ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2020;■:■■■-■■■

ORIGINAL RESEARCH

Association Between Exercise Capacity and Health-Related Quality of Life During and After Cardiac Rehabilitation in Acute Coronary Syndrome Patients: A Substudy of the OPTICARE Randomized Controlled Trial

Marie de Bakker, MSc,[a] Iris den Uijl, MSc,[b,c] Nienke ter Hoeve, PhD,[b,c] Ron T. van Domburg, PhD,[a] Marcel L. Geleijnse, MD, PhD,[a] Rita J. van den Berg-Emons, PhD,[c] Eric Boersma, PhD, FESC,[a] Madoka Sunamura, MD, PhD[b]

From the [a]Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam; [b]Capri Cardiac Rehabilitation Rotterdam, Rotterdam; and the [c]Department of Rehabilitation Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.

Abstract

Objective: To examine the strength of the association between exercise capacity and health-related quality of life (HRQOL) during and after cardiac rehabilitation (CR) in patients with acute coronary syndrome (ACS) who completed CR.

Design: Prospective cohort study.

Setting: Outpatient CR center.

Participants: Patients (N = 607) with ACS who completed CR.

Interventions: Multidisciplinary 12-week exercise-based CR program.

Main Outcome Measures: At baseline (pre-CR), the 6-Minute Walk Test (6MWT) was performed to determine exercise capacity, and the MacNew Heart Disease Health-related Quality of Life questionnaire was used to assess HRQOL. Measurements were repeated immediately after completion of CR (post-CR): at 12 months and 18 months follow-up. Multivariable linear regression, including an interaction term for time and exercise capacity, was applied to study the association between exercise capacity and HRQOL at different time points relative to CR, whereas model parameters were estimated by methods that accounted for dependency of repeated observations within individuals.

Results: Mean age in years ± SD was 58±8.9 and 82% of participants were male. Baseline mean 6MWT distance in meters ± SD was 563±77 and median (25th-75th percentile) global HRQOL was 5.5 (4.6-6.1) points. Mean 6MWT distance ($P<.001$) and the global ($P<.001$), physical ($P<.001$), emotional ($P<.001$) and social ($P<.001$) domains of HRQOL improved significantly during CR and continued to improve during follow-up post-CR. Independent of the timing relative to CR (ie, pre-CR, post-CR, or during follow-up), a difference of 10 m 6MWT distance was associated with a mean difference in the global HRQOL domain of 0.007 (95% confidence interval [CI], 0.001-0.014) points ($P=.029$) and a mean difference in the physical domain of 0.009 (95% CI, 0.001-0.017) points ($P=.023$).

Conclusions: Better exercise capacity was significantly associated with higher scores on the global and physical domains of HRQOL, irrespective of the timing relative to CR, albeit these associations were weak. Hence, CR programs in secondary prevention should continue to aim at enhancing both HRQOL and exercise capacity.

Archives of Physical Medicine and Rehabilitation 2020;■:■■■-■■■

Even though mortality rates related to cardiovascular diseases (CVDs) have declined substantially in the past decades,[1] acute coronary syndrome (ACS) remains a source of high morbidity, mortality, and a large economic burden.[2,3] Almost half of the

Clinical Trial Registration No.: NCT01395095.

Supported by the Capri Cardiac Rehabilitation Rotterdam and the Zilveren Kruis Healthcare Insurance Company (grant no. Z687).

Disclosures: none.

0003-9993/20/$36 - see front matter © 2020 by the American Congress of Rehabilitation Medicine
https://doi.org/10.1016/j.apmr.2019.11.017

major coronary events annually occur in survivors of coronary heart disease.[4] Patients with a so-called recurrent event are more likely to have rehospitalizations, longer lengths of inpatient stay, and a higher probability of revascularization during follow-up than patients with a new coronary event.[5] These findings underline the importance of effective secondary prevention in patients with ACS.

Cardiac rehabilitation (CR) programs are multifaceted interventions that are recommended in international guidelines.[6,7] The secondary prevention strategy is designed to modify cardiovascular risk factors and improve physical, psychological, and social functioning of patients.[6-8] Previous randomized controlled trials (RCTs) and meta-analyses have demonstrated that exercise-based CR reduces mortality, morbidity, and hospital admissions.[8-10] In addition, it has been shown that exercise capacity and patient-reported physical functioning consistently improve after CR.[11-13] Another important indicator of treatment effect is psychological well-being and health-related quality of life (HRQOL).[13] A recent meta-analysis studying the effect of CR on HRQOL in patients with ACS reported an incremental benefit of receiving CR compared to usual care.[14]

Since patients with ACS improve both HRQOL and exercise capacity when participating in CR programs, an association between HRQOL and exercise capacity could be expected. Nonetheless, HRQOL is a multifactorial and multidimensional concept that depends on a variety of factors.[15] The expected association between exercise capacity and HRQOL would, therefore, be weak. Previous studies with a cross-sectional design have shown varying results on the relation between exercise capacity and HRQOL in patients with coronary artery disease (CAD) who are entering CR.[16-19] For instance, Strong et al[18] indicated a positive but weak association between exercise capacity and quality of life scores in patients entering CR after coronary artery bypass graft (CABG) surgery. On the other hand, Staniute et al[17] showed that a reduced physical component of HRQOL was moderately associated with reduced exercise capacity in patients with CAD who are admitted to CR. In contrast, no significant association between emotional state and exercise capacity was found by Bunevicius et al[19] in patients with CAD who were admitted to a rehabilitation program. Consequently, the relation between exercise capacity and HRQOL at different time points relative to the start of CR remains unknown. Therefore, the purpose of the current study was to examine the strength of the association between exercise capacity and HRQOL before and after CR in patients diagnosed with ACS.

