A secondary analysis of data from the OPTICARE randomized controlled trial investigating the effects of extended cardiac rehabilitation on functional capacity, fatigue, and participation in society

Nienke ter Hoeve\textsuperscript{1,2}, Madoka Sunamura\textsuperscript{1}, Henk J Stam\textsuperscript{2}, Ron T van Domburg\textsuperscript{3} and Rita JG van den Berg-Emons\textsuperscript{2}

Abstract

Objective: In this secondary analysis of data from the OPTICARE trial, we compared the effects of two behavioral interventions integrated into cardiac rehabilitation to standard rehabilitation with regard to functional capacity, fatigue, and participation in society.

Design: This is a randomized controlled trial.

Setting: This study was conducted in a cardiac rehabilitation setting.

Subjects: A total of 740 patients with acute coronary syndrome were recruited for this study.

Interventions: Patients were randomized to (1) three months of standard rehabilitation; (2) cardiac rehabilitation plus nine months after-care with face-to-face group lifestyle counseling; or (3) cardiac rehabilitation plus nine months after-care with individual lifestyle telephone counseling.

Main measures: Functional 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, 12, and 18 months.

Results: Additional face-to-face sessions resulted at 12 months in 12.49 m more on the 6-minute walk test compared to standard rehabilitation ($P = .041$). This difference was no longer present at 18 months. Prevalence of fatigue decreased from 30.2% at baseline to 11.9% at 18 months compared to an improvement from 37.3% to 24.9% after standard rehabilitation (between-group difference: odds ratio = 0.47; $P = .010$). The additional improvements in functional capacity seemed to be mediated by increases in

\textsuperscript{1}Capri Cardiac Rehabilitation, Rotterdam, The Netherlands
\textsuperscript{2}Department of Rehabilitation Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands
\textsuperscript{3}Department of Cardiology, Erasmus University Medical Centre, Rotterdam, The Netherlands

Corresponding author:
Nienke ter Hoeve, Department of Rehabilitation Medicine, Erasmus University Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: n.terhoeve@erasmusmc.nl
daily physical activity. No mediating effects were found for fatigue. No additional improvements were seen for participation in society. Additional telephonic sessions did not result in additional intervention effects.

**Conclusion:** Extending cardiac rehabilitation with a face-to-face behavioral intervention resulted in additional long-term improvements in fatigue and small improvements in functional capacity up to 12 months. A telephonic behavioral intervention provided no additional benefits.

**Keywords**
Participation (WHO ICF), physical fitness, lifestyle change, acute coronary syndrome, behavioral

Received: 19 June 2018; accepted: 14 March 2019

**Introduction**
Cardiac rehabilitation programs focus on the adoption of a healthy lifestyle and optimization of cardiovascular risk factors and are known to decrease the risks of death and re-hospitalization. Other important gauges of cardiac rehabilitation success are improvements in aerobic capacity, fatigue, and participation in society. Aerobic capacity is known to be related to re-hospitalization and mortality, and fatigue and participation in society are known to affect quality of life. To date, cardiac rehabilitation results for these outcomes have been suboptimal in patients with acute coronary syndrome.

In the OPTICARE (OPTimal CArdiac REhabilitation) randomized controlled trial, two novel cardiac rehabilitation interventions based on behavioral techniques (one offered face-to-face in groups and one offered individually by phone) were evaluated in patients with acute coronary syndrome. The primary aim of these interventions was to further improve cardiovascular health and physical activity. Although the novel interventions did not lead to additional improvements in cardiovascular health, additional improvements in physical activity were observed. Because the novel interventions addressed a wide range of health behaviors and psychosocial problems, the interventions may more broadly affect (functional) aerobic capacity, fatigue, and participation in society. Previous studies have shown that behavioral lifestyle interventions can lead to improvements in these outcomes. We hypothesized that, in addition to direct effects of the novel interventions, improvements may also be mediated by improvements in moderate-to-vigorous physical activity (e.g. brisk walking or biking) and sedentary behavior (behaviors requiring very low energy expenditure, mainly sitting or lying during waking hours).

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

**Methods**
This study concerns a secondary analysis of data from the OPTICARE randomized controlled trial. The trial was carried out between November 2011 and August 2014 at Capri Cardiac Rehabilitation in the Netherlands. The study, which has been described in detail previously, was prospectively registered at ClinicalTrials.gov (NCT01395095) and was approved by the Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam, the Netherlands (MEC-2010-391). Patients referred for cardiac rehabilitation were invited to participate. Inclusion criteria were acute coronary syndrome 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 cardiac rehabilitation participation.

