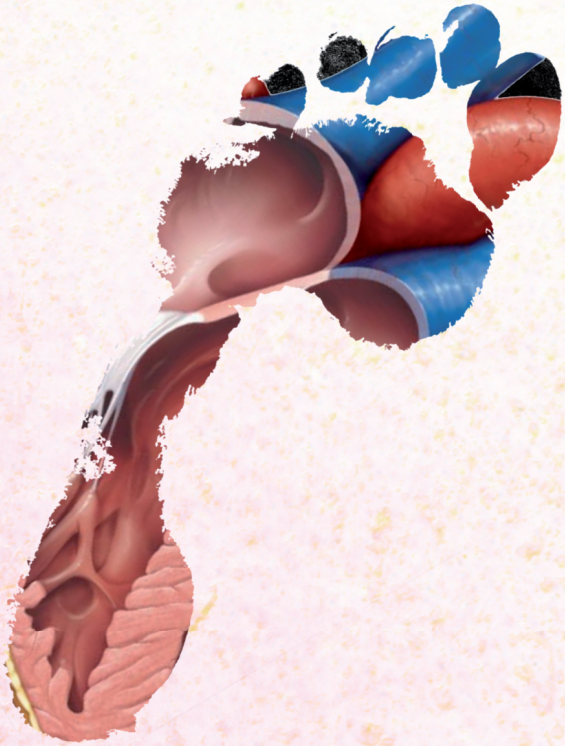
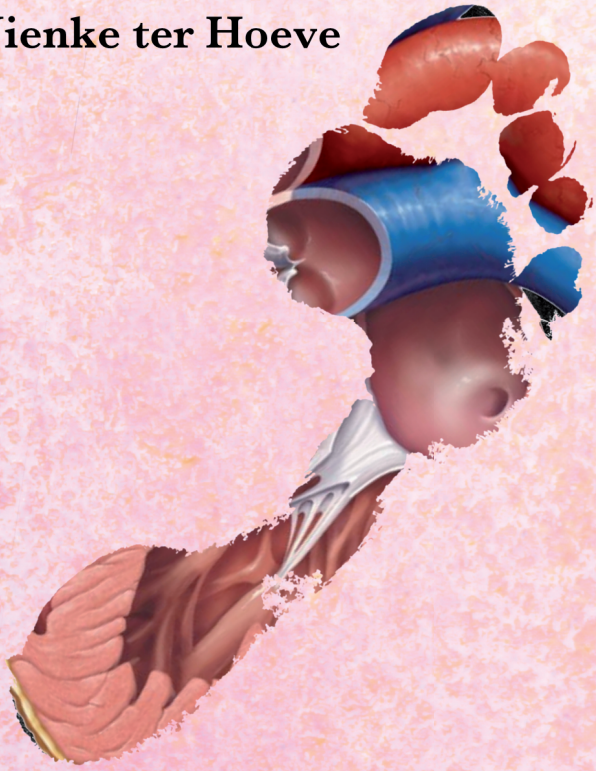


Optimizing Cardiac Rehabilitation

Nienke ter Hoeve



Optimizing Cardiac Rehabilitation

Nienke ter Hoeve

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Optimizing Cardiac Rehabilitation

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Dinsdag 29 mei 2018 om 15.30 uur

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Nienke ter Hoeve
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Erasmus University Rotterdam

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Overige leden:	Prof. dr. ir. H. Boersma Prof. dr. J.J. van Busschbach Prof. dr. W.J.M. Scholte op Reimer
Copromotoren:	Dr. H.J.G. van den Berg-Emons Dr. R.T. van Domburg

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CONTENTS

Chapter 1

General introduction

The focus of this thesis is on physical activity in patients participating in cardiac rehabilitation (CR) following coronary heart disease (CHD). Both the effects of standard CR and CR extended with behavioural interventions is investigated. Secondary outcomes include sedentary behaviour, fatigue and participation in society. This chapter gives background information on the patient population, on CR, and on the primary and secondary outcomes. Additionally, the theoretical background of the investigated behavioural interventions is described. The chapter concludes with the aims and outline of this thesis.

CORONARY HEART DISEASE

CHD is the most common type of cardiovascular disease and is caused by the growth of plaque inside the coronary arteries (atherosclerosis), resulting in a reduced flow of oxygen-rich blood.[1] Acute coronary syndrome (ACS) is a subcategory of CHD and includes myocardial infarction and unstable angina pectoris. The most common treatment of patients with CHD is the prescription of cardio-protective medication (such as aspirin and statins) or invasive treatment such as a percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).[1] During a PCI, catheterization is used to open the blocked artery, often combined with the placement of a stent. During CABG, a bypass is created to circumvent the blocked coronary arteries. The average length of hospitalization after a myocardial infarction is currently circa 5 days.[2,3]

In 2015, over 700.000 people with CHD were living in the Netherlands, a country with circa 17 million inhabitants. The incidence of new cases was over 70.000 patients with myocardial infarction and almost 40.000 patients with angina pectoris.[1,4] Improvements in medical treatment have increased survival rates.[1,3,4] However, in the Netherlands still 9000 people died caused by CHD in 2015[1,4] and cardiovascular diseases remain the number one cause of death in Europe, accounting for 45% of deaths.[3] With a yearly cost of 2.1 milliard euros in the Netherlands, the economic impact of CHD is high.[1]