List of abbreviations:

6MWT	**6-Minute Walk Test**
ACS	**acute coronary syndrome**
CABG	**coronary artery bypass graft**
CAD	**coronary artery disease**
CI	**confidence interval**
CR	**cardiac rehabilitation**
CVD	**cardiovascular disease**
HRQOL	**health-related quality of life**
OPTICARE	**Optimal Cardiac Rehabilitation**
RCT	**randomized controlled trial**

Methods

Study population

Patients referred to the outpatient rehabilitation center at Capri Cardiac Rehabilitation were invited to participate in the Optimal Cardiac Rehabilitation (OPTICARE) study between November 2011 and August 2014. The OPTICARE study was originally designed to study the effects of extended CR programs and is a multicenter, open, multidisciplinary RCT with an 18-month follow-up. The study design is described previously in more detail.[20] Patients were eligible for participation in the OPTICARE study if they were admitted to a CR program after diagnosis of an ACS, at least 18 years old, and proficient in Dutch. ACS was defined as persistent (>20min) chest pain suggestive of myocardial ischemia, which is unresponsive to nitroglycerine and is accompanied by ST-T changes (electrocardiographic evidence) or cardiac troponin elevations (biochemical evidence), regardless of in-hospital treatment. Patients with severe physical or cognitive impairments that could limit CR participation were not eligible. The medical ethics committee of the Erasmus Medical Center in Rotterdam approved the study protocol (MEC-2010-391) and all of the included patients provided written informed consent.

All patients who completed >75% of the exercise part of the CR program (≥18 training sessions) and with at least 1 patient-reported HRQOL measurement and 1 6-Minute Walk Test (6MWT) measurement were included in the present study.

CR program

The standard CR program consists of group exercises of 1.5 hours, which are offered at least 2 times a week for 12 weeks under the supervision of a multidisciplinary team. The standard program is offered according to the Dutch guidelines[21,22] and is currently offered to all patients referred to Capri Cardiac Rehabilitation. The physical training program was strictly obligatory, but the option to participate in education sessions was offered to all patients. These sessions were designed to stimulate adoption of a heart-healthy lifestyle by providing information on cardiovascular disease risk factors, medical information, dietary advice, and coping with emotions. In addition, patients admitted to the CR program had the opportunity to participate in counseling sessions addressing stress management, smoking cessation, and diet or an individually based psychological program. The 2 extended CR programs investigated in the OPTICARE study consisted of extra face-to-face lifestyle counseling (CR+F) or extra individual telephonic lifestyle counseling (CR+T) in addition to standard CR.[20] More specifically, patients randomized to the CR+F intervention group were required to participate in 3 group counseling sessions under supervision of a physiotherapist during the 12-week standard CR program and at 4, 6, and 12 months after the start of CR. Patients randomized to the CR+T intervention group were offered 5-6 individual telephone coaching sessions during the first 6 months after completion of standard CR.

Patients were randomized to standard CR, CR+F, and CR+T in a 1:1:1 ratio. Since interaction models in the present study (data not shown) showed no differences in the association between exercise capacity and HRQOL between patients in the standard CR program and the extended programs of the OPTICARE study, all patients were analyzed together.

