte die score het gemiddelde niveau van de normatieve Nederlandse bevolking. De MCS-score (= mentale status) verbeterde ook: patiënten <60 jaar lieten een grotere verbetering zien dan hun oudere tegenhangers (verandering na 1 jaar: 5.3 versus 2.1). Toch werden de gemiddelde niveaus van de normatieve Nederlandse bevolking niet bereikt door de jongere patiënten <60 jaar (47,6 <60 jaar versus 49,3> 60 jaar versus 50 normatieve Nederlandse bevolking). We concludeerden dat een op maat gemaakt CR-programma met meer focus op de mentale status van patiënten mogelijk een nuttig effect kan hebben voor jongere patiënten.

In **Hoofdstuk 4** bestudeerden we longitudinale veranderingen in fysieke activiteit en sedentair gedrag met behulp van objectieve versnellingsmeters bij 135 AMI-patiënten die pPCI ondergingen. Sedentair gedrag is bekend als een onafhankelijke risicofactor voor een

lagere gezondheid. Patiënten bereikten een kleine verbetering van 5 extra min / dag matige tot hoge intensieve fysieke activiteit (MVPA) tijdens CR. Meer substantiële verbeteringen werden gezien in sedentair gedrag (22 minder min / dag). Ongeacht deze verbeteringen besteden patiënten nog relatief weinig tijd aan MVPA aan het einde van CR (bijvoorbeeld slechts de helft van de deelnemers bereikte de aanbevolen dagelijkse doelstelling van 6500 stappen) en brachten zij ook veel tijd zittend door (9 uur / dag). We concludeerden dat de standaard CR onvoldoende was om fysieke activiteit en sedentair gedrag te veranderen.

In **hoofdstuk 5** hebben we onderzocht of CR invloed had op de participatie in de samenleving (huishoudelijke, beroepsmatige en recreatieve activiteiten) bij 121 AMI-patiënten die pPCI ondergingen. We vonden geen verandering in de participatiepercentages gedurende CR. Het percentage van de patiënten dat beperkingen ervaarde bij de participatie in de samenleving daalde echter wel na 1 jaar follow-up (van 69% tot 29%). Ook de ontevredenheid over die participatie daalde (van 71% tot 53%). Ondanks deze verbeteringen bleef het aandeel van patiënten dat beperkingen ervaarde bij participatie in de samenleving (29%) en ontevreden was over hun participatie (53%) na 1 jaar follow up, fors. We concludeerden dat een geïndividualiseerde aanpak tijdens CR gericht op participatie activiteiten waarin beperkingen en ontevredenheid wordt ervaren, nodig lijkt.

In **Hoofdstuk 6** onderzochten we vermoeidheid tijdens en na CR bij 121 AMI-patiënten die pPCI ondergingen, met behulp van de Fatigue Severity Scale (FSS). De prevalentie van ernstige vermoeidheid daalde tijdens CR (van 17.7% tot 10.6%) en na 1 jaar follow-up (tot 8.1%). Na 1 jaar follow-up was de prevalentie van ernstig vermoeide patiënten echter nog steeds hoger dan bij de algemene populatie (3.5%). Aerobe capaciteit (gemeten met 6 min wandeltest) was zwak geassocieerd met vermoeidheid (p-waarde 0.030), terwijl depressieve symptomen (gemeten met de HADS vragenlijst) sterker geassocieerd waren (p-waarde <0.001). Voor patiënten met ernstige vermoeidheid lijken aanvullende interventies noodzakelijk, vooral gericht op de mentale componenten van vermoeidheid, in plaats van op de fysieke componenten.

In **Hoofdstuk 7** werd het verband onderzocht tussen huwelijksgeluk en eenzaamheid en de subjectieve gezondheidstoestand bij 223 pPCI-patiënten die deelnamen aan CR. De vragenlijst Short Form 12 (SF-12) werd gebruikt om de subjectieve gezondheidsstatus te meten, die werd uitgedrukt als een samenvattende fysieke score (PCS) en een samenvattende score van de mentale componenten (MCS). Het MCS-niveau na 1 jaar follow-up van patiënten met een minder goede relatie en eenzame patiënten was lager dan de gemiddelde gezonde Nederlandse bevolking (respectievelijk 47.3 versus 50 en 46.1 versus 50). We concludeerden dat extra zorg en ondersteuning moet worden gegeven aan deze patiënten in een CR-programma.

In **Hoofdstuk 8** wordt de relatie beschreven tussen de body mass index (BMI) en de subjectieve gezondheidsstatus op basis van de SF-12 vragenlijst tussen patiënten die CR ondergingen in vergelijking met degenen die dat niet deden. We hebben 3 BMI-groepen

gekozen: normaal gewicht (BMI <25, N = 75), overgewicht (BMI 25 tot 30, N = 122) en obese (BMI> 30, N = 45) patiënten. In de groep met overgewicht was de subjectieve gezondheid significant verbeterd vlak na CR (Odds Ratio 3.4) en deze verbeteringen werden gehandhaafd na 1 jaar follow-up (Odds Ratio 5.1). De subjectieve gezondheidstoestand van patiënten met een normaal gewicht en van patiënten met obesitas, verbeterde niet.