CARDIAC REHABILITATION

In the first year after CHD, the risk of suffering a recurrent cardiovascular event is 20%.[5,6] Risk factors for the development of (recurrent) cardiovascular problems include high cholesterol, hypertension, diabetes, obesity and unhealthy lifestyle habits such as smoking, unhealthy diet and no regular physical activity.[7] Adherence to a healthy lifestyle is estimated to result in a 20 to 35% mortality risk reduction in patients with CHD, which

is comparable to the effects of cardio-protective drugs.[8] Despite the ample evidence of the benefits of a healthy lifestyle, results of the EUROASPIRE study still show a high prevalence of unhealthy lifestyles and suboptimal control of risk factors among a large group of European patients with CHD.[9,10]

CR has been recognized as essential for secondary prevention in patients after CHD.[11-13] CR has evolved from exercise-only programs to more comprehensive programs including psychological and educational interventions. Currently, CR in the Netherlands lasts 6-12 weeks and, in line with both the European and American guidelines, focuses on the adoption of a healthy lifestyle and the optimization of aerobic capacity, cardiovascular risk factors and psychosocial status.[11-13] The programs are led by a multidisciplinary team consisting of physical therapists, cardiologists, rehabilitation physicians, social workers, psychologists, psychiatrists, and dieticians.[13] Meta-analyses and systematic reviews have shown substantial benefits of CR on risk factors such as lipid profile, blood pressure and smoking rate, but also on quality of life, aerobic capacity, mortality, and hospital readmissions.[14-17] Economic evaluations also indicated that CR is a cost-effective intervention.[16,18] Notwithstanding these benefits, long-term maintenance of results seems less optimal. After completion of CR a deterioration of benefits is often reported.[19-21] The standard 3-month CR period is possibly insufficient to incorporate lifestyle changes into daily life.

PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR

Physical activity can be defined as bodily movements produced by skeletal muscles that increase energy expenditure.[22] In patients with CHD, regular physical activity is associated with a substantially lower risk of recurrent cardiovascular events and a 25% mortality risk reduction.[8,23] In addition, physical activity positively influences blood pressure, lipid profile, body mass index and diabetes.[24,25] Despite the extensive benefits of having an active lifestyle, only 40% of European patients with CHD report regular physical activity.[10] Since physical activity is an important tool for large-scale cardiovascular disease prevention with effects comparable to cardio-protective medication, promoting physical activity should be given high priority.[8,26] Although Dutch, European and American guidelines recommend implementing physical activity counselling into CR[11-13], structural counselling programs are often lacking and only general advice on the benefits of physical activity is given. A clear overview of the literature with regard to the effects of current standard CR on physical activity is lacking, but it has been suggested that current CR is insufficient for changes in physical activity and more structural counselling programs using behavioural techniques might be needed.[27,28]

Physical activity and sedentary behaviour are different concepts, but often confused with one another.[29] Sedentary behaviour can be defined as a behaviour (during waking hours) that requires very low energy expenditure, mainly sitting or lying.[29] Someone can have an active lifestyle (e.g. frequently exercising during leisure time) and simultaneously have a sedentary lifestyle (e.g. accumulating long sedentary periods at work). Recent studies in general populations have shown that sedentary behaviour is, independent of physical activity, related to health outcomes such as diabetes, cardiovascular disease, and mortality.[30-34] Taking regular active breaks during sedentary time might counteract the detrimental effects of prolonged sedentary periods.[35,36] Current CR programs generally do not address sedentary behaviour. Studies investigating the consequences of sedentary behaviour in patients participating in CR are scarce. A first study showed that sedentary time is long among CR graduates and associated with a higher body mass index and lower aerobic capacity.[30]

FATIGUE AND PARTICIPATION IN SOCIETY

Perceived fatigue after myocardial infarction was reported to be high and is described as one of the most disturbing symptoms.[37] It is unknown whether CR is effective in improving fatigue. Since fatigue is known to be associated with depression and aerobic capacity[38] and CR is known to positively influence these outcomes [14,15,39], it can be hypothesized that CR might also lead to improvements in fatigue. In addition, previous studies have found an association between physical activity and fatigue and between sedentary behaviour and fatigue.[40] Interventions that aim to improve physical activity and sedentary behaviour during CR might therefore also positively impact fatigue.

Another understudied CR outcome is participation in society. The CR guidelines recommend optimizing participation in society with regard to domestic, occupational, and recreational activities.[13] With regard to occupational activities, previous studies have shown that 80% of patients with ACS have returned to work within 1 year.[41] Research on participation in domestic and recreational activities, such as going out and housekeeping is scarce. CR could have a direct or indirect effect on participation in society. Improvements in aerobic capacity, often seen during CR[14,15], could influence physical strain of daily activities, which in turn could improve participation in society.[42] In line with our hypothesis for fatigue, participation in society could also be improved by CR interventions that aim to increase physical activity.[43]

Both fatigue and participation in society deserve more attention as an outcome of CR since they are known to affect quality of life.[44,45]