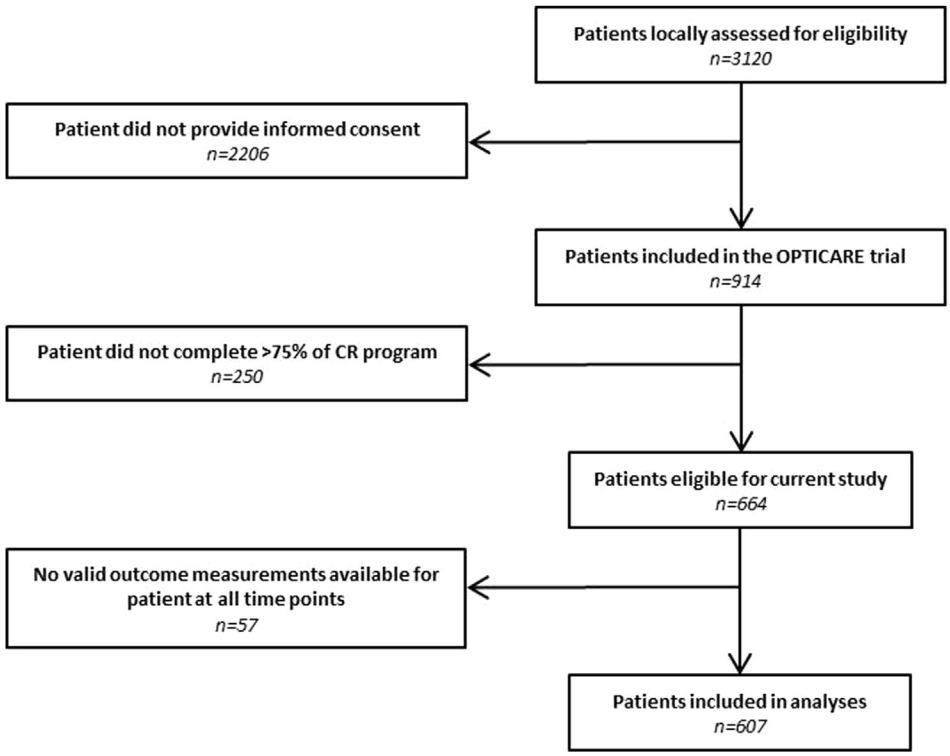

Fig 1 Patient flowchart.

Patient characteristics

Information on the presence of cardiac risk factors (such as diabetes, dyslipidemia, and hypertension), cardiac disease history, medication use, and the therapeutic intervention at index were subtracted from the medical file of the participant. Smoking status before the index event was determined during an interview by one of the social workers of Capri Cardiac Rehabilitation. Baseline data on educational, employment, and marital status was collected by using a self-designed questionnaire. The Hospital Anxiety and Depression scale was used to measure anxiety and depression. This valid questionnaire consists of an anxiety and depression subscale and answers are given on a 4-point scale from "never" to "almost always."[23,24] Higher scores on the depression subscale indicate higher levels of depression and higher scores on the anxiety subscale indicate higher levels of anxiety.

Health-related quality of life

The HRQOL of patients was assessed using the MacNew Heart Disease Health-Related Quality of Life (MacNew) questionnaire at baseline (pre-CR), at completion of CR (post-CR), and during follow-up at 12 and 18 months. The MacNew questionnaire is a disease-specific, validated, and reliable self-administered instrument measuring physical and psychological well-being in patients with ACS.[25] The questionnaire consists of 27 items reflecting a global, emotional, physical, and social domain of HRQOL. Each item was rated on a 7-point scale, where "1" indicates poor HRQOL and "7" indicates good HRQOL. The minimal clinically important difference of the MacNew Questionnaire is 0.5 points.[26]

Exercise capacity

The 6MWT was used to assess the (functional) exercise capacity of patients included in the OPTICARE study and was performed according to American Thoracic Society guidelines.[27] The 6MWT is a reliable and valid submaximal exercise test and is responsive to relevant clinical changes during CR.[28] Exercise capacity was determined as the number of meters a patient walks within 6 minutes over a point-to-point, 30-meter-long walking track during which standardized words of encouragement were given every minute. Patients performed the 6MWT at baseline, at completion of CR, and during follow-up at 12 and 18 months. The 6MWT at baseline was performed at the start of the second exercise session of the 12-week CR program. During the first exercise session, patients were familiarized with a walking protocol to accommodate patients who may fear exercise and to avoid a possible learning effect.[28] The minimal clinically important difference of the 6WMT is 25 m.[29]

Statistical analysis

Descriptive statistics were used to present baseline characteristics. Linear regression analyses was performed to address the research questions, whereas a generalized estimating equation approach was used to estimate the model parameters to correct for the dependency of repeated observations within 1 individual.[30]

First, 2 separate models were used to analyze (1) the change in HRQOL and (2) the change in exercise capacity. By adding the different time points as dummy variables to the generalized linear models, the change in outcome variable post-CR compared to pre-CR was determined. Similarly, the change in outcome variable at 12-month and 18-month follow-up compared to post-CR was

Table 1 Clinical characteristics of study population

Demographic Characteristics	N = 607
Sex (male), n (%)	497 (81.9)
Mean age (y) ± SD	58.0±8.9
Education,* n (%)	
High	158 (26.0)
Intermediate	341 (56.2)
Low	27 (4.4)
Employment,† n (%)	
Employed	293 (48.3)
Unemployed	190 (31.3)
Marital status,‡ n (%)	
Married/partner	439 (72.3)
Single	90 (14.8)
Risk Factors	
Overweight, n (%)	468 (77.1)
Diabetes, n (%)	73 (12.0)
Dyslipidemia, n (%)	210 (34.6)
Hypertension, n (%)	256 (42.2)
Smoking (pre-ACS), n (%)	230 (37.9)
Cardiac History	
Myocardial infarction, n (%)	47 (7.7)
Angina, n (%)	36 (5.9)
PCI, n (%)	56 (9.2)
CABG, n (%)	7 (1.2)
Stroke/TIA, n (%)	17 (2.8)
Medication at Baseline	
Acetylsalicylic acid, n (%)	586 (96.5)
Oral anticoagulant, n (%)	39 (6.4)
Thienopyridine, n (%)	502 (82.7)
Statin, n (%)	587 (96.7)
Beta blocker, n (%)	496 (81.7)
ACE inhibitor, n (%)	430 (70.8)
Angiotensin II receptor blocker, n (%)	80 (13.2)
Calcium blocker, n (%)	87 (14.3)
Nitrate, n (%)	218 (35.9)
Diuretic, n (%)	67 (11.0)
Psychotropic, n (%)	33 (5.4)
CR Characteristics	
Therapeutic intervention at index, n (%)	
No revascularization	48 (7.9)
PCI	469 (77.3)
CABG	88 (14.5)
No. of training sessions	24.6 (5.0)
Anxiety and Depression at Baseline	
HADS anxiety score, median (IQR)	4 (2-7)
HADS depression score, median (IQR)	2 (1-5)

Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; ACE, angiotensin-converting-enzyme; HADS, Hospital Anxiety and Depression Scale.