DEEL 2

In **Hoofdstuk 9** wordt de rationale van de OPTImal CArdiac REhabilitation (OPTICARE) – studie beschreven. In OPTICARE bestudeerden we de effecten van twee geavanceerde en uitgebreide CR-programma's die zijn ontworpen om permanente aanpassing van een gezonde levensstijl te stimuleren, in vergelijking met de huidige standaard CR. De populatie bestond uit ACS-patiënten die een pPCI hadden ondergaan. We wilden effecten evalueren op het gebied van cardiaal risicoprofiel, dagelijkse fysieke activiteit, kwaliteit van leven en de consumptie van gezondheidszorg.

Hoofdstuk 10 beschrijft de belangrijkste bevindingen van de OPTICARE-studie. Een totaal van 914 patiënten was 1: 1: 1 gerandomiseerd naar: (1) 3 maanden standaard CR; (2) standaard CR, aangevuld met drie face-to-face pedometer-gebaseerde counseling sessies voor fysieke activiteit, gevolgd door drie groepsfitnesstrainingen en algemene leefstijladvies-sessies in de eerste 9 maanden na standaard CR (CR + F); of (3) standaard CR aangevuld met in de 9 maanden volgend op standaard CR 5 tot 6 telefonische algemene leefstijlsessies (CR + T). In de intention-to-treat-analyse vonden we geen statistisch significant verschil in de SCORE-riskscore na 18 maanden tussen de 3 groepen: tussen CR + F en standaard CR (3.30% versus 3.47%, p = 0.48), of CR + T en alleen CR (3.02% versus 3.47%, p = 0.39). In een per-protocolanalyse waren twee van de drie beïnvloedbare SCORE-parameters gunstiger bij de CR + F dan standaard CR: roken (13.4% versus 21.3%; p <0.001) en totaal cholesterol (3.9 versus 4.3 mmol / L; p <0.001). Het percentage rokers was ook lager in CR + T in vergelijking met standaard CR (12.9% versus 21.3%; p <0.05). Het uitbreiden van CR met extra gedragstherapie (groepssessies of individuele telefonische sessies) levert geen extra voordelen op met betrekking tot de SCORE-parameters. Patiënten bereiken grotendeels al hun streefwaarden vlak na standaard CR met betrekking tot te beïnvloeden risicofactoren met weinig heropnames in het ziekenhuis.

In **Hoofdstuk 11** gebruikten we de OPTICARE-onderzoeksgegevens om te bestuderen of het niet afmaken van het standaard CR-programma geassocieerd was met een hoger percentage belangrijke cardiovasculaire gebeurtenissen (MACE). Tijdens een mediane follow-up van 2.7 jaar hadden patiënten die de standaard CR niet afmaakten een hogere MACE (11.3 % versus 3.8 %) dan hun tegenhangers die CR hadden afgemaakt. Roken lijkt een sterke voorspeller voor niet-voltooiing: 11.5% van de rokers voltooide CR versus 58.9% van de niet-rokers.

In **Hoofdstuk 12** worden de resultaten beschreven van de extra-gedragsinterventies van de OPTICARE-studie op fysieke activiteit, gebaseerd op 731 patiënten met accelerometrie metingen. In vergelijking met standaard CR, verbeterde het toevoegen van 3 pedometer-gebaseerde counseling sessies voor fysieke activiteit (initiële fase CR + F) het aantal dagelijkse stappen (513 extra stappen) en de tijd die wordt doorgebracht in langere MVPA-perioden (> 10 minuten, wat wordt geduid als gezondheidswinst). Er waren geen veranderingen in de totale MVPA-tijd of tijd in sedentair gedrag. Na het beëindigen van de initiële CR fase, namen de verbeteringen in het aantal stappen gedeeltelijk weer af, ongeacht de extra-gedragssessies (nazorg) die volgden. De extra verbeteringen van een langdurige MVPA bleven echter gehandhaafd. Er werden geen extra voordelen gevonden voor de CR + T-interventie. Op basis daarvan raden we aan om counseling sessies voor fysieke activiteit, inclusief objectieve feedback (CR + F) aan de standaard CR toe te voegen, hoewel optimalisatie van de nazorg nodig is.

In **hoofdstuk 13** werden de voordelen van de extra gedragsinterventies op aerobe capaciteit en vermoeidheid geëvalueerd bij alle 914 OPTICARE-patiënten. De CR + F-interventie was succesvol in het behoud van aerobe capaciteitswinsten tot 12 maanden (gemiddeld 12.49 m meer op 6 MWT) en het bereiken van lange termijn verbeteringen in de prevalentie van ernstige vermoeidheid (4.2% versus 10.2%). Er werden geen verdere verbeteringen waargenomen voor participatie in de samenleving. Er werden geen extra voordelen gevonden voor de CR + T-interventie. De extra winst die geboekt wordt in aerobe capaciteit en vermoeidheid verhogen de klinische relevantie van de CR + F-interventie.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Although CR is a class I recommended intervention in coronary artery disease (CAD) patients (1,2) referral rates remains poor worldwide (3), and the Netherlands is no exception (4). Electronic CR referral systems may increase referral rates (5), still, however, there is insufficient evidence to make practice recommendations for increasing uptake and adherence to CR. Particularly, studies to identify useful interventions to stimulate under-representing patient groups, such as women and elderly, are still missing. Based on our experiences in the OPTICARE, we hypothesise that individually tailored approaches may increase the likelihood of success. We designed a trial to explore a dedicated CR program in obese patients, which is currently underway (OPTICARE-XL). Initiatives in other high-risk groups should be welcomed.