BEHAVIOURAL INTERVENTIONS

There are several theoretical models explaining (changes in) health behaviour, such as the social cognitive theory, the theory of planned behaviour, the health belief model and the transtheoretical model of change.[46,47] Although there are clear differences between these theories, there is also overlap between the models in for instance the determinants of health behaviour.[46] The social cognitive theory describes self-efficacy, knowledge, outcome expectations, goals and perceived facilitators as important determinants of health behaviour.[46] These determinants overlap with determinants described by for instance the theory of planned behaviour (e.g. self-efficacy, outcome expectation and goals), the health belief model (e.g. outcomes expectations and perceived facilitators) and the transtheoretical model of change (e.g. self-efficacy).[46,48] It has been hypothesized that behaviour change techniques (such as self-monitoring and goal setting) can influence these determinants, leading to changes in health behaviour which, in turn, could lead to changes in health.[49,50] Therefore, an important step when designing a behavioural intervention is to select appropriate (evidenced-based) behaviour change techniques.[49,51] In this thesis, we did not favour a certain theoretical model or aim to investigate the working mechanism of separate behaviour change techniques. Rather, we were interested in the synergistic effects of combining evidence-based behaviour change techniques (grounded in multiple theoretical models) in a pragmatic behavioural intervention. Results of reviews and meta-analyses have shown that giving information on consequences of behaviour, self-monitoring, goal setting, planning, receiving feedback, identifying barriers and developing plans for relapse prevention are promising techniques to change health behaviour in cardiac patients.[27,28,52-54] Combining these techniques seems more successful than using a single strategy.[28,52] In addition, reviews and meta-analyses have shown that motivational interviewing is an effective counselling method to guide people with behaviour changes.[55-57] Motivational interviewing is defined as a directive counselling style for eliciting behaviour change by helping people to explore and resolve ambivalence.[58]

Previous studies have shown promising results after adding behavioural interventions aiming at further improvements in lifestyle (such as sufficient physical activity) to CR.[59-62] However, the impact of these studies are limited. Most protocols were designed to evaluate short-term effectiveness; knowledge about long-term maintenance is scarce. Additionally, the behavioural interventions were often not integrated into existing CR programs. For successful implementation into daily clinical practice, pragmatic trials that use existing infrastructure are needed. Lastly, previous studies largely rely on self-reported measures for changes in physical activity that are known to have poor validity and reliability.[63]

OUTLINE OF THIS THESIS

Objectives

The main objective of this thesis was to evaluate the added value of (pragmatic) behavioural lifestyle interventions integrated into standard CR on physical activity in patients with ACS. Secondary, the intervention effects on sedentary behaviour, cardiovascular health, aerobic capacity, perceived level of fatigue and participation in society were studied. Furthermore, the effects of standard CR with regard to the understudied outcomes physical activity, sedentary behaviour, fatigue and participation in society were described. To study the effects of standard CR, data collected in the *Capri Monitor* longitudinal cohort was used. To study the additional effects of two novel behavioural lifestyle interventions, data collected in the *OPTICARE* randomized controlled trial was used.

Capri monitor

Capri Monitor is a longitudinal cohort study of patients who participate in multidisciplinary standard CR at Capri (CR centre located in Rotterdam and The Hague in the Netherlands). The Capri program is in line with the Dutch guidelines and lasts around 6-12 weeks.[13] In this period patients participate twice a week in a 1.5-hour exercise program consisting of gymnastic exercise to increase muscle strength, running/brisk walking, sports activities and relaxation exercises. Additionally, patients can participate in educational sessions on healthy diet, cardiovascular risk factors and psychosocial problems. Upon indication and motivation, patients can also participate in a stress management program, a dietary program, a smoking cessation program and/or an individualized psychologic program. An extensive measurement protocol was performed at the start of rehabilitation, at the completion of CR and at 1-year follow-up. For this thesis, patients that were referred to CR after CHD were selected and data on fatigue, participation in society, and aerobic capacity was used.

OPTICARE

In the OPTICARE randomized controlled trial the additional effects of two novel behavioural lifestyle interventions (CR+F intervention using face-to-face group counselling and CR+T intervention using individual telephonic counselling) added to standard CR after an ACS were investigated (See Figure 1.1).

The CR+F intervention was developed by Capri by an expert group consisting of physical therapists, social workers, psychologists, dieticians and researchers. The content of this intervention was based on the following evidence-based behavioural change techniques: information about health behaviour, self-monitoring, goal setting, feed-

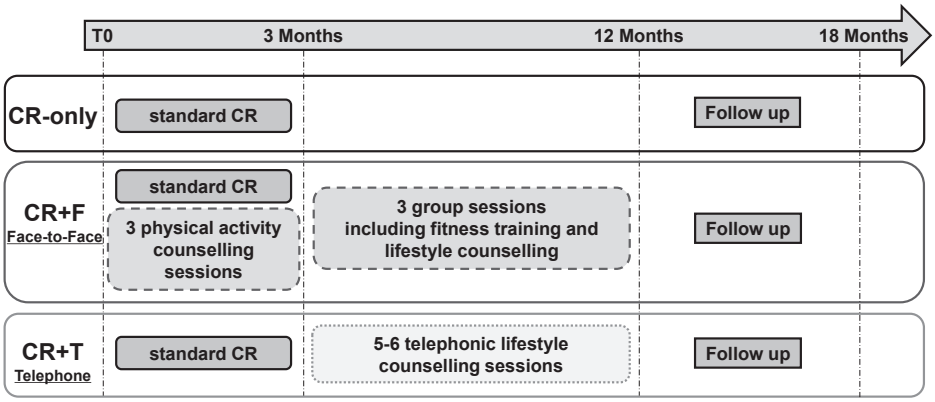

Figure 1.1 Design of the OPTICARE study
CR+F= cardiac rehabilitation plus face-to-face group counselling; CR+T= cardiac rehabilitation plus individual telephonic counselling; CR-only= standard cardiac rehabilitation; m=months.