Randomization was performed with opaque sealed envelopes, which were prepared and sequentially numbered by an independent statistician who
used a computer random number generator. Patients were randomized (1:1:1) to standard cardiac rehabilitation or to one of the two novel interventions:

1. **Standard cardiac rehabilitation**: Standard cardiac rehabilitation lasted three months. In this period, patients completed two 75-minute exercise sessions per week. In addition, patients could participate 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 three-month cardiac rehabilitation program (initial phase), no after-care was offered.

2. **Cardiac rehabilitation plus face-to-face counseling**: During the initial phase, patients participated in the standard three-month cardiac rehabilitation program plus three 75-minute counseling sessions (at four-week intervals) designed to increase physical activity level. During these sessions, information was also provided about the benefits of frequently interrupting sedentary time. 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. To support the coaching, pedometers (Yamax Digiwalker SW-200; Yamax, Inc., Tokyo, Japan) were used to provide the patients with continuous objective feedback about daily physical activity level.

After the initial three-month cardiac rehabilitation program, a nine-month after-care program was offered. This program consisted of three 2-hour group sessions with four to eight patients at one, three, and nine months after completion of cardiac rehabilitation. Each session comprised 1 hour of exercise and 1 hour of healthy lifestyle counseling. The counseling sessions focused on permanent adoption of a healthy lifestyle (i.e. healthy diet and optimal physical activity), but also on psychosocial problems. During these sessions, patients were coached alternatingly by a physical therapist, dietician, and social worker.

3. **Cardiac rehabilitation plus telephonic counseling**: This intervention was based on the existing Coaching Patients on Achieving Cardiovascular Health (COACH) program. During the initial phase, patients participated only in standard cardiac rehabilitation. After the initial phase, patients participated in a nine-month individual after-care program comprised of five to six telephone coaching sessions at five- to six-week intervals. During the coaching sessions, patients were encouraged to self-monitor their coronary risk factors (e.g. weight, blood pressure, or cholesterol) and make an action plan. In addition, patients developed a personal plan for permanent adoption of a heart-healthy lifestyle (i.e. healthy diet and sufficient physical activity). Progress was discussed during each session.

Patients in all three groups attended usual follow-up appointments with their cardiologist.

In all patients, functional capacity, fatigue, participation in society, physical activity, and sedentary behavior were measured at four occasions: at randomization; at completion of standard cardiac rehabilitation (3 months after randomization); at completion of after-care (12 months after randomization); and 6 months after completion of after-care (18 months after randomization). Measurements were performed by trained research assistants. Both patient and testers were not blinded to group allocation:

- Functional capacity was measured with a 6-minute walk test, performed according to the American Thoracic Society guidelines. Patients were asked to walk back and forth along a 30-m 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 6-minute walk test has
found to be a valid and reliable outcome measure and is responsive to relevant clinical changes during cardiac rehabilitation.23

- Fatigue was measured using the nine-item Fatigue Severity Scale. The Fatigue Severity Scale is widely used and validated in healthy subjects and patients with sleeping disorders, multiple sclerosis, and stroke.24–26 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 Fatigue Severity Scale score.11,26,27 Being fatigued was defined as a score of one standard deviation above the mean score for healthy persons (score higher than 4) and being severely fatigued as a score of two standard deviations above the mean score for healthy persons (score higher than 5.2).26

- Participation in society was assessed using the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P), a 32-item questionnaire concerning participation in domestic activities (e.g. housekeeping), occupational activities (e.g. paid and voluntary work), and recreational activities (e.g. going out and leisure activities). The questionnaire addresses three subdomains of participation: frequency, perceived restrictions, and satisfaction. For each subdomain, a separate score from 0 to 100 was calculated, with higher scores indicating better participation. The questionnaire has been validated for cardiac patients.28

- 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 eight consecutive days, except while sleeping and during bathing. 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 four valid days. The ActiGraph converts accelerations on three axes into activity counts. Using ActiLife software, counts were summed over a sampling interval (epoch) of 15 seconds. Using MATLAB version R2011 (MathWorks, Natick, MA, USA), a vector magnitude of counts on the three axes ($\sqrt{x^2 + y^2 + z^2}$) was calculated and time in moderate-to-vigorous-intensity physical activity ($\geq 672.5$ counts per 15 seconds)$^{29}$ and sedentary time ($\leq 37.5$ counts per 15 seconds)$^{30}$ were determined. Steps per day were also captured by the accelerometer. To correct for differences in accelerometer wear time between patients, moderate-to-vigorous-intensity physical activity time and sedentary time were expressed as percentages of wear time and the number of steps as mean steps per minute of wear time.