Is it still necessary to refer CAD patients to CR?

This thesis shows that 'standard' CR, as developed in the 1970s, still provides beneficial effects: patients who participated in OPTICARE, and who completed regular CR had favourable SCORE risk, mainly because of well-controlled blood pressure and lipid profile, already at the start of CR and very low cardiovascular event rates during longer-term follow-up. Nevertheless, as OPTICARE used the SCORE risk as major endpoint, we believe it is time to shift to other goals in CR: from cardiovascular risk, with focus on cardiovascular events, to cardiovascular health, with focus on relevant endpoints that are less well-controlled by medication, such as physical activity and sedentary behaviour. Still, there is no watershed between 'risk' and 'health', as physical activity does influence mortality through several pathways, including reducing chronic inflammation, improving coronary blood flow or augmenting cardiac function (6). Other important targets are experienced fatigue, and participation in society through which patients are able to resume their professional lives quickly, thus reducing health care costs.

Blended care

Time has come to thoroughly investigate the reasons for non-referral by physicians, and the reasons for non-attendance by the patients themselves, for, as we demonstrated, this problem is still not clarified. In anticipation on the results of these investigations, E-health interventions may be added to CR programs to improve CR participation and completion. Evidence exists that simple text-message services are effective (7-10) and that using home-based trainings with E-Health guidance can lead to improved cost-effectiveness (11). Compliance might also be higher for home-based sessions, although results in this thesis indicated that compliance was not higher for a telephonic aftercare programme. Also, previous studies showed the importance of, at least partly, face-to-face contact in regard to improvement of physical activity physical activity (12). For these reasons, so-called "blended care", a combination of face-to-face sessions and home-based sessions with E-Health

guidance, might be worth investigating. Other simple "guidance tools", such as wearing a pedometer, may also be effective, as we demonstrated in OPTICARE.

Collaboration

In the Netherlands, several randomized trials to improve secondary prevention have been conducted the past few years (11,13-15). Apparently, Dutch researchers have a pioneering role in this respect. Each trial had its own objective and specific design. The Response investigators focussed on nurse-coordinated prevention programmes, which resulted in reduction of cardiovascular risk factors (Response-1) (13). By using a comprehensive set of community-based, widely available lifestyle interventions, a significant improvement in 3 lifestyle-related risk factors (weight reduction, increasing physical activity, and smoking cessation) was reached. Remarkably, partner participation was associated with a significantly greater success rate (Response-2) (15). Kraal *et al.* (11) focussed on home-base cardiac rehabilitation with tele-monitoring guidance. This led to a higher patient satisfaction and improved cost-effectiveness compared to centre-based CR. Janssen *et al.* (14) concentrated on post CR care, and showed that a relatively brief, theory-based lifestyle program is capable of inciting and maintaining improvements in exercise adherence, suggesting that patients may need ongoing attention and guidance, for example in the form of (internet-based) booster sessions. The design and specific focus being different, the above mentioned initiatives (including OPTICARE) sought for a cost-efficient secondary prevention strategy that can easily be adopted by CAD patients, and that promotes the maintenance of a healthy life style. We believe, this common denominator, can (and should) form the basis for a far-reaching collaboration to develop new initiatives, and run nation-wide, adequately powered clinical trials, aiming at a further improvement of secondary prevention outcomes in CAD patients.

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Appendix

DANKWOORD

Waarom besluit je alsnog te promoveren, terwijl je al jaren gewoon je klinisch werk doet naar alle tevredenheid als perifeer cardioloog? Antwoord: omdat ik het leuk vind om onderzoek te doen en het toevallig op mijn pad kwam.

In 2007 kwam ik terug "op stal". Heimwee dreef me weer naar de regio Rijnmond en door mijn beperkte aanstelling in het toenmalige Vlietland ZH kon ik ingaan op het aanbod van Marten Kazemier, de "founder" van Capri Hartrevalidatie om cardiologisch eindverantwoordelijke te worden.
Samen met de nieuwe directeur Niek Baart bliezen we Capri nieuw leven in. Het pand aan de Parklaan werd drastisch gerenoveerd, zo ook alle bestaande protocollen. We brainstormden dat het zonde was om niets te doen met alle uitkomstmaten van de vele honderden patiënten die jaarlijks bij Capri revalideren.
Bij toeval kwam ik Ron van Domburg tegen die mij reeds in het eerste jaar als ANIO'S in het EMC in 1991 enorm had geholpen met een (uiteindelijk niet gepubliceerd) artikel. Ron met zijn eindeloze database van de in het EMC gedotterde patiënten, had ook interesse in de data van Capri.
Nadat we de resultaten van de fameuze Gospel trial uit Italië hadden gelezen, bedachten we "dat kunnen wij ook". En zo ontstond de OPTICARE-studie. Ron zou een AIOS erop zetten als ik zelf niet wilde promoveren. Dat was mijn eer te na en ik committeerde mij met als voorwaarde dat NIEMAND in mijn nek moest gaan hijgen en ik het tempo zelf mocht bepalen. Het was eind 2010….vele subsidieaanvragen volgden zonder succes. Uiteindelijk door de financiële steun van Capri zelf en de samenwerking met Zilveren Kruis/Achmea kon de OPTICARE studie toch gestart worden.
De grootste hick up in het traject was in 2013. Mijn lichaam besloot roet in het eten te gooien. Terwijl ik had gedacht juist in de tijd van operatie en 38 bestralingen veel artikelen te kunnen schrijven, kwam er in die tijd geen letter op papier. De psyche is toch een raar iets! Met name in die tijd was ik mijn promotor en co-promotores erg dankbaar. Nooit legden zij mij druk op en nooit viel er een kritische noot toen er maandenlang geen progressie kwam in mijn "referralpaper".