back, barrier identification and relapse prevention. The CR+F intervention consisted of 3 months of standard CR with the addition of three face-to-face physical activity group counselling sessions led by physical therapists trained in motivational interviewing. During the sessions, information was given on the health consequences of both physical activity and sedentary behaviour. Patients used a pedometer for continuous objective feedback on physical activity and to set goals. A booklet with assignments focusing on for instance goal setting, barrier identification and relapse prevention was used during the sessions. The initial CR program was followed by 9 months of aftercare with three group sessions, each comprising a 1-hour exercise program and 1 hour of healthy lifestyle counselling. The exercise program served as self-monitoring of aerobic capacity and also intended to stimulate interaction between patients in the group. The counselling sessions in the aftercare program focused on the permanent adoption of a healthy lifestyle (i.e., healthy diet and optimal physical activity), but also on psychosocial problems. During the sessions, information on consequences of health behaviours was repeated and there was a focus on relapse prevention. During these sessions, patients were coached alternatingly by a dietician, a social worker and a physical therapist. All coaches were trained in motivational interviewing. Finally, 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 (SBP) <140 mmHg.

The CR+T intervention consisted of 3 months of standard CR, followed by 9 months of aftercare with five to six healthy lifestyle, telephonic counselling sessions. This intervention was based on an existing behavioural program that already had been proven effective in Australia.[64] Similar behaviour change techniques as described above were used in this intervention. During the phone calls information was given on risk factors

(e.g. cholesterol, blood pressure) and health behaviours (e.g. diet, physical activity). Patients were stimulated to self-monitor their own risk factors (for instance measuring cholesterol at their doctor's office) and to set goals. 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. The coaching was offered by the Medical Service Center of the health insurance company "Zilveren Kruis", which consisted of specialized nurses who were trained in motivational interviewing.

The OPTICARE aimed to evaluate effects from a cardiology viewpoint on cardiovascular risk factors (the focus of a separate thesis) and from a rehabilitation medicine viewpoint on physical activity (current thesis). Measurements were performed at randomization, after standard CR, at the end of after-care, and 6 months later (see Figure 1.1).

Short overview of this thesis

Figure 1.2 shows a schematic overview of the content of this thesis.

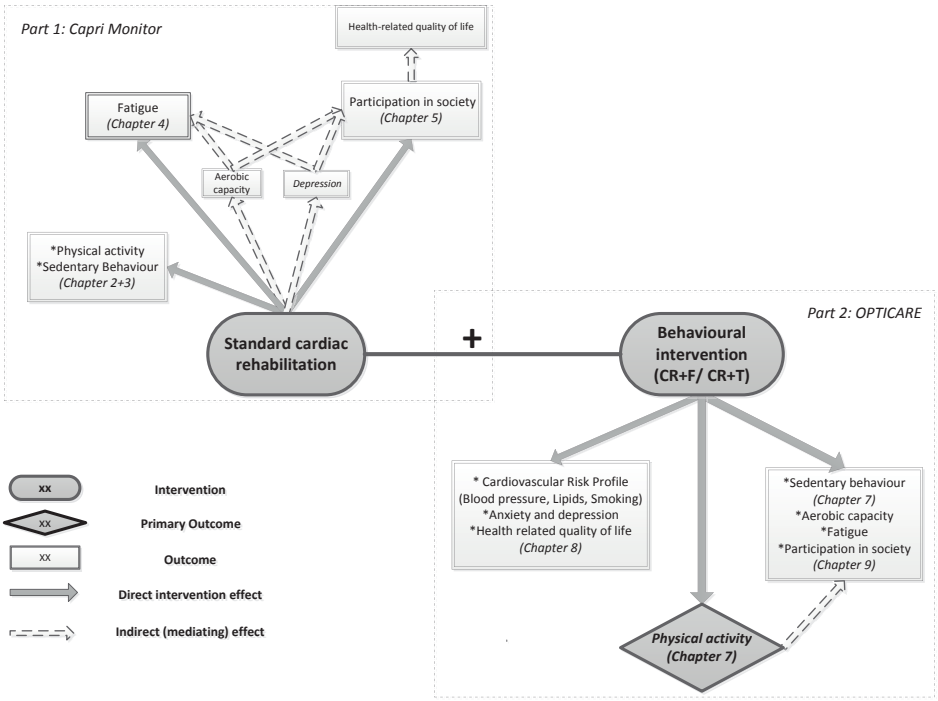

Figure 1.2 Outline of the thesis
CR+F = cardiac rehabilitation plus face-to-face group counselling; CR+T = cardiac rehabilitation plus individual telephonic counselling.

In **Part I** the focus is on short- and long-term outcomes of current standard CR after CHD.

The literature regarding the effects of CR on physical activity is systematically summarized in **Chapter 2**. Changes during and after CR in objectively measured physical activity and sedentary behaviour are described in **Chapter 3;** in fatigue and its association with aerobic capacity and depression in **Chapter 4;** and in participation in society and its association with health-related quality of life in **Chapter 5**.