* Data missing for n = 81.

† Data missing for n = 124.

‡ Data missing for n = 78.

assessed. Subsequently, baseline characteristics that were significantly associated with the outcome variable of interest were added to the models as possible confounders. These possible confounders can be found in supplemental table S1 (available online only at http://www.archives-pmr.org/).

Second, the association between exercise capacity and HRQOL was assessed. The association between exercise capacity and HRQOL is presented as the difference in HRQOL associated with a 10-m difference in 6MWT distance. The association was evaluated at different time points during the study period (ie, pre-CR, post-CR, at 12mo follow-up and at 18mo follow-up). The factor time and an interaction term for exercise capacity and time were added to the model to study whether the association between exercise capacity and HRQOL was significantly different at different time points relative to the start of CR. In case of a significant interaction, the results of the regression analyses are presented separately for the different time points. Otherwise, the results of the regression analyses are presented for all time points together. Multivariable analyses were performed with correction for the same possible confounders as described above.

Missing data were handled by multiple imputations using the MICE package in R.[a] The geepack package[b] was used to fit the marginal models using a generalized estimating equation approach in R. All statistical tests were performed in R version 3.4.1.[c] A 2-sided P value<.05 was considered significant.

Results

Baseline characteristics

In total, 914 patients participated in the OPTICARE study, of whom 664 (72.6%) completed >75% of the CR program. In 57 of those patients, no HRQOL or 6MWT measurements were available. Therefore, 607 patients were included in the present analyses (fig 1). The mean patient age in years ± SD was 58±8.9, and 81.9% were male (table 1). The incidence of traditional cardiovascular risk factors, such as overweight (77.1%) and hypertension (42.2%), was high in the study population. Most patients were treated with percutaneous coronary intervention (77.3%) and the mean number of CR training sessions ± SD was 24.6±5.0. At baseline, 97% of the patients were taking aspirin and statins, 83% thienopyridines, 82% beta blockers, 71% angiotensin-converting enzyme inhibitors, and 5.4% psychotropic medication. Patients excluded of the present analysis were, on average, 2 years younger (P = .003), more likely to have a history of smoking (54% vs 38%; P<0.001), and used fewer statins (94% vs 97%; P = .025) but more thienopyridines (89% vs 83%; P = .014) than the patients included in the present analyses.

Exercise capacity and HRQOL

The mean exercise capacity was 563 m at baseline and increased with 37.4 m (95% CI [confidence interval], 31.1-43.6; P<.001) during CR, which remained statistically significant after correction for possible confounders (P<.001; table 2). At 12 months and 18 months follow-up the exercise capacity of included patients continued to increase significantly after correction for possible confounders with 8.7 m (95% CI, 0.7-16.7; P = .033) and 15.2 m (95% CI, 7.6-22.9; P<.001), respectively as compared to post-CR.

The median global, physical, emotional, and social HRQOL before CR was 5.5 (interquartile range [IQR], 4.6-6.1), 5.3 (IQR, 4.3-6.1), 5.4 (IQR, 4.4-6.1), and 5.9 (IQR, 4.9-6.4) points, respectively. All 4 domains of HRQOL increased significantly

Table 2 Changes in exercise capacity and HRQOL

Outcome	Comparison	Unadjusted	Adjusted*	
		Mean Change (95% CI)	Mean Change (95% CI)	*P* Value
Exercise Capacity				
6MWT, m	Post-CR vs pre-CR	37.4 (31.1-43.6)	32.0 (22.9-41.0)	<.001
	12-mo follow-up vs post-CR	-3.0 (-9.3 to 3.3)	8.7 (0.7-16.7)	.033
	18-mo follow-up vs post-CR	-3.0 (-9.6 to 3.7)	15.2 (7.6-22.9)	<.001
HRQOL Measured on a 7-point Likert Scale				
Global	Post-CR vs pre-CR	0.47 (0.37-0.57)	0.32 (0.23-0.41)	<.001
	12-mo follow-up vs post-CR	0.14 (0.04-0.23)	0.09 (0.01-0.17)	.033
	18-mo follow-up vs post-CR	0.22 (0.11-0.32)	0.15 (0.08-0.23)	<.001
Physical	Post-CR vs pre-CR	0.61 (0.50-0.72)	0.47 (0.36-0.58)	<.001
	12-mo follow-up vs post-CR	0.18 (0.06-0.30)	0.14 (0.02-0.25)	.018
	18-mo follow-up vs post-CR	0.24 (0.12-0.36)	0.19 (0.05-0.32)	.007
Emotional	Post-CR vs pre-CR	0.35 (0.24-0.46)	0.18 (0.09-0.28)	<.001
	12-mo follow-up vs post-CR	0.09 (-0.02 to 0.20)	0.04 (-0.05 to 0.12)	.382
	18-mo follow-up vs post-CR	0.17 (0.06-0.27)	0.09 (0.01-0.17)	.027
Social	Post-CR vs pre-CR	0.49 (0.38-0.61)	0.37 (0.26-0.47)	<.001
	12-mo follow-up vs post-CR	0.20 (0.09-0.31)	0.16 (0.05-0.27)	.004
	18-mo follow-up vs post-CR	0.32 (0.21-0.43)	0.27 (0.16-0.38)	<.001

* Adjusted for possible confounders, which are presented in supplemental table S1.

during CR and during follow-up, with exception of the emotional domain at 12 months follow-up (table 2).