Professor Boersma, beste Eric, mijn promotor,
Ik weet nog heel goed dat ik voor het eerst bij jou op de kamer kwam om samen met Ron te praten over onze plannen van de OPTICARE-studie. Ik had het zweet op mijn voorhoofd om al je vragen adequaat te beantwoorden. Wetenschap was toch wel iets heel anders dan patiëntenzorg en vergde activiteit van andere hersencellen dan die je dagelijks gebruikt. Daardoor heb ik vanaf het begin ongelooflijk veel van je geleerd. Je was nooit te beroerd om statistische analyses die we gebruikten vanaf "scratch" aan mij uit te leggen. Ook al was ik een "atypische promovendus", je nam altijd ruim de tijd voor mij en kreeg ik zelfs als iedere

andere promovendus jaarlijks een kerstkaart van je, wat ik zeer attent van je vond. Soms was het een uitdaging om mijn stuk boven aan je grote stapel te krijgen, maar je commentaar en aanpassingen waren altijd het wachten dubbel en dwars waard! Met name ben ik trots op het hoofdstuk “Discussion and Future Perspectives”. Het is exact hoe ik de toekomst zie. Het was een grote eer om met jou te mogen werken en ik hoop dat we nog vele projecten samen mogen doen!

Dr van Domburg, Ron, mijn co-promotor,
Jouw rotsvast vertrouwen in mij, je optimisme en het altijd “lichter” maken van alle problemen hebben er voor gezorgd dat mijn boekje uiteindelijk af is gekomen en dat de OPTICARE-studie in “Heart” is gepubliceerd. Vanaf het begin riep je: “Hotline sessie ESC Rome 2016 !”, terwijl Nienke en ik dachten: “yeah right, dream on…” maar het is ons gelukt!! Zonder jou had ik het nooit gered. Ook in de laatste fase van mijn promotie bleef je mij steunen ondanks de ziekte van Ellen.
Ellen, aan jou ook veel dank dat je bereid was Ron aan ons af te staan, terwijl hij al lang en breed was gepensioneerd.

Dr Geleijnse, Marcel, mijn andere co-promotor,
Wij kennen elkaar al een eeuwigheid vanaf de tijd dat onze carrières nog nauwelijks waren begonnen. In die tijd was het heel raar opleidingsassistent in het Thoraxcentrum te zijn zonder dat je gepromoveerd was. Ik was dan ook één van de weinigen, waar natuurlijk regelmatig opmerkingen en grappen over werden gemaakt. Toentertijd zei ik al tegen je: “OK Geleijnse, als het ooit zover komt, word jij mijn co-promotor” en jij hebt je aan je afspraak gehouden!
Zoals onze collega Bas van Dalen al in zijn dankwoord memoreerde, was jouw heldere wetenschappelijke blik, feitenkennis en talent voor schrijven alom in het Thoraxcentrum geroemd lang voor je staflid werd, waardoor dus toen en nu nog steeds de profetische uitspraak geldt: “als je ooit iets met onderzoek wil doen binnen de cardiologie, zorg dan dat je Marcel er bij betrekt.”
Niets hierover is te veel gezegd. Je commentaren brachten ons altijd verder. Je kritiek was altijd opbouwend: behalve je ergernis over spaties die er wel/niet stonden en over het feit dat ik ondanks mijn boekje slechts “kennis heb gemaakt” met het programma “Word”! Nooit liet je merken dat mijn schrijverstalent te wensen over liet. Jij wist er altijd iets leesbaars van te maken.
Ook was het altijd genieten om even de regionale- en buurtroddels en de landelijke politiek door te nemen als we klaar waren met het doornemen van een artikel. Weet je zeker dat Thierry Baudet geen broer van je is? Marcel, ontzettend veel dank voor al je steun en hulp. En ja, nu mag je alsnog je speech (zonder censuur) houden die je al van plan was te geven toen ik cardioloog werd, maar waar onze collega’s een stokje voor staken!

De leden van de kleine commissie: Professor Jaap Deckers, Professor Henk Stam en Professor Ron Peters.

Beste Jaap,
Ik leerde je kennen als achterwacht toen ik als kersverse ANIO's met weinig ervaring op de CCU in het Thoraxcentrum begon. Ook al stond je met een luier in je ene hand en een krijsende baby in je andere, je bleef rustig en je gaf adequaat advies. Ik heb jou altijd enorm bewonderd voor de rust die je uitstraalde en om je diplomatieke houding. Van dit laatste maakte je ook optimaal gebruik toen bleek dat hetzelfde onderzoek aan twee assistenten was gegeven. Zo belandde ik destijds bij Cardialysis. Dank dat je ondanks je pensionering in mijn kleine commissie zitting wilde nemen.