In **Part II** the outcomes of the OPTICARE trial are described in patients with ACS.

Chapter 6 provides insights into the rationale and design of the OPTICARE trial. **Chapter 7** describes the primary results of the interventions on physical activity and sedentary behaviour. **Chapter 8** focuses on the results with regard to cardiovascular health, depression and anxiety, and health-related quality of life. In **Chapter 9** secondary effects of the interventions on aerobic capacity, fatigue and participation in society are described and whether these effects are mediated by physical activity and sedentary behaviour.

In the concluding **Chapter 10**, the main findings of the different chapters are integrated and interpreted. Methodological considerations, clinical implications and directions for future research are discussed.

REFERENCES

1. Deckers, J., M. Abawi, S. Khatibi, and Y. Feng, *ABC van de cardiologie*. 2012, Rotterdam: 2010
2. Saczynski, J.S., D. Lessard, F.A. Spencer, J.H. Gurwitz, et al., *Declining length of stay for patients hospitalized with AMI: impact on mortality and readmissions.* Am J Med, 2010. **123**(11): p. 1007-15.
3. Townsend, N., L. Wilson, P. Bhatnagar, K. Wickramasinghe, et al., *Cardiovascular disease in Europe: epidemiological update 2016.* Eur Heart J, 2016. **37**(42): p. 3232-3245.
4. Buddeke, J., I. Van Dis, F. Visseren, I. Vaartjes, et al., *Hart- en vaatziekten in Nederland 2016, cijfers over prevalentie, ziekte en sterfte.* 2016, Den Haag: Hartstichting.
5. Piepoli, M.F., U. Corra, P. Dendale, I. Frederix, et al., *Challenges in secondary prevention after acute myocardial infarction: A call for action.* Eur J Prev Cardiol, 2016. **23**(18): p. 1994-2006.
6. Jernberg, T., P. Hasvold, M. Henriksson, H. Hjelm, et al., *Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective.* Eur Heart J, 2015. **36**(19): p. 1163-70.
7. Yusuf, S., S. Hawken, S. Ounpuu, T. Dans, et al., *Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study.* Lancet, 2004. **364**(9438): p. 937-52.
8. Iestra, J.A., D. Kromhout, Y.T. van der Schouw, D.E. Grobbee, et al., *Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review.* Circulation, 2005. **112**(6): p. 924-34.
9. Kotseva, K., D. De Bacquer, C. Jennings, V. Gyberg, et al., *Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999-2013.* Glob Heart, 2017. **12**(4): p. 315-22
10. Kotseva, K., D. Wood, D. De Bacquer, G. De Backer, et al., *EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries.* Eur J Prev Cardiol, 2016. **23**(6): p. 636-48.
11. Piepoli, M.F., U. Corra, W. Benzer, B. Bjarnason-Wehrens, et al., *Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 1-17.
12. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
13. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
14. Taylor, R.S., A. Brown, S. Ebrahim, J. Jolliffe, et al., *Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials.* Am J Med, 2004. **116**(10): p. 682-92.
15. Lavie, C.J. and R.V. Milani, *Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention.* Prog Cardiovasc Dis, 2011. **53**(6): p. 397-403.

16. Anderson, L., N. Oldridge, D.R. Thompson, A.D. Zwisler, et al., *Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis.* J Am Coll Cardiol, 2016. **67**(1): p. 1-12.
17. de Vries, H., H.M. Kemps, M.M. van Engen-Verheul, R.A. Kraaijenhagen, et al., *Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients.* Eur Heart J, 2015. **36**(24): p. 1519-28.
18. Wong, W.P., J. Feng, K.H. Pwee, and J. Lim, *A systematic review of economic evaluations of cardiac rehabilitation.* BMC Health Serv Res, 2012. **12**: p. 243.
19. Gupta, R., B.K. Sanderson, and V. Bittner, *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**(1): p. 11-8.
20. Willich, S.N., J. Muller-Nordhorn, M. Kulig, S. Binting, et al., *Cardiac risk factors, medication, and recurrent clinical events after acute coronary disease; a prospective cohort study.* Eur Heart J, 2001. **22**(4): p. 307-13.
21. Hansen, D., P. Dendale, A. Raskin, A. Schoonis, et al., *Long-term effect of rehabilitation in coronary artery disease patients: randomized clinical trial of the impact of exercise volume.* Clin Rehabil, 2010. **24**(4): p. 319-27.
22. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.
23. Chow, C.K., S. Jolly, P. Rao-Melacini, K.A. Fox, et al., *Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes.* Circulation, 2010. **121**(6): p. 750-8.
24. Mora, S., N. Cook, J.E. Buring, P.M. Ridker, et al., *Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms.* Circulation, 2007. **116**(19): p. 2110-8.
25. Daubenmier, J.J., G. Weidner, M.D. Sumner, N. Mendell, et al., *The contribution of changes in diet, exercise, and stress management to changes in coronary risk in women and men in the multisite cardiac lifestyle intervention program.* Ann Behav Med, 2007. **33**(1): p. 57-68.
26. Giannuzzi, P., A. Mezzani, H. Saner, H. Bjornstad, et al., *Physical activity for primary and secondary prevention. Position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur J Cardiovasc Prev Rehabil, 2003. **10**(5): p. 319-27.
27. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
28. Chase, J.A., *Systematic review of physical activity intervention studies after cardiac rehabilitation.* J Cardiovasc Nurs, 2011. **26**(5): p. 351-8.
29. Bussmann, J.B. and R.J. van den Berg-Emons, *To total amount of activity..... and beyond: perspectives on measuring physical behavior.* Front Psychol, 2013. **4**: p. 463.
30. Prince, S.A., C.M. Blanchard, S.L. Grace, and R.D. Reid, *Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates.* Eur J Prev Cardiol, 2016. **23**(8): p. 818-25.
31. Biswas, A., P.I. Oh, G.E. Faulkner, R.R. Bajaj, et al., *Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis.* Ann Intern Med, 2015. **162**(2): p. 123-32.
32. Chau, J.Y., A.C. Grunseit, T. Chey, E. Stamatakis, et al., *Daily sitting time and all-cause mortality: a meta-analysis.* Plos One, 2013. **8**(11): e80000.