Patients were only included in the data analysis if at least one measurement after baseline was available. We compared baseline differences between patients included and excluded from analysis and baseline differences between patients randomized to standard cardiac rehabilitation or one of the novel interventions using Student’s $t$-tests and chi-square 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 with exchangeable correlation structures were performed to determine intervention effects of the two novel interventions compared to standard cardiac rehabilitation on functional capacity, fatigue, and participation in society. First, separate overall models were created for each outcome (functional 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 $\times$ time. By changing the order of the time variable, between-group differences (intervention effects) could be calculated for improvement between baseline and 3 months, improvement between baseline and 12 months, and improvement between baseline and 18 months.
In all models, standard cardiac rehabilitation served as a reference group, and age and sex were added as confounders. The regression coefficient B represented between-group differences (intervention effects) 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. Missing baseline data were balanced between groups. Because generalized estimating equation models correct for missing data, other time-points (end-points) did not require data imputation.

The generalized estimating equations were performed using the original dataset and all five data-sets containing imputed baseline values. Pooled results are reported. We considered a $P$-value smaller than .05 to be statistically significant. Only in case both novel interventions would result in significant intervention effects as compared to standard cardiac rehabilitation, a post hoc comparison between the two novel interventions would be performed with adjustment for multiple testing.

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. Missing baseline data were balanced between groups. Because generalized estimating equation models correct for missing data, other time-points (end-points) did not require data imputation.31

The generalized estimating equations were performed using the original dataset and all five data-sets containing imputed baseline values. Pooled results are reported. We considered a $P$-value smaller than .05 to be statistically significant. Only in case both novel interventions would result in significant intervention effects as compared to standard cardiac rehabilitation, a post hoc comparison between the two novel interventions would be performed with adjustment for multiple testing. SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for all analyses.

In case significant intervention effects were found for any of the novel interventions compared to standard cardiac rehabilitation, additional analyses were performed to explore the mediating effects of moderate-to-vigorous-intensity physical activity 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.

Results

In total, 914 patients with acute coronary syndrome were enrolled, of whom 141 patients quit cardiac rehabilitation 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 1). The excluded patients were, on average, two years younger ($P = .017$), more likely to have a history of smoking ($P < .001$), and less likely to use statins ($P < .001$). The remaining 740 patients (mean age (SD) = 57.2 (9.1) years, 600 (81.1%) male) were included in the analysis (Table 1). The three groups were balanced with respect to baseline characteristics (see Table 1). 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.

Regarding functional capacity, significant intervention effects were found between baseline and 12 months for cardiac rehabilitation plus face-to-face counseling (Tables 2, 3 and Supplemental Figure S1). On average, participants in the cardiac rehabilitation plus face-to-face counseling group improved 12.49 m more on the 6-minute walk test between baseline and 12 months than patients in the standard cardiac rehabilitation group ($P = .041$; outcomes corrected for age and sex). This difference was no longer present at 18 months. No intervention effects were found for cardiac rehabilitation plus telephonic counseling (Table 3). Exploratory analysis revealed that the intervention effects for cardiac rehabilitation plus face-to-face counseling were mediated by moderate-to-vigorous-intensity physical activity time (15.8%), sedentary time (5.3%), and daily step count (36.9%).

Regarding fatigue, patients randomized to cardiac rehabilitation plus face-to-face counseling had a greater improvement in Fatigue Severity Scale scores between baseline and 18 months compared to patients randomized to standard cardiac rehabilitation ($P = .053$, outcomes corrected for age and sex) (See Table 2 and Table 3). Furthermore, prevalence of fatigue and severe fatigue decreased more between baseline and 18 months in the cardiac rehabilitation plus face-to-face counseling group compared to the standard cardiac rehabilitation group ($P = .010$; $P = .038$, outcomes corrected for age and sex) (Table 3). No intervention effects were found for cardiac rehabilitation plus telephonic counseling (Table 3; Supplemental Figure S1). Exploratory mediation analysis revealed...
that physical activity and sedentary behavior did not explain the intervention effects observed for fatigue. No intervention effects were found on any subdomain of participation in society for either novel intervention (Table 3).

**Discussion**

Extending cardiac rehabilitation with a face-to-face behavioral group intervention focused on permanent healthy lifestyle adoption resulted in small additional improvements in functional capacity up to 12 months and more substantial improvements...
Table 1. Participant baseline characteristics ($n = 740$).