Association between exercise capacity and HRQOL during and after CR

There was no significant difference in the association between exercise capacity and HRQOL at the different time points relative to the start of CR (ie, pre-CR, post-CR, at 12mo follow-up and 18mo follow-up; data not shown). Consequently, results are presented for all time points together.

Exercise capacity was positively associated with all 4 domains of HRQOL (fig 2). For instance, the mean global HRQOL differed by 0.013 (95% CI, 0.006-0.021; $P=.001$) points per 10-m difference in the 6MWT distance. Moreover, the physical, emotional, and social domain of the patient-reported HRQOL differed by 0.015 (95% CI, 0.005-0.024; $P=.004$), 0.009 (95% CI, 0.00-0.018; $P=.004$), and 0.012 (95% CI, 0.006-0.018; $P<.001$) per 10-m difference in the 6MWT distance, respectively. After adjustment for possible confounders, the difference in the global ($P=.029$) and physical domain ($P=.023$) of HRQOL per 10-m difference in the 6MWT distance remained statistically significant, but was lost for the other 2 HRQOL domains.

Discussion

The current study examined the longitudinal association between exercise capacity and HRQOL in 607 patients with established ACS who completed a CR program. During the CR program, patients showed an increase in exercise capacity and several domains of HRQOL that continued to improve during follow-up. Before, during, and after CR, a higher exercise capacity was associated with a higher score on the global and physical domains of HRQOL. Hence, patients who improved in 6MWT distance also improved in HRQOL, although the effect size was limited.

Several studies with a cross-sectional design have provided evidence for an association between exercise capacity and HRQOL in patients with CVD. For instance, Nogueira et al[31] showed a mild to moderate correlation between the distance covered in the 6MWT and the final score of the Minnesota Living with Heart Failure Questionnaire in patients with cardiac failure. Another cross-sectional study in patients who underwent CABG surgery demonstrated a significant correlation between the physical domain of HRQOL and peak oxygen uptake, which is a well-known measure for exercise capacity.[18] Moreover, a relatively large study of patients with CAD, of whom 90% had symptomatic heart failure (ie, New York Heart Association functional class II-III), showed a positive association between the global and physical aspect of HRQOL and the 6MWT distance before enrolment in CR.[17] In contrast, Verrill et al[32] suggested no apparent correlation between the performance in the 6MWT and quality of life scores in patients with medically or surgically treated coronary heart disease.

Longitudinal data on the association between exercise capacity and HRQOL are scarce. The findings by Chen et al,[16] who studied elderly patients with CAD, concur with our study. We found that a 10-m difference in 6MWT distance was related with a 0.007 point difference on the global domain of HRQOL and a 0.009 point difference on the physical component. Interestingly, the results in the current study were independent of timing relative to CR (ie, pre-CR, post-CR, and during follow-up), meaning that the improvement in exercise capacity and HRQOL was similar across all time points. Although the association was clearly significant from statistical point of view, the clinical importance of this small effect is low. Apparently, HRQOL is mainly dependent on other aspects than exercise capacity.[15,33,34] All in all, our data suggest that the route to improve HRQOL via an improvement in physical activity is not strong: a difference of 10 m in exercise capacity was associated with a 0.007-point gain in HRQOL in patients who completed CR. Yet, it should be kept in mind that no inferences on causality can be made based on the associations presented in the current study. Therefore, our data suggest that the route to improve