33. Wilmot, E.G., C.L. Edwardson, F.A. Achana, M.J. Davies, et al., *Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis.* Diabetologia, 2012. **55**(11): p. 2895-905.
34. Healy, G.N., K. Wijndaele, D.W. Dunstan, J.E. Shaw, et al., *Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).* Diabetes Care, 2008. **31**(2): p. 369-71.
35. Healy, G.N., D.W. Dunstan, J. Salmon, E. Cerin, et al., *Breaks in sedentary time: beneficial associations with metabolic risk.* Diabetes Care, 2008. **31**(4): p. 661-6.
36. Kim, Y., G.J. Welk, S.I. Braun, and M. Kang, *Extracting objective estimates of sedentary behavior from accelerometer data: measurement considerations for surveillance and research applications.* Plos One, 2015. **10**(2): e0118078.
37. Alsen, P. and M. Eriksson, *Illness perceptions of fatigue and the association with sense of coherence and stress in patients one year after myocardial infarction.* J Clin Nurs, 2016. **25**(3-4): p. 526-33.
38. Bunevicius, A., A. Stankus, J. Brozaitiene, S.S. Girdler, et al., *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**(2): p. 310-6.
39. Rutledge, T., L.S. Redwine, S.E. Linke, and P.J. Mills, *A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease.* Psychosom Med, 2013. **75**(4): p. 335-49.
40. Ellingson, L.D., A.E. Kuffel, N.J. Vack, and D.B. Cook, *Active and sedentary behaviors influence feelings of energy and fatigue in women.* Med Sci Sports Exerc, 2014. **46**(1): p. 192-200.
41. Boudrez, H. and G. de Backer, *Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting.* Acta Cardiologica, 2000. **55**(6): p. 341-349.
42. Nieuwenburg-van Tilborg, E.M., A.M. Horstman, B. Zwarts, and S. de Groot, *Physical strain during activities of daily living of patients with coronary artery disease.* Clin Physiol Funct Imaging, 2014. **34**(2): p. 83-9.
43. Britton, A., E. Brunner, M. Kivimaki, and M.J. Shipley, *Limitations to functioning and independent living after the onset of coronary heart disease: what is the role of lifestyle factors and obesity?* Eur J Public Health, 2012. **22**(6): p. 831-5.
44. Brink, E., G. Grankvist, B.W. Karlson, and L.R. Hallberg, *Health-related quality of life in women and men one year after acute myocardial infarction.* Qual Life Res, 2005. **14**(3): p. 749-57.
45. Thraen-Borowski, K.M., A. Trentham-Dietz, D.F. Edwards, K.F. Koltyn, et al., *Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors.* Journal of Cancer Survivorship, 2013. **7**(3): p. 369-378.
46. Bandura, A., *Health promotion by social cognitive means.* Health Educ Behav, 2004. **31**(2): p. 143-64.
47. Marcus, B.H. and L.R. Simkin, *The transtheoretical model: applications to exercise behavior.* Med Sci Sports Exerc, 1994. **26**(11): p. 1400-4.
48. Ashford, S., J. Edmunds, and D.P. French, *What is the best way to change self-efficacy to promote lifestyle and recreational physical activity? A systematic review with meta-analysis.* Br J Health Psychol, 2010. **15**(Pt 2): p. 265-88.
49. Sakakibara, B.M., S.A. Lear, S.I. Barr, O. Benavente, et al., *Development of a Chronic Disease Management Program for Stroke Survivors Using Intervention Mapping: The Stroke Coach.* Arch Phys Med Rehabil, 2017. **98**(6): p. 1195-1202.
50. Hardeman, W., S. Sutton, S. Griffin, M. Johnston, et al., *A causal modelling approach to the development of theory-based behaviour change programmes for trial evaluation.* Health Educ Res, 2005. **20**(6): p. 676-87.