| Characteristics | CR+F ($n = 251$) | CR+T ($n = 245$) | CR-only ($n = 244$) | Between-group differences |
|-----------------|-----------------|-----------------|-------------------|------------------------|
| Male, n (%)     | 202 (80.5)      | 202 (82.4)      | 196 (80.3)        | 0.799                  |
| Age, mean (SD), years | 57.5 (8.8)      | 56.7 (9.2)      | 57.5 (9.2)        | 0.533                  |
| Partnered, n (%)$^a$ | 169 (80.5)      | 168 (84.0)      | 171 (83.4)        | 0.599                  |
| Employed, n (%)$^b$ | 123 (64.7)      | 112 (60.5)      | 107 (56.0)        | 0.220                  |
| Therapeutic intervention index event, n (%) | | | | 0.711 |
| No revascularization | 17 (6.8) | 24 (9.8) | 18 (7.4) | |
| Percutaneous coronary intervention | 201 (80.1) | 180 (73.5) | 193 (79.1) | |
| Coronary artery bypass graft | 33 (13.1) | 41 (16.7) | 33 (13.5) | |
| Cardiac history, n (%) | | | | |
| Myocardial infarction | 20 (8) | 21 (8.6) | 20 (8.2) | 0.970 |
| Angina pectoris | 12 (4.8) | 14 (5.7) | 14 (5.7) | 0.865 |
| Percutaneous coronary intervention | 23 (9.2) | 23 (9.4) | 25 (10.2) | 0.912 |
| Coronary artery bypass graft | 3 (1.2) | 1 (0.4) | 5 (2.0) | 0.254 |
| Stroke/transient ischemic attack | 10 (4.0) | 3 (1.2) | 5 (2.0) | 0.122 |
| Medication, n (%) | | | | |
| Acetylsalicylic acid | 240 (95.6) | 240 (98.0) | 237 (97.1) | 0.312 |
| Oral anticoagulant | 13 (5.2) | 17 (6.9) | 11 (4.5) | 0.478 |
| Thienopyridine | 211 (84.1) | 196 (80.0) | 210 (86.1) | 0.185 |
| Cholesterol lowering medication | 240 (95.6) | 236 (96.3) | 237 (97.1) | 0.668 |
| Beta-blocker | 208 (82.9) | 200 (81.6) | 200 (82.0) | 0.933 |
| ACE inhibitor | 181 (72.1) | 171 (69.8) | 169 (69.3) | 0.761 |
| Angiotensin II receptor blocker | 32 (12.7) | 31 (12.7) | 33 (13.5) | 0.952 |
| Calcium blocker | 34 (13.5) | 37 (15.1) | 36 (14.8) | 0.874 |
| Nitrate | 104 (41.4) | 76 (31.0) | 86 (35.2) | 0.052 |
| Diuretic | 27 (10.8) | 27 (11.0) | 24 (9.8) | 0.905 |
| Psychotropic | 11 (4.4) | 15 (6.1) | 16 (6.6) | 0.541 |
| Risk factors, n (%) | | | | |
| Diabetes | 34 (13.5) | 24 (9.8) | 35 (14.3) | 0.268 |
| Dyslipidemia | 70 (27.9) | 87 (35.5) | 101 (41.4) | 0.007 |
| Family history | 134 (53.4) | 128 (52.2) | 136 (55.7) | 0.732 |
| Smoking history | 109 (43.4) | 95 (38.8) | 89 (36.5) | 0.272 |
| Hypertension | 109 (43.4) | 96 (39.2) | 98 (40.2) | 0.602 |
| Overweight | 194 (77.3) | 186 (75.9) | 187 (76.6) | 0.906 |
| Cardiac rehabilitation compliance | | | | |
| Number of training sessions, mean (SD) | 23.5 (6.4) | 22.9 (5.2) | 23.0 (5.6) | 0.475 |
| Educational sessions, n (%)$^c$ | 199 (79.2) | 185 (75.5) | 184 (75.4) | 0.844 |
| Counseling sessions, n (%)$^c$ | 88 (35.0) | 82 (33.5) | 72 (28.7) | 0.539 |
| Additional face-to-face sessions, n (%)$^c$ | 243 (96.8) | – | – | |
| Additional telephonic sessions, n (%)$^c$ | – | 196 (80.0) | – | |

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

$^a$Data missing for $n = 41$ (CR+F), $n = 45$ (CR+T), and $n = 39$ (CR-only).

$^b$Data missing for $n = 61$ (CR+F), $n = 60$ (CR+T), and $n = 53$ (CR-only).

$^c$Number of patients participating in at least one session.
Table 2. Observed data for functional capacity, fatigue, and participation in society for all three groups.