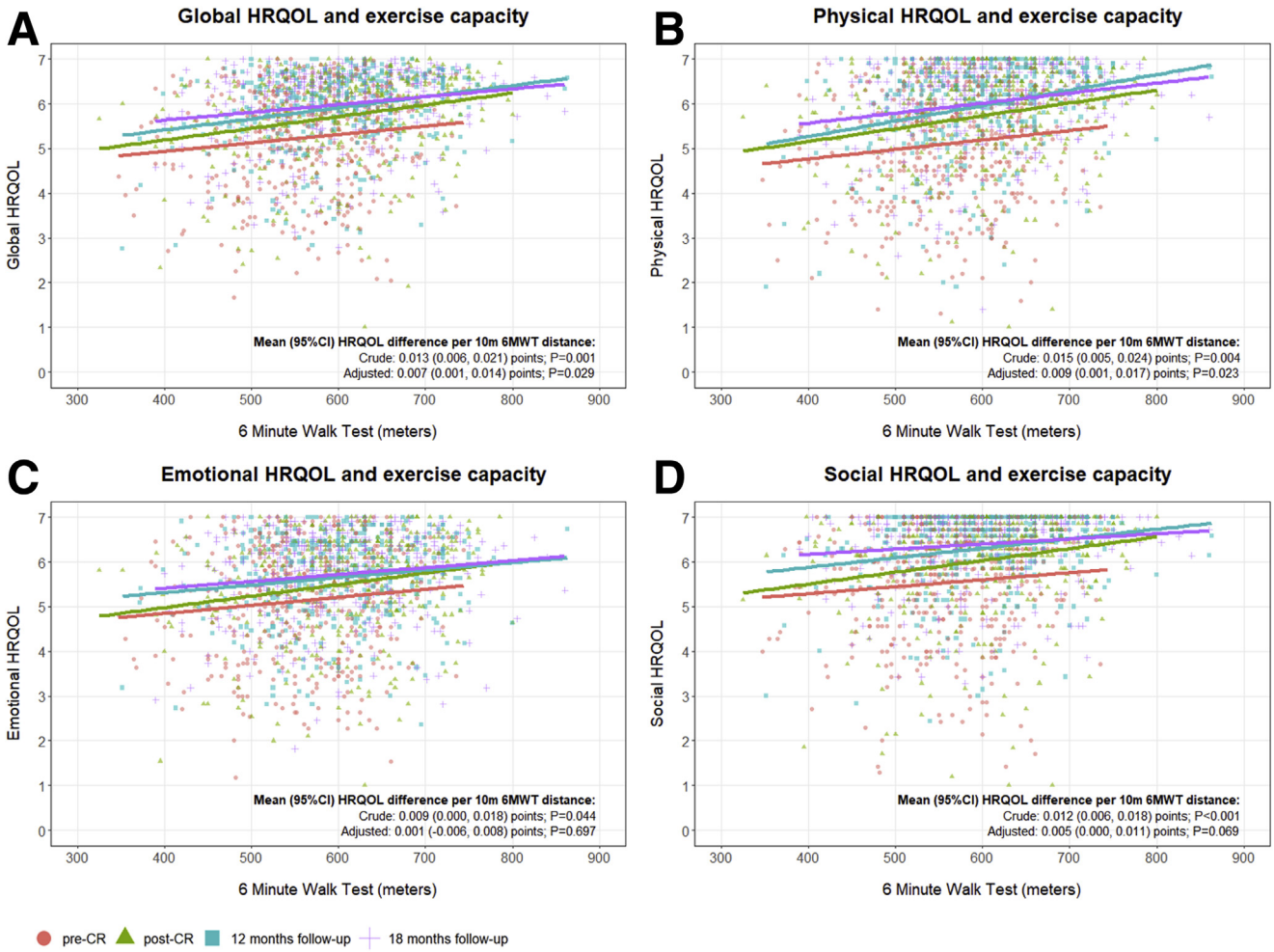

Fig 2 The association between exercise capacity and HRQOL at different time points. The distance covered in meters during the 6MWT is plotted against the 4 domains of HRQOL on a 7-point scale: (A) global, (B) physical, (C) emotional, and (D) social. Data points are depicted separate for each time point relative to CR: pre-CR (orange), post-CR (green), 12-month follow-up (blue), and 18-month follow-up (purple). We performed linear regression and present the estimated mean difference in HRQOL per 10 meters difference in 6MWT distance for all time points together. Adjustments were made for sex, age, level of education, employment status, marital status, overweight, diabetes, hypertension, smoking (pre-ACS), HADS anxiety score, and HADS depression score. Abbreviation: HADS, Hospital Anxiety and Depression Scale.

exercise capacity via an improvement in HRQOL is not strong as well. Hence, attempts to optimize CR programs should keep focusing on both aspects separately. That said, we are aware that the average (baseline) 6MWT distance and HRQOL scores were at the high end of the spectrum observed in patients who are early post-ACS.[26,35] Despite this, our study still observes improvements in exercise capacity, which are higher than the minimal clinically important difference of 25 m.[29] Similarly, improvements of HRQOL in all 4 domains exceed the minimal clinically important difference of 0.5 points during the study period.[26]

CR programs aim to reduce mortality and the number of hospitalizations, modify cardiovascular risk factors, increase patient education, and enhance physical fitness and quality of life.[6-8] The effectiveness of CR interventions for patients with cardiac disease has been studied rigorously in the past.[9,10,36-38] However, fewer data are available regarding the long-term effects of CR programs. An observational study in 105 patients referred to a hospital-based comprehensive outpatient cardiac rehabilitation program following a myocardial infarction showed a significant increase in HRQOL after completion of CR. Even though the HRQOL deteriorated during the 12-month follow-up period, the improvements in HRQOL remained significantly higher than at baseline.[39] Similarly, Gupta et al[40] showed a significant increase in 6MWT distance after completion of CR compared to baseline and significant worsening in the 6MWT distance (although not lower than at baseline) when comparing measurements directly after CR completion with 1-year follow-up in patients with CAD. In contrast, a small RCT in patients with ACS referred to a residential rehabilitation center indicated that the improvements in exercise capacity found during CR were maintained after a follow-up period of 2 years.[41] In our study, improvements in the exercise capacity and HRQOL of patients with established ACS after completion of the 12-week CR program were found, which persisted during a follow-up period of 18 months. The differences in effectiveness of CR during long-term follow-up could be attributed to a difference in content and structure of the CR programs in previously mentioned studies, such as frequency and duration of exercise sessions. Our findings affirm the importance of CR programs in improving the long-term physical and psychological well-being of adherent patients with ACS.