Beste Henk,
Al jaren maak jij je binnen de revalidatiegeneeskunde hard voor de hartrevalidatie en ben je actief betrokken bij het reilen en zeilen binnen Capri. Als revalidatiearts heb jij een andere invalshoek en heb je mij geleerd wat bewegen ook voor onze patiëntenpopulatie kan doen. Het proefschrift van Nienke is daar het bewijs van. Heel veel dank voor je immer nuttige input bij alle gezamenlijke artikelen.

Beste Ron,
Van iedereen die betrokken is bij mijn proefschrift ken ik jou het langste. Nadat ik na een paar maanden ANIO's te zijn geweest in Breda besloten had de cardiologie te kiezen, kwam ik voor een promotieplek bij jou solliciteren. Het is niets geworden, mede omdat ik bleef volhouden alleen te willen komen als jij mij de garantie van een opleidingsplaats kon geven. Ik weet nog goed dat je toen tegen mij zei: "als je iets zo graag wilt, gaat het je waarschijnlijk ook lukken." En zie….
In de afgelopen jaren hebben we veel gesproken over preventie, gedragsveranderingen bij patiënten, en vooral hoe dat te bereiken. Dit waren inspirerende gesprekken en altijd blijf jij daarin optimistisch en blijf je de kar in Nederland trekken. Ook in de CPH-commissie (= de Nederlandse commissie Preventie en Hartrevalidatie) heb je een belangrijke rol. Je hebt een enthousiast team om je heen en ondanks de "020 versus 010" theorie, kunnen onze twee teams uitstekend met elkaar overweg. Ik hoop nog vele projecten in de toekomst met jullie te mogen doen.

De leden van mijn grote commissie: Professor Peter de Jaegere, Professor Wilma Scholte Op Reimer.

Beste Peter,
De MUSIC studie, herinner je die nog? Ik was project manager bij Cardialysis en had de eer met jou te mogen werken als principal investigator van een groot internationaal onderzoek.

De secuurheid waarmee jij dit onderzoek leidde, was indrukwekkend en de loyaliteit naar mij, nog niet eens een echte onderzoeker, was groot. Je maakte mij gewoon mede-auteur tussen alle groten der aarde. Ik word nog emotioneel als ik jou en Sophie zie staan met jullie jongens op de receptie van mijn huwelijk in mei 1997.

Beste Wilma,
Wij kennen elkaar uit de tijd dat ik arts-assistent was en jij "zuster op 1200". Toen al werkte ik graag met je: altijd aardig, nooit gestresst, je zaakjes goed in orde. Intussen heb je een enorme carrière achter de rug, waar ik diepe respect voor heb. Ik voel me vereerd dat je in mijn grote commissie zit.

Nienke ter Hoeve,
Wij werden verbonden met elkaar door de OPTICARE-studie. Eigenlijk allebei zo "blue" in het leiden EN uitvoeren van zo'n gerandomiseerd onderzoek. Jij liet je nooit kisten, verhief nooit je stem, liet nooit je onvrede merken, raakte nooit gestresst. Totaal anders dan ik, die nog wel eens heetgebakerd kon reageren. Menig moment was ik jaloers op je gelijkmatige karakter. Misschien vulden we elkaar daarom zo goed aan. Voor je startte, kon je al enorm goed schrijven en toonde je een scherpe geest waar ik dankbaar gebruik van heb gemaakt. Ook was je nooit te beroerd om al mijn soms triviale appjes te beantwoorden in de laatste fase van mijn promotie, zelfs al was het soms weekend of bijna nacht. Dank voor de fijne samenwerking en geduld in al die jaren. Ik verheug me op jouw promotie binnenkort en ook om met je te blijven samenwerken in onze toekomstige projecten.

Rita van den Berg,
Met Nienke boften we dat wij jou, haar co-promotor, er "gratis en voor niks" bijkregen. Samen met Ron van Domburg bewaakte jij de voortgang van de OPTICARE. Je vermogen om goed te kunnen luisteren en dan pas diplomatiek te reageren, heb ik altijd bewonderd. Dankzij jou hebben we de subsidie voor de XL binnengehaald. Laten we daar een net zo geslaagd project van maken als we hebben gedaan met de OPTICARE!

Voor het organisatietalent en de puntjes op de i kregen we gelukkig Myrna van Geffen in onze schoot geworpen en voor echte researchkennis Saskia Versluis, bijgestaan door verpleegkundige Els Altink. Toen jullie er bij kwamen, werd er pas echt orde in de chaos gecreëerd. Wat was dat een zaligheid!
Saskia, het was een eer om na al die jaren weer met je te mogen werken, ook al was het in een hele andere setting dan op een CCU en dank dat we mochten meegenieten van de Olympische resultaten van je dochter!
Myrna, helaas besloot je dat je ambities elders lagen. Het is goed te horen dat je alle mogelijkheden krijgt je verder te ontwikkelen bij Decathlon.

Els, ik hoop dat je vanuit de hemel kan meegenieten de 17e!
Gelukkig is Verena ons als tweede research verpleegkundige komen versterken nu Saskia van haar welverdiende pensioen geniet. En met de komst van het XL project hebben we een nieuwe promovendus in ons midden, Iris den Uijl.
Iris, dank voor al je hulp in de laatste weken als mijn “digibeet-zijn” mij weer dwars zat.
Niet te vergeten al die tientallen studenten die Ron steeds uit zijn hoge hoed toverde. Dank voor de honderden wandeltesten, data invoer, controle van data etc, etc.
Kimberley, Joost, Angela, Rebecca, dank voor jullie subanalyses die tot mooie publicaties hebben geleid. En natuurlijk Boris Galjart: jij dank voor je hulp bij het submitten van menig artikel: dat heeft mij heel veel tijd en stress gescheeld. Mede dankzij jullie allen is mijn boekje nu al klaar!