|                      | CR + F               | CR + T               | CR-only              |
|----------------------|----------------------|----------------------|----------------------|
|                      | Baseline 3 months 12 months 18 months | Baseline 3 months 12 months 18 months | Baseline 3 months 12 months 18 months |
| **Functional capacity, mean ± SD** |                      |                      |                      |
| 6MWT, m              | 564 ± 82 608 ± 84 611 ± 87 600 ± 85 | 567 ± 76 601 ± 89 590 ± 75 597 ± 79 | 557 ± 80 598 ± 82 594 ± 76 596 ± 82 |
| **Fatigue, mean ± SD** |                      |                      |                      |
| FSS score            | 3.29 ± 1.48 2.81 ± 1.30 2.62 ± 1.22 2.56 ± 1.18 | 3.32 ± 1.52 2.91 ± 1.38 2.82 ± 1.45 2.74 ± 1.33 | 3.33 ± 1.38 3.00 ± 1.37 2.78 ± 1.38 2.87 ± 1.46 |
| **Fatigue, prevalence (%)** |                      |                      |                      |
| Fatigue (FSS > 4.0)  | 15.9 10.3 8.9 7.7 | 17.9 18.2 13.5 13.3 | 24.9 15.5 13.2 14.1 |
| Severe fatigue (FSS > 4.0) | 13.8 5.6 4.5 4.2 | 15.1 7.0 7.7 6.0 | 9.7 7.5 7.5 10.2 |
| **Participation in society, mean ± SD** |                      |                      |                      |
| Frequency score      | 38.6 ± 11.1 37.2 ± 10.9 36.8 ± 9.6 36.5 ± 11.1 | 35.9 ± 10.6 37.3 ± 10.6 35.9 ± 11.9 36.2 ± 10.6 | 37.9 ± 10.7 36.7 ± 10.6 36.6 ± 10.4 36.2 ± 10.4 |
| Restriction score    | 90.9 (22:100) 100 (37:100) 100 (71:100) 100 (52:100) | 89.4 ± 6.100 100 (29:100) 100 (41:100) 90.0 (10:100) | 90.0 (10:100) 100 (56:100) 100 (0:100) 100 (7:100) |
| Satisfaction score   | 68.0 ± 15.6 73.8 ± 15.8 74.3 ± 14.2 74.5 ± 15.6 | 68.6 ± 14.8 74.5 ± 15.1 73.6 ± 15.8 76.3 ± 13.6 | 69.7 ± 15.9 73.4 ± 15.8 75.1 ± 16.0 73.8 ± 16.4 |

CR + F, cardiac rehabilitation plus face-to-face group counseling; CR + T, cardiac rehabilitation plus individual telephonic counseling; CR-only, standard cardiac rehabilitation; 6MWT, 6-minute walk test; FSS, Fatigue Severity Scale.

*Scores violated normality assumption, therefore median (range) values are displayed.
Table 3. Generalized estimating equation results for intervention effects over all time-points, between baseline and 3 months, between baseline and 12 months, and between baseline and 18 months.