51. Bartholomew, L.K., G.S. Parcel, and G. Kok, *Intervention mapping: a process for developing theory- and evidence-based health education programs.* Health Educ Behav, 1998. **25**(5): p. 545-63.
52. Janssen, V., V. De Gucht, E. Dusseldorp, and S. Maes, *Lifestyle modification programmes for patients with coronary heart disease: a systematic review and meta-analysis of randomized controlled trials.* Eur J Prev Cardiol, 2013. **20**(4): p. 620-40.
53. Aldcroft, S.A., N.F. Taylor, F.C. Blackstock, and P.D. O'Halloran, *Psychoeducational rehabilitation for health behavior change in coronary artery disease: a systematic review of controlled trials.* J Cardiopulm Rehabil Prev, 2011. **31**(5): p. 273-81.
54. Michie, S., C. Abraham, C. Whittington, J. McAteer, et al., *Effective techniques in healthy eating and physical activity interventions: a meta-regression.* Health Psychol, 2009. **28**(6): p. 690-701.
55. O'Halloran, P.D., F. Blackstock, N. Shields, A. Holland, et al., *Motivational interviewing to increase physical activity in people with chronic health conditions: a systematic review and meta-analysis.* Clin Rehabil, 2014. **28**(12): p. 1159-71.
56. Armstrong, M.J., T.A. Mottershead, P.E. Ronksley, R.J. Sigal, et al., *Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials.* Obes Rev, 2011. **12**(9): p. 709-23.
57. Rubak, S., A. Sandbaek, T. Lauritzen, and B. Christensen, *Motivational interviewing: a systematic review and meta-analysis.* Br J Gen Pract, 2005. **55**(513): p. 305-12.
58. Miller, W.R. and S. Rollnick, *Motivational interviewing, preparing people for change*. 2002: The Guilford Press.
59. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network.* Arch Intern Med, 2008. **168**(20): p. 2194-204.
60. Butler, L., S. Furber, P. Phongsavan, A. Mark, et al., *Effects of a pedometer-based intervention on physical activity levels after cardiac rehabilitation: a randomized controlled trial.* J Cardiopulm Rehabil Prev, 2009. **29**(2): p. 105-14.
61. Janssen, V., V. De Gucht, H. van Exel, and S. Maes, *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence.* J Behav Med, 2014. **37**(2): p. 308-21.
62. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
63. Le Grande, M.R., P.C. Elliott, M.U. Worcester, B.M. Murphy, et al., *An evaluation of self-report physical activity instruments used in studies involving cardiac patients.* J Cardiopulm Rehabil Prev, 2008. **28**(6): p. 358-69.
64. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.

PART 1

Standard cardiac rehabilitation

Chapter 2

Does cardiac rehabilitation after an acute cardiac syndrome lead to changes in physical activity habits? Systematic review

Nienke ter Hoeve
Bionka M.A. Huisstede
Henk J. Stam
Ron T. van Domburg
Madoka Sunamura
Rita J. G. van den Berg-Emons

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ABSTRACT

Background: Optimal physical activity levels have health benefits for patients with an acute coronary syndrome (ACS) and are an important goal of cardiac rehabilitation (CR).

Purpose: To systematically review literature regarding short-term (<6 months after completion of CR) and long-term effects (≥6 months after completion) of standard CR on physical activity levels in patients with ACS.

Data sources: PubMed, EMBASE, CINAHL and PEDro were systematically searched for relevant randomized controlled trials (RCTs) from 1990 until 2012.

Study selection: Randomized controlled trials (RCTs) investigating CR for patients with ACS reporting physical activity level were reviewed.

Data extraction: Two reviewers independently selected articles, extracted data, and assessed methodological quality. Result were summarized with a best-evidence synthesis. Results were categorized as: 1) center-based/home-based CR vs no intervention, 2) comparison of different durations of CR, and 3) comparison of 2 types of CR.

Data synthesis: A total of 26 RCTs were included. Compared with no intervention, there was, at most, conflicting evidence for center-based CR and moderate evidence for home-based CR for short-term effectiveness. Limited evidence and no evidence were found for long-term maintenance for center-based and home-based CR, respectively. When directly compared with center-based CR, moderate evidence showed that home-based CR has better long-term effects. There was no clear evidence that increasing training volume, extending duration of CR or adding an extra intervention to CR is more effective.

Limitations: Because of the variety of CR interventions and the variety of outcome measures in the included RCTs, pooling of data was not possible. Therefore, a best-evidence synthesis was used.

Conclusions: It would appear that center-based CR is not sufficient to improve and maintain physical activity habits. Home-based programs might be more successful, but the literature on these programs is limited. More research on finding successful interventions to improve activity habits is needed.

INTRODUCTION

New drug therapies and revascularization techniques developed since the 1980s have dramatically changed the care of patients with cardiovascular conditions. Although cardiovascular disease is still the leading cause of death worldwide,[1] since the introduction of these treatments, survival rates have increased, hospitalization has shortened, and cardiac function has been better preserved.[2,3] Healthy lifestyle management is crucial for successful secondary prevention for this growing number of surviving patients.[2,4] Cardiac rehabilitation (CR), including lifestyle education, has become increasingly important.