Lisbeth Utens en haar collegae, dank voor jullie waardevolle co-auteurschap.
Lisbeth, erg spijtig dat regio Zuid een andere week herfstvakantie heeft. Ik had je graag als opponent gezien.

Alle collega’s bij Capri,
In het begin riep ik heel hard dat jullie geen steentje hoefden bij te dragen aan mijn onderzoek! Dat bleek de halve waarheid. Eerst was het een kiezeltje, later zelfs keien maar intussen is wetenschap goed geïntegreerd in het hele bedrijf.
Egbert, Nathalie en Ronald dank voor het leiden van alle extra bijeenkomsten van de OPTICARE.
Tanja, onze “terugkomsessie-zuster” speciale dank aan jou. Wat heb jij veel avonden opgeofferd voor ons. Met een extra pakje karnemelk was jij altijd bereid om ons bij te staan samen met tal van je collega verpleegkundigen, diëtistes, maatschappelijk werkers en studenten. Allen heel veel dank! De zelfbereide salades en soepen om de eeuwige broodjes kipfilet te vervangen was denk ik wel een lokkertje.

Natuurlijk ook veel dank aan de verpleegkundigen van de Hart Coach van Zilveren Kruis en aan Rosalie Klinkhamer en Onno van der Galien.
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Professor Zijlstra, beste Felix, je trok wit weg toen Ron en ik vroegen de stafgang te mogen gebruiken voor onze 6-minuten-wandeltesten tot je begreep dat het na kantoortijd was. Dank voor dit gebaar en je financiële support voor de receptie.

Nog een stukje hoe dit allemaal zo gekomen is en waarin ik ook de mensen wil danken die daar een grote rol in hebben gespeeld.

Ik kan me niet anders herinneren dan dat ik altijd dokter heb willen worden. In mijn studietijd was ik er zeker van dat het psychiatrie zou worden. Het menselijk brein en de psyche boeiden mij enorm en ik probeerde mijn CV ook zo veel mogelijk af te stemmen op deze wens. Totdat ik de co-schap psychiatrie in ging. Wat een deceptie!! Omdat ik al jaren in het studententeam "psychiatrie" van het EMC had gewerkt, kende ik veel patiënten. Vele van hen bleken echter ongeneeslijk. Bovendien bleek ik zelf helemaal geen voelsprieten te hebben voor de psychiatrie. Het bekende "niet-pluis/pluis" gevoel ontbrak volkomen. Na een grote crisis over deze deceptie begon ik per toeval mijn carrière in de cardiologie in Breda. Wijlen Peter Dunselman had altijd al beweerd dat hij meteen had gezien dat ik cardioloog zou worden. En inderdaad was ik al na een paar weken gegrepen door het vak. Met name de snelheid van zowel de diagnostiek als therapie en het overzichtelijke (het is maar één orgaan) bleek mij goed te liggen.
Dr van den Bos, Arjan, jij hebt er voor gezorgd dat ik uiteindelijk in het Thoraxcentrum kon gaan werken. Zonder jouw brief was dat waarschijnlijk nooit gelukt en daar blijf ik je nog altijd dankbaar voor.
Wijlen professor Roelandt had de toekomst eigenlijk al voorspeld in mijn eerste sollicitatiegesprek met hem. Hij zag mijn overwegend psychiatrische CV en zei dat ik onderzoek moest gaan doen met als onderwerp een combinatie van psyche, gedrag en hartziekten. Hij heeft gelijk gekregen.
Mijn opleiders, Maarten Simoons, Aggie Balk, Folkert ten Cate en Tjebbe Galema, jullie hebben mij gemaakt tot de cardioloog die ik nu ben geworden, inclusief mijn interesse in preventie.
Aggie, we noemden je in onze opleiding terecht onze "generaal"! Dank voor je steun en inzet om me weer naar de Rijnmond regio terug te halen.
Mijn collega's in Weert, Huber, Andre en Jan, het was zeker niet onze samenwerking wat me terugdreef naar 010. Goed te horen dat de hartrevalidatie afdeling nog steeds bestaat! En nog steeds onder de bezielende leiding van Franka en Eugenie!

Grady, Han, Rob, Hans, Marc, LoeKie, dank dat jullie me alsnog wilden aannemen ook al had ik eerst Weert boven jullie verkozen. Tezamen hebben we een bloeiende praktijk opgebouwd en door de fusie uitgebreid met collega's 'van de andere kant' en van de Havenpoli. Tezamen zijn we met 19! We gaan er een mooie tent van maken!

Beste Marten,
Dank voor je vertrouwen in mij om mij aan te trekken. Mede dankzij jou kon ik terugkeren naar mijn geliefde stad.

Beste Niek,
Het lot bracht ons tezamen. Toen Marten Kazemier van zijn welverdiende pensioen ging genieten, vond men dat het directeurschap gescheiden moest worden van het medische. Ze

hadden het niet beter kunnen regelen! Jij bent een bestuurder zonder dubbele agenda. Jij hebt de wetenschap altijd gestimuleerd maar bemoeide je nooit met de inhoud. Andersom bemoeide ik mij nooit met geldzaken en dankzij jou zit Capri nu in een modern jasje, zijn we straks twee proefschriften rijker en doen een studie met een Zon MW subsidie. Veel zaken om trots op te zijn!