|                               | CR+F vs. CR-only | CR+T vs. CR-only |          |          |
|-------------------------------|------------------|------------------|----------|----------|
|                               | B\textsuperscript{b} | CI               | P-value  | B\textsuperscript{b} | CI               | P-value  |
| **Functional capacity \((n = 674)\)** |                  |                  |          |          |
| 6MWT, m                       |                  |                  |          |          |
| Overall                       | 6.83             | -3.45, 17.12     | .192     | 3.82     | -14.39, 6.74    | .477     |
| \(\Delta T0–3\text{ months}\) | 6.84             | -5.75, 19.43     | .287     | -0.14    | -13.77, 13.48   | .984     |
| \(\Delta T0–12\text{ months}\) | **12.49**        | **0.53, 24.46**  | **.041** | -9.20    | -20.89, 2.48    | .122     |
| \(\Delta T0–18\text{ months}\) | 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     |
| \(\Delta T0–3\text{ months}\) | -0.13            | -0.35, 0.09      | .235     | -0.04    | -0.26, 0.18     | .708     |
| \(\Delta T0–12\text{ months}\) | -0.13            | -0.37, 0.11      | .296     | -0.02    | -0.28, 0.23     | .872     |
| \(\Delta T0–18\text{ months}\) | -0.24            | -0.49, 0.03      | .053     | -0.09    | -0.34, 0.15     | .453     |
| **Prevalence of fatigue**     |                  |                  |          |          |
| \(FSS > 4.0\)                |                  |                  |          |          |
| Overall                       | **0.62\textsuperscript{c}** | **0.41, 0.94** | **.024** | 0.95\textsuperscript{c} | 0.63, 1.45 | **.832** |
| \(\Delta T0–3\text{ months}\) | 0.75\textsuperscript{c} | 0.45, 1.23       | .260     | 1.07\textsuperscript{c} | 0.65, 1.77 | .778     |
| \(\Delta T0–12\text{ months}\) | 0.63\textsuperscript{c} | 0.35, 1.13       | .119     | 1.01\textsuperscript{c} | 0.57, 1.79 | .969     |
| \(\Delta T0–18\text{ months}\) | **0.47\textsuperscript{c}** | **0.26, 0.84** | **.010** | 0.76\textsuperscript{c} | 0.43, 1.35 | .356     |
| **Prevalence of severe fatigue \((FSS > 5.2)\)** | | | | | | |
| Overall                       | 0.55\textsuperscript{c} | 0.30, 1.01       | .056     | 0.70\textsuperscript{c} | 0.38, 1.28 | .250     |
| \(\Delta T0–3\text{ months}\) | 0.72\textsuperscript{c} | 0.31, 1.63       | .428     | 0.83\textsuperscript{c} | 0.37, 1.84 | .644     |
| \(\Delta T0–12\text{ months}\) | 0.57\textsuperscript{c} | 0.24, 1.35       | .199     | 0.80\textsuperscript{c} | 0.34, 1.92 | .623     |
| \(\Delta T0–18\text{ months}\) | **0.39\textsuperscript{c}** | **0.17, 0.95** | **.038** | 0.53\textsuperscript{c} | 0.24, 1.17 | .117     |
| **Participation in society \((n = 671)\)** | | | | | | |
| Frequency score               |                  |                  |          |          |
| Overall                       | -0.46            | -1.92, 1.01      | .540     | 0.73     | -0.71, 2.16     | .320     |
| \(\Delta T0–3\text{ months}\) | -0.18            | -1.96, 1.60      | .842     | 0.98     | -0.79, 2.74     | .277     |
| \(\Delta T0–12\text{ months}\) | -1.06            | -2.92, 0.80      | .263     | -0.03    | -2.15, 2.08     | .977     |
| \(\Delta T0–18\text{ months}\) | -0.30            | -2.26, 1.65      | .760     | 1.10     | -0.77, 2.98     | .248     |
| Restrictions score\textsuperscript{d} |                  |                  |          |          |
| Overall                       | 1.03\textsuperscript{c} | 0.73, 1.46       | .858     | 0.93\textsuperscript{c} | 0.66, 1.32 | .698     |
| \(\Delta T0–3\text{ months}\) | 1.03\textsuperscript{c} | 0.68, 1.55       | .903     | 1.09\textsuperscript{c} | 0.70, 1.67 | .698     |
| \(\Delta T0–12\text{ months}\) | 0.95\textsuperscript{c} | 0.60, 1.51       | .824     | 0.82\textsuperscript{c} | 0.51, 1.30 | .386     |
| \(\Delta T0–18\text{ months}\) | 1.07\textsuperscript{c} | 0.67, 1.70       | .777     | 0.86\textsuperscript{c} | 0.54, 1.36 | .524     |
| Satisfaction score            |                  |                  |          |          |
| Overall                       | 0.32             | -1.93, 2.57      | .778     | 1.08     | -1.24, 3.39     | .361     |
| \(\Delta T0–3\text{ months}\) | 0.67             | -1.96, 3.31      | .618     | 1.50     | -1.13, 4.12     | .264     |
| \(\Delta T0–12\text{ months}\) | -0.76            | -3.59, 2.06      | .596     | -0.72    | -3.68, 2.24     | .632     |
| \(\Delta T0–18\text{ months}\) | 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+T, cardiac rehabilitation plus individual telephonic counseling; CR-only, standard cardiac rehabilitation; FSS, Fatigue Severity Scale; \(n\) = number of patients who had at least one outcome post-baseline on the specified outcome and were included in the analysis.
Significance is P<0.05.

\textsuperscript{a}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.

\textsuperscript{b}B, regression coefficient, represents the between-group difference and the intervention effect relative to CR-only over all time-points or at the specified time-point.

\textsuperscript{c}Odds ratios are shown for dichotomous variables to indicate the odds (relative risk) relative to CR-only at the specified time-point.

\textsuperscript{d}Scores violated normality assumption, dichotomized scores used for analysis.
in prevalence of fatigue up to at least 18 months. The additional improvements in functional capacity seemed to be mediated by improvements in physical activity. Extending cardiac rehabilitation with a telephonic behavioral program did not lead to additional improvements in functional capacity or fatigue. Furthermore, neither the telephonic nor the face-to-face intervention further improved participation in society compared to standard cardiac rehabilitation only.

A previous study indicated that the minimal clinically important difference for the 6-minute walk test for patients after an acute coronary syndrome is 25 m. All three groups in our trial showed improvements far above the 25 m during the initial three-month cardiac rehabilitation period (see Table 2). These improvements remained above 25 m at long-term follow-up. A small additional improvement of 12.5 m was seen at the 12-month follow-up for patients participating in additional face-to-face sessions. Because the additional telephonic sessions did not result in additional improvements in functional capacity, we hypothesize that the stronger focus on physical activity during the face-to-face intervention could be an important element to improve functional capacity. Indeed, an exploratory analysis showed that the found intervention effects were mediated by improvements in both moderate-to-vigorous-intensity physical activity time and daily step count. The additional improvement in functional capacity was not maintained at long-term follow-up. Since relevant and long-lasting improvements were already seen after standard cardiac rehabilitation, we conclude that most patients do not seem to need additional programs regarding functional capacity.