Study limitations

Some study limitations deserve discussion. Namely, patients who were excluded from analyses were, on average, younger, more likely to smoke, and used relatively fewer statins; however, they used more antiplatelet medication than the patients that were included in the current analyses. The drop-out rates in CR tend to be higher among younger patients and those with more risk factors, which is in line with the results of the present analysis.[42,43] Therefore, the results of the current study are probably most valid among the more adherent patients. Another limitation of the current study is the use of the 6MWT to determine exercise capacity. Previous studies reported a learning effect for repeated 6MWTs, which could also result in improvements during CR.[28] However, by performing 1 practice session during the first exercise session of the 12-week CR program, it was attempted to reduce the potential learning effect. Despite this, patients who walk a great distance in the 6MWT at baseline have less scope for improvements than patients who walk only a short distance. This so-called ceiling effect may occur in the patients who already have a relatively good exercise capacity before attending CR. A similar ceiling effect may occur for patients who have a relatively high HRQOL score at baseline. The consequence of the ceiling effect is most likely an underestimation of the correlation between HRQOL and exercise capacity. Nevertheless, this study still observes improvements in exercise capacity, which are higher than the minimal clinically important difference of 25 m.[29] Similarly, improvements of HRQOL in all 4 domains exceed the minimal clinically important difference of 0.5 points during the study period.[26]

Conclusions

Better exercise capacity was significantly associated with higher scores on the global and physical domain of HRQOL in patients with ACS who completed CR, irrespective of the timing relative to CR, albeit these differences were small. Hence, CR programs in secondary prevention should continue to aim at enhancing both HRQOL and exercise capacity.

Suppliers

a. MICE package; Stef van Buuren.
b. geepack package; Søren Højsgaard.
c. R version 3.4.1; The R Foundation for Statistical Computing.

Keywords

Acute coronary syndrome; Cardiac rehabilitation; Health-related quality of life; Rehabilitation; Walk test

Corresponding author

Marie de Bakker, MSc, Department of Cardiology, Erasmus University Medical Center, Rg-419, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. *E-mail address:* m.debakker@erasmusmc.nl.

Acknowledgments

We thank the coordinating center members Myrna van Geffen, MSc, Verena van Marrewijk, BSc, and Saskia Versluis, BSc, for their contribution. We thank the Capri Cardiac Rehabilitation Center employees and Zilveren Kruis Achmea nurses. We thank the medical students from the Erasmus Medical Center for their continual support in collecting data.

References

1. National Institutes of Health. Morbidity & mortality: 2012 chart book on cardiovascular, lung, and blood diseases. Available at: https://www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf. Accessed September 18, 2018.
2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation 2011;123:e18-209.
3. Zhao Z, Winget M. Economic burden of illness of acute coronary syndromes: medical and productivity costs. BMC Health Serv Res 2011;11:35.
4. Briffa TG, Hobbs MS, Tonkin A, et al. Population trends of recurrent coronary heart disease event rates remain high. Circ Cardiovasc Qual Outcomes 2011;4:107-13.
5. Shetty S, Halpern R, McCollam PL. Cost of care for new versus recurrent acute coronary syndrome patients. J Med Econ 2008;11:81-99.
6. National Institute for Health and Care Excellence. Secondary prevention after a myocardial infarction. Available at: https://www.nice.org.uk/guidance/qs99. Accessed October 12, 2019.
7. Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 2014;21:664-81.
8. Lam G, Snow R, Shaffer L, Londe ML, Spencer K, Caulin-Glaser T. The effect of a comprehensive cardiac rehabilitation program on 60-day hospital readmissions after an acute myocardial infarction. J Am Coll Cardiol 2011;57:E597.
9. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2011;7:CD001800.
10. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011;162:571-84.
11. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. N Engl J Med 2001;345:892-902.
12. Lavie CJ, Milani RV. Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. Prog Cardiovasc Dis 2011;53:397-403.
13. Dugmore LD, Tipson RJ, Phillips MH, et al. Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. Heart 1999;81:359-66.
14. Francis T, Kabboul N, Rac V, et al. The effect of cardiac rehabilitation on health-related quality of life in patients with coronary artery disease: a meta-analysis. Can J Cardiol 2019;35:352-64.
15. Pragodpol P, Ryan C. Critical review of factors predicting health-related quality of life in newly diagnosed coronary artery disease patients. J Cardiovasc Nurs 2013;28:277-84.
16. Chen CH, Chen YJ, Tu HP, Huang MH, Jhong JH, Lin KL. Benefits of exercise training and the correlation between aerobic capacity and functional outcomes and quality of life in elderly patients with coronary artery disease. Kaohsiung J Med Sci 2014;30:521-30.