Mijn para-nimfen “Duckje en Mickje”,
“Duckje”, Eline, van vriendin-van-een-vriendin naar collega naar dierbare vriendin en paranimf. Samen Business Class, ge-upgrade naar New Orleans, angstig mijn eerste poster koker vastklemmend tot ESC Berlijn, met onze doekjes in onze ‘perfect outfit maar dan wel met lusjes eruit. Jjij stond aan de wieg van mijn wetenschappelijke carrière. Van jou leerde ik in 1993 een RCT te leiden, de zin van een goed CRF, DDE (double data entry) al die dingen waar ik helemaal groen als gras was. Altijd heb ik gezegd dat als ik ooit promoveer jij mijn paranimf zou zijn. Maar veel eerder mocht ik je getuige zijn op je huwelijk 12 jaar geleden. Wat was het een mooie dag! Toen ik in 2011 weer begon met een ‘beetje wetenschap’ kon ik altijd bij je terecht. Zo fijn dat je mij zult bijstaan op deze dag!
“Mickje”, Micky, mijn andere paranimf we waren 18 toen we elkaar leerden kennen en soul mates vanaf het begin. Lang voor we onze echtgenoten leerden kennen, deelden we al lief en leed. Ook al woon jij in ‘t Gooi en ik in Rotterdam, het gevoel van soulmates is nooit veranderd. Dank dat je me wilt bijstaan bij deze mijlpaal!

Alle vriendinnen die met mij mijn 50-jarige verjaardag vierden, jullie weten dat het voor mij een emotioneel moment was om mijn 50ste verjaardag te vieren. Ik zou opnieuw jullie stuk voor stuk willen toespreken maar dan wordt het dankwoord wel erg lang! Wat is het leven van een vrouw zonder haar vriendinnen? Ik ben gezegend met jullie allemaal en hoop samen met jullie oud te worden. Mijn Lenzerheide-vriendinnen en mijn Vague-vriendinnen, dank voor de gezellige weekendjes weg, vol geklets en bulderend gelach! Vague-schaaf: DT, KT!!!
Toch speciale dank aan één vriendin, in relatie tot dit boekje een speciale vermelding waard: Pauline. Jij hebt van al mijn vriendinnen het geklaag en gesteun in het laatste half jaar het meest moeten aanhoren zodanig dat je de namen van alle betrokkenen intussen wel kan dromen. Pauline, 17 oktober krijg je de gezichten te zien achter de verhalen! Veel dank voor je groot luisterend oor.

Behalve mijn dierbare vriendinnen, wil ik twee mannen noemen,
Peetje, Peter, samen met Caroline en jullie meiden Sanne en Floor, zijn jullie onze familie-die-in-het-echt-geen-familie is. Wij delen al jaren alle lief en leed. Dank voor de ontelbare Paastripjes die zijn geweest en ongetwijfeld zullen volgen.
Pieter, “boodschappenjongen”, de laatste jaren was het letterlijk “ in sickness and in health”. Dank voor al je steun, ook voor Paul tijdens mijn ziekte en de stressvolle controles daarna.

Caro, Heleen en ik hebben onze portie wel gehad en op naar vele jaren van gezondheid voor ons allen.
“De cirkel is rond”
Otosan,
Thank you for bringing me to this country, and to this town which truly become my home. You have always told me to make sure that I can take care of myself and earn my own money, even being a woman: well otosan, I have succeeded: “de cirkel is rond”.
My PhD on October 17th , your son’s 50th birthday on October 20th, your grandson becoming 18 on October 21st. I truly hope that you can be here with okasan to celebrate it all!!

Tenslotte mijn gezin:
Nooit had ik durven dromen dat ik een leven zou krijgen met kinderen. In die tijd was het niet gebruikelijk zwangerschappen te combineren met je carrière. Maar ik kreeg twee kinderen, Anton en Alice die intussen zijn uitgegroeid tot bijna volwassenen. Lieve Anton en Alice, mijn leven zou geen zin hebben zonder jullie. Wat is mama trots op de mensen die jullie zijn geworden.
Anton, sportief, introvert, veel IQ, je doorloopt je school zonder al te veel inspanningen. Hockey is je lust en je leven. Dank voor alle spannende hockeywedstrijden en overwinningen op de NK’s.
Alice, extravert, creatief, veel EQ , je kwam lachend op de wereld en nu nog steeds laat je graag anderen lachen. Vol energie stort je je in de dingen die je interesseren, zoals het ontwerp van de kaft van dit boekje. Toen je eenmaal inspiratie had, was het in enkele minuten gepiept. Van het hele boekje ben ik het meest trots op jouw ontwerp. Wat is het prachtig geworden!! Veel dank, lievie!
Last but not least mijn dierbare echtgenoot Paul, “mijn eeuwige rots in de branding”, al jaren deelden we een comfortabel leven wat bestond uit werken, veel etentjes en vele reisjes. Samen gingen we de wereld over, altijd hebben we elkaar vrijgelaten om onze eigen passies en interesses te ontwikkelen. Ook toen het leven ingewikkelder werd toen de kinderen kwamen, bleek dit goed te werken. Toen ik ziek van heimwee aangaf terug te willen naar Rotterdam, heb jij me daarin gesteund, ondanks het feit dat jij het leven in het Zuiden prima vond. Daar ben ik je eeuwig dankbaar voor. Het is ons samen gelukt twee kinderen tot prachtige individuen te maken en borstkanker te verslaan! Het duurt niet lang of ons leven wordt weer “met z’n tweeën”. Het zal weer net zo fijn worden als vroeger schat, ook al gaan we onze kids natuurlijk vreselijk missen thuis om ons heen!