To our knowledge, this is the first study to assess the secondary effects of a lifestyle intervention integrated into cardiac rehabilitation on fatigue. In addition to improving functional capacity, the additional face-to-face sessions improved perceived fatigue (including severe fatigue). Patients reached fatigue levels even lower than those reported for healthy persons (11.9% vs. 18%). In contrast, those randomized to standard cardiac rehabilitation continued to have a high prevalence of fatigue (24.9%). With regard to prevalence of severe fatigue, the prevalence among those randomized to cardiac rehabilitation with additional face-to-face sessions (4.2%) approached that of healthy persons (3.5%) by study end. As with previous results, the prevalence of severe fatigue in our study remained high following standard cardiac rehabilitation only (10.2%). The improvements in fatigue are clinically important, as fatigue is known to influence quality of life. 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 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 functional capacity seen after the additional face-to-face sessions lowered the physical strain associated with activities of daily life, which consequently decreased feelings of fatigue. In addition, the face-to-face coaching method (as opposed to individual telephone coaching) may have contributed.

Adding behavioral interventions to standard cardiac rehabilitation (using face-to-face group or individual telephonic coaching) did not affect participation in society. In a previous study, it was found that a lifestyle intervention with a focus on improving physical activity also resulted in improvements in participation in society. However, in this patient group with spinal cord injury, baseline levels for participation in society are lower, leaving more room for improvements. This could probably explain the discrepancy with our results. As participation in society is associated with quality of life, future research should focus on finding effective interventions to improve participation in society. We hypothesize that a more individualized approach, focusing on areas in which participation problems are experienced, may be needed.

Some study limitations deserve discussion. First, patients who were lost to follow-up and excluded from analyses were, on average, younger and more likely to smoke. Cardiac rehabilitation drop-out rates tend to be higher among younger patients and
those with more risk factors. Therefore, our results are probably most valid among the more adherent patients. Second, the 6-minute walk test was found to be a valid and reliable test and responsive to clinically meaningful changes in a cardiac rehabilitation population. Nevertheless, a ceiling effect might occur in patients with a higher functional capacity at start of rehabilitation. Third, the power analysis for this randomized controlled trial was performed using the primary outcome SCORE (Systematic COronary Risk Evaluation) risk function. The study was not designed and powered for the outcomes analyzed in this article. Therefore, our results should be considered as exploratory, we cannot rule out that our findings are partly due to coincidence. Nonetheless, post hoc power analysis revealed that we were powered for all three outcomes to detect a between-group difference of at least 10%. Finally, we did not perform official mediation analyses. However, our exploratory analyses do offer insight into possible mediators of findings.

Clinical messages

- Extending cardiac rehabilitation with face-to-face behavioral sessions resulted in long-term additional improvements in fatigue.
- The face-to-face intervention resulted in small additional improvements in functional capacity up to 12 months.
- Benefits in functional capacity seemed to be mediated by physical activity.
- Extending cardiac rehabilitation with a telephone program provided no benefits.

Acknowledgements

The authors thank the participants, Capri Cardiac Rehabilitation staff who collected data and served as coaches for the face-to-face counseling and the nurses from Zilveren Kruis Achmea who served as coaches for the telephonic counseling. They thank Myrna van Geffen, Verena van Marrewijk, and Saskia Versluis for recruiting patients, organizing the challenging study logistics, and collecting data. They also thank the medical students from Erasmus MC who assisted with data collection.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This investigator-initiated study was co-financed by Capri Cardiac Rehabilitation Rotterdam (The Netherlands), who financed the face-to-face counseling intervention, and the Zilveren Kruis healthcare insurance company (The Netherlands), who financed the telephonic counseling intervention.

Supplemental material

Supplemental material for this article is available online.

ORCID iD

Nienke ter Hoeve https://orcid.org/0000-0002-7447-3025

References

1. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016; 67(1): 1–12.
2. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2007; 115(20): 2675–2682.
3. De Vries H, Kemps HM, van Engen-Verheul MM, et al. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. Eur Heart J 2015; 36(24): 1519–1528.
4. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. Eur J Cardiovasc Prev Rehabil 2010; 17(1): 1–17.
5. Revalidatiecommissie NVVC/NHS en projectgroep PAAHR. Multidisciplinaire Richtlijn Hartrevalidatie 2011 [Multidisciplinary guidelines cardiac rehabilitation]. Utrecht: Nederlandse Vereniging voor Cardiologie, 2011.
6. Beatty AL, Schiller NB and Whooley MA. Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the heart and soul study. Arch Intern Med 2012; 172(14): 1096–1102.
7. Taylor C, Tsakirides C, Moxon J, et al. Submaximal fitness and mortality risk reduction in coronary heart disease: a retrospective cohort study of community-based exercise rehabilitation. *BMJ* Open 2016; 6(6): e011125.

8. Ter Hoeve N, van Geffen ME, Post MW, et al. Participation in society in patients with coronary artery disease before and after cardiac rehabilitation. *Arch Phys Med Rehabil* 2015; 96(6): 1110–1116.