17. Staniute M, Bunevicius A, Brozaitiene J, Bunevicius R. Relationship of health-related quality of life with fatigue and exercise capacity in patients with coronary artery disease. Eur J Cardiovasc Nurs 2014;13:338-44.
18. Strong PC, Lee SH, Chou YC, Wu MJ, Hung SY, Chou CL. Relationship between quality of life and aerobic capacity of patients entering phase II cardiac rehabilitation after coronary artery bypass graft surgery. J Chin Med Assoc 2012;75:121-6.
19. Bunevicius A, Stankus A, Brozaitiene J, Girdler SS, Bunevicius R. Relationship of fatigue and exercise capacity with emotional and physical state in patients with coronary artery disease admitted for rehabilitation program. Am Heart J 2011;162:310-6.
20. Sunamura M, Ter Hoeve N, van den Berg-Emons HJ, et al. OPTImal CArdiac REhabilitation (OPTICARE) following acute coronary syndromes: rationale and design of a randomised, controlled trial to investigate the benefits of expanded educational and behavioural intervention programs. Neth Heart J 2013;21:324-30.
21. Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, et al. Improving guideline adherence for cardiac rehabilitation in the Netherlands. Neth Heart J 2011;19:285-9.
22. van Engen-Verheul MM, Kemps HM, de Keizer NF, et al. Revision of the Dutch clinical algorithm for assessing patient needs in cardiac rehabilitation based on identified implementation problems. Eur J Prev Cardiol 2012;19:504-14.
23. Doyle F, McGee HM, De La Harpe D, Shelley E, Conroy R. The Hospital Anxiety and Depression Scale depression subscale, but not the Beck Depression Inventory-Fast Scale, identifies patients with acute coronary syndrome at elevated risk of 1-year mortality. J Psychosom Res 2006;60:461-7.
24. Stafford L, Berk M, Jackson HJ. Validity of the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9 to screen for depression in patients with coronary artery disease. Gen Hosp Psychiatry 2007;29:417-24.
25. De Gucht V, Van Elderen T, van der Kamp L, Oldridge N. Quality of life after myocardial infarction: translation and validation of the MacNew Questionnaire for a Dutch population. Qual Life Res 2004;13:1483-8.
26. Dixon T, Lim LL, Oldridge NB. The MacNew heart disease health-related quality of life instrument: reference data for users. Qual Life Res 2002;11:173-83.
27. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
28. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness–a systematic review. Physiotherapy 2012;98:277-86.
29. Gremeaux V, Troisgros O, Benaim S, et al. Determining the minimal clinically important difference for the six-minute walk test and the 200-meter fast-walk test during cardiac rehabilitation program in coronary artery disease patients after acute coronary syndrome. Arch Phys Med Rehabil 2011;92:611-9.
30. Twisk JWR. Applied longitudinal data analysis for epidemiology: a practical guide. New York: Cambridge University Press; 2013.
31. Nogueira ID, Servantes DM, Nogueira PA, et al. Correlation between quality of life and functional capacity in cardiac failure. Arq Bras Cardiol 2010;95:238-43.
32. Verrill DE, Barton C, Beasley W, Lippard M, King CN. Six-minute walk performance and quality of life comparisons in North Carolina cardiac rehabilitation programs. Heart Lung 2003;32:41-51.
33. Dickens C, Cherrington A, McGowan L. Depression and health-related quality of life in people with coronary heart disease: a systematic review. Eur J Cardiovasc Nurs 2012;11:265-75.
34. Duenas M, Ramirez C, Arana R, Failde I. Gender differences and determinants of health related quality of life in coronary patients: a follow-up study. BMC Cardiovasc Disord 2011;11:24.
35. Fiorina C, Vizzardi E, Lorusso R, et al. The 6-min walking test early after cardiac surgery. Reference values and the effects of rehabilitation programme. Eur J Cardiothorac Surg 2007;32:724-9.
36. Oldridge NB, Pakosh MT, Thomas RJ. Cardiac rehabilitation in low- and middle-income countries: a review on cost and cost-effectiveness. Int Health 2016;8:77-82.
37. Doll JA, Hellkamp A, Thomas L, et al. Effectiveness of cardiac rehabilitation among older patients after acute myocardial infarction. Am Heart J 2015;170:855-64.
38. Yang X, Li Y, Ren X, et al. Effects of exercise-based cardiac rehabilitation in patients after percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Sci Rep 2017;7:44789.
39. Yohannes AM, Doherty P, Bundy C, Yalfani A. The long-term benefits of cardiac rehabilitation on depression, anxiety, physical activity and quality of life. J Clin Nurs 2010;19:2806-13.
40. Gupta R, Sanderson BK, Bittner V. Outcomes at one-year follow-up of women and men with coronary artery disease discharged from cardiac rehabilitation: what benefits are maintained? J Cardiopulm Rehabil Prev 2007;27:11-8. quiz 9-20.
41. Boesch C, Myers J, Habersaat A, Ilarraza H, Kottman W, Dubach P. Maintenance of exercise capacity and physical activity patterns 2 years after cardiac rehabilitation. J Cardiopulm Rehabil 2005;25:14-21. quiz 2-3.
42. Sunamura M, Ter Hoeve N, Geleijnse ML, et al. Cardiac rehabilitation in patients who underwent primary percutaneous coronary intervention for acute myocardial infarction: determinants of programme participation and completion. Neth Heart J 2017;25:618-28.
43. Mikkelsen T, Korsgaard Thomsen K, Tchijevitch O. Non-attendance and drop-out in cardiac rehabilitation among patients with ischaemic heart disease. Dan Med J 2014;61:A4919.