Promoveren: ik kan het iedere perifere cardioloog aanraden die op zoek is naar een nieuwe uitdaging, behalve het laatste half jaar, vooral als je een digibeet bent zoals ik!

CURRICULUM VITAE

Madoka Sunamura was born on March 2nd 1965, in Toyama Japan. At the age of 7 she moved with her family to the Netherlands. After graduating from secondary school (Erasmiaans Gymnasium in Rotterdam), she started her Study Medicine at the Erasmus University in Rotterdam.
In 1995 Cardiology Residency commenced with 2 years of internal medicine in Merwede Hospital in Dordrecht (currently called the Albert Schweitzer Ziekenhuis): after that she worked 4 years as a resident at the Department of Cardiology at the Thoraxcenter in Rotterdam.
Between 2003 and 2007 she worked as a cardiologist at the Sint Jans Gasthuis in Weert, where she founded the department of Cardiac Rehabilitation.
In 2007 she returned to her beloved town of Rotterdam and started to work at Holy Ziekenhuis (currently called Fransicus Vlietland & Gasthuis): at the same time she became advisor and researcher at Capri Hartrevalidatie where she conceived the idea of the OPTICARE study together with Ron van Domburg and the Department of Rehabilitation of Erasmus Medical Center, eventually leading to this thesis.
Currently, she is still working as a general cardiologist with special attention to cardiac rehabilitation, non-invasive imaging and management at Franciscus Vlietland & Gasthuis. At Capri Hartrevalidatie, she coordinates several research projects and is advisor to the Management Team.
She is a member of the Dutch Prevention and Cardiac Rehabilitation Committee (CPH), one of the Dutch CVD Prevention Coordinators of the ESC, and incoming chairman of the Rijnmond Cardiologen Club (CCR).

She is married to Paul Driessen and together they have 2 children: Anton (2000) and Alice (2002).

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International Journal of Cardiology 2018 Mar 15;255:221-228

PORTFOLIO: SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

2017	Good Research Practice_GCP-WMO	8
	Franciscus Teach the Teacher, begeleiden van arts-assistenten (2-daags)	9
	Cardio Congress Highlights AHA congres 2017	2
	Venice Arrhythmias	18
	Cardio Congress Highlights ESC congres 2017	2
	Cardio Congress Highlights ACC congres 2017	2
	Refereeravond Cardiologen Club Rijnmond 2017	6
	Haagse Cursus Echocardiografie	12
2016	Hands-on Cardiovasculaire MRI	16
	Cardio Congress Highlights AHA congres 2016	2
	ESC 2016	24
	Cardio Congress Highlights ACC congres 2016	2
	Refereeravond Cardiologen Club Rijnmond 2016	6
2015	Cardiac CT course Nijmegen CWZ LEVEL B	24
	Refereeravond Cardiologen Club Rijnmond	6
	Lustrum symposium Cardiologen Club Rijnmond	3
	Cardiac CT course Nijmegen CWZ LEVEL A	4
	GCP TRAINING beginners en gevorderden	8
2014	Refereeravond Cardiologen Club Rijnmond 2014	6
	ESC Barcelona 2014	24
2013	Cardiology Review Course 2014:BCS&MAYO CLINIC	12
	Voorjaarscongres NVVC 2013	15
	Haagse Cursus Echocardiografie	11
2012	ESC Congress 2012	24
	Cardiology and Vascular Medicine 2012, An ESC UPDATE Programme	6
	Refereeravond Cardiologen Club Rijnmond 2012	6
	GCP TRAINING beginners en gevorderden	8
	ACC Telereview 2012	3
	Haagse Cursus Echocardiografie	11
	Hands-on Cardiac CT Course	16
2011	Cardiovascular Exchange Summit 2011	13
	Najaarscongres NVVC	8
	Cardiology and Vascular Medicine 2011, An ESC UPDATE Programme	11
	Refereeravond Cardiologen Club Rijnmond 2011	6
	Haagse Cursus Echocardiografie	11
	Cardiomyopathy and Valve Disease: from diagnosis to therapy	11

Lectures and teaching activities on Cardiac Rehabilitation:

Kick off NVVC Connect 2012
Refereeravond Cardiologen Club Rijnmond 2012
Studenten Minor Onderwijs 2012
Onderwijs opledingsassistenten cardiologie EMC 2015
6e Regionale Hartfalen Bijeenkomst 2016
Gezamenlijke zorg voor het falende hart; Verbinden van 1e, 2e en 3e lijn 2017
Coeur course "Ischemic Heart Disease" 2018

Posters at international conferences

10-year mortality improvements after cardiac rehabilitation in ACS patients treated with primary percutaneous intervention 13/2/16 ESC Rome
Low referral rate to cardiac rehabilitation after primary percutaneous coronary intervention predicted by clinical variables 14/11/13 EuroPrevent

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