9. Brink E, Grankvist G, Karlsson BW, et al. Health-related quality of life in women and men one year after acute myocardial infarction. *Qual Life Res* 2005; 14(3): 749–757.

10. Moholdt T, Aamot IL, Granoien I, et al. Long-term follow-up after cardiac rehabilitation: a randomized study of usual care exercise training versus aerobic interval training after myocardial infarction. *Int J Cardiol* 2011; 152(3): 388–390.

11. Van Geffen ME, Ter Hoeve N, Sunamura M, et al. Fatigue during and after cardiac rehabilitation. *J Rehabil Med* 2015; 47(6): 569–574.

12. Sunamura M, Ter Hoeve N, van den Berg-Emons RJ, 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(7–8): 324–330.

13. Sunamura M, Ter Hoeve N, van den Berg-Emons RJG, et al. Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes. *Heart* 2018; 104(5): 430–437.

14. Ter Hoeve N, Sunamura M, Stam HJ, et al. Effects of two behavioral cardiac rehabilitation interventions on physical activity: a randomized controlled trial. *Int J Cardiol* 2018; 255: 221–228.

15. Slaman J, Roebroeck M, van der Slot W, et al. Can a lifestyle intervention improve physical fitness in adolescents and young adults with spastic cerebral palsy? A randomised controlled trial. *Arch Phys Med Rehabil* 2014; 95(9): 1646–1655.

16. Rogers LQ, Courneya KS, Anton PM, et al. Effects of a multicomponent physical activity behavior change intervention on fatigue, anxiety, and depressive symptomatology in breast cancer survivors: randomized trial. *Psychooncology* 2017; 26(11): 1901–1906.

17. Nooijen CF, Stam HJ, Sluis T, et al. A behavioral intervention promoting physical activity in people with subacute spinal cord injury: secondary effects on health, social participation and quality of life. *Clin Rehabil* 2017; 31(6): 772–780.

18. Kulinski JP, Khera A, Ayers CR, et al. Association between cardiorespiratory fitness and accelerometer-derived physical activity and sedentary time in the general population. *Mayo Clin Proc* 2014; 89(8): 1063–1071.

19. Prince SA, Saunders TJ, Gresty K, et al. A comparison of the effectiveness of physical activity and sedentary behaviour interventions in reducing sedentary time in adults: a systematic review and meta-analysis of controlled trials. *Obes Rev* 2014; 15(11): 905–919.

20. Puetz TW. Physical activity and feelings of energy and fatigue: epidemiological evidence. *Sports Med* 2006; 36(9): 767–780.

21. Vale MJ, Jelinek MV, Best JD, et al. Coaching patients on achieving cardiovascular health (COACH): a multicenter randomized trial in patients with coronary heart disease. *Arch Intern Med* 2003; 163(22): 2775–2783.

22. 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: 111–117.

23. Bellet RN, Adams L and Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness—a systematic review. *Physiotherapy* 2012; 98(4): 277–286.

24. Nadarajah M, Mazlan M, Abdul-Latif L, et al. Test-retest reliability, internal consistency and concurrent validity of Fatigue Severity Scale in measuring post-stroke fatigue. *Eur J Phys Rehabil Med* 2017; 53(5): 703–709.

25. Learmonth YC, Dlugonski D, Pilutti LA, et al. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci* 2013; 331(1–2): 102–107.

26. Valko PO, Bassetti CL, Bloch KE, et al. Validation of the fatigue severity scale in a Swiss cohort. *Sleep* 2008; 31(11): 1601–1607.

27. Merkies IS, Schmitz PI, Samijn JP, et al. Fatigue in immune-mediated polyneuropathies. *Neurology* 1999; 53(8): 1648–1654.

28. Post MWM, van der Zee CH, Hennink J, et al. Validity of the Utrecht Scale for Evaluation of Rehabilitation-participation. *Disabil Rehabil* 2012; 34(6): 478–485.

29. Sasaki JE, John D and Freedson PS. Validation and comparison of ActiGraph activity monitors. *J Sci Med Sport* 2012; 2012: 460271.

30. Carr LJ and Mahar MT. Accuracy of intensity and inclinometer output of three activity monitors for identification of sedentary behavior and light-intensity activity. *J Obes* 2012; 2012: 460271.

31. Twisk J and de Vente W. Attrition in longitudinal studies. How to deal with missing data. *J Clin Epidemiol* 2002; 55(4): 329–337.

32. Tchijevitch O. 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(4): 611–619.

33. Groenewegen P, Korsgaard Thomsen K and Tchijevitch O. Non-attendance and drop-out in cardiac rehabilitation among patients with ischaemic heart disease. *Dan Med J* 2014; 61(10): A4919.

34. 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(11): 618–628.