An important goal of CR is to improve daily physical activity levels. Regular physical activity reduces cardiac mortality by 20-30% in patients with myocardial infarction.[5] Besides improving cardiac mortality, having an active lifestyle also has positive effects on the most important cardiovascular risk factors such as lipid profile, blood pressure and body composition.[6,7]

The core of current standard CR consists of exercise programs led by physical therapists, complemented with educational or psychosocial interventions**.** Previous reviews reported that besides reducing cardiovascular risk factors and improving quality of life, standard CR does improve physical fitness.[8,9] However, improved fitness (what a person can do) does not automatically result in a more active lifestyle (what a person really does in daily life).[10]

A review published in 1998 suggested that CR is not sufficient to change physical activity habits in the long term.[11] However, medical practice has changed greatly since this review was written. The introduction of new drug therapies and revascularization techniques has shortened the time available in hospital for lifestyle education, putting more emphasize on CR.[2,3] Moreover, a shift was seen from exercise-only CR to comprehensive programs including lifestyle education. It is unclear whether current standard CR programs are sufficient to improve and maintain physical activity levels. Therefore, the purpose of this study was to systematically review the recent scientific literature regarding the effect of current standard CR on levels of daily physical activity after an acute coronary syndrome (ACS). To establish whether any improvements are maintained over time, we focused not only on the effects achieved immediately after CR but also on the effects in the long term.

METHODS

Data sources and searches

We systematically searched PubMed, EMBASE, CINAHL, and PEDro for relevant randomized controlled trials (RCTs). The search was limited to RCTs published between 1990 and December 2012. RCTs published before 1990 were excluded because there have been major changes in medical practice since the development of new drugs and revascularization techniques in the 1980s. The search strings consisted of keywords related to 'heart disease', 'cardiac rehabilitation' and 'randomized controlled trials', and can be found in detail in Appendix 2A.

Study selection

Randomized controlled trials fulfilling the following criteria were included:

1) The study population consisted of patients who had recently (<1 year) either survived ACS, or undergone coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). ACS usually occurs as a result of one of three problems: ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina. In the Netherlands these patients are usually treated with primary or elective PCI or CABG.

2) The intervention investigated was a CR program that lasted for at least 4 weeks. We defined CR as a structured exercise program combined with psychosocial and educational interventions undertaken in a center-based or home-based setting. As the exercise program forms the core of CR, interventions were categorized based on the location where the exercise program was performed. Thus, interventions containing a center-based exercise program were classified into the category center-based CR and interventions containing a home-based exercise program into the category home-based CR. Exercise-only interventions were excluded because this type of intervention is no longer considered as standard CR.[2,6,12]

3) An outcome measure for physical activity was reported. Physical activity was defined as any bodily movement produced by skeletal muscles and resulting in energy expenditure.[13]

4) Minimal follow-up was completion of the CR intervention.

5) The article was written in English, Dutch, French or German.

Two reviewers (N.H., R.D.) independently selected relevant articles based on the inclusion criteria. Before reading the full text, a first selection was based on titles and abstracts. If an article was not available, we tried to obtain it by contacting the author. Disagreement between the 2 reviewers was discussed. If needed, a third reviewer (B.H.) resolved disagreements.

Data extraction and quality assessment

Data on outcome measures for level of daily physical activity, study population, sample size, CR intervention, and control intervention were extracted by one reviewer (N.H.) using a standardized form, and were checked by a second reviewer (R.D.). Data on outcome measures for physical activity were divided into short-term and long-term effects. Short-term effects were defined as effects measured less than 6 months after completion of CR; long-term effects were defined as effects measured 6 months or longer after completion of CR. In case multiple measurements within the short term or long term were reported in a single RCT, the measurement closest to completion of CR was used for analysis of short-term effectiveness and the measurement closest to 1 year after completion of CR was used for analysis of long-term effectiveness. If data on the same RCT and population were reported in multiple publications, we extracted and presented them as originating from a single RCT. Disagreement was resolved by discussion or by the third reviewer (B.H.).

Two reviewers (N.H., R.D.) independently assessed the methodological quality of included RCTs using the list published by Furlan et al.[14] This list consists of 12 items that are scored as yes (+), no (-) or unsure (+/-). A study was considered of 'high quality' if at least 6 questions (≥50%) were scored as yes. Disagreement was resolved by discussion or by resorting to a third reviewer (B.H.).

Data synthesis and analysis

Due to the heterogeneity of CR interventions and the outcome measures for physical activity, pooling of data was not possible. Therefore, we used a best-evidence synthesis.[15] This method allows methodological quality and outcomes of the RCTs to be taken into account. Strength of evidence for the effectiveness of CR to improve physical activity in the short term (<6 months after completion of CR) and in the long term (≥6 months after completion of CR) was ranked as shown in Table 2.1.[15]

Table 2.1 Strength of evidence

1 Strong evidence	Consistent (i.e. similar finding in >75% of the RCTs) significant findings (p<0.05) in at least 2 high-quality RCTs.
2 Moderate evidence	Consistent significant findings in at least 2 low-quality RCTs and/or one high-quality RCT.
3 Limited evidence	Significant findings in one low-quality RCT.
4 Conflicting evidence	Inconsistent (i.e. similar findings in <75% of the RCTs) significant findings in multiple RCTs.
5 No evidence	One or more RCT found, but no significant differences were reported between groups.
6 No RCT found.	No RCT found.

RCT= randomized controlled trial.

RESULTS

Literature search and characteristics of the selected RCTs

Our initial search resulted in 2919 eligible articles. We finally included 26 RCTs (Figure 2.1). Of these, 9 RCTs compared CR with no intervention, 10 RCTs compared CR programs of different duration and 7 RCTs compared 2 different types of CR (Table 2.2). When measuring physical activity, 21 RCTs used a self-report instrument (e.g. questionnaire or activity diary), 3 RCTs used a pedometer, and 2 RCTs used both a self-report instrument and an accelerometer (Table 2.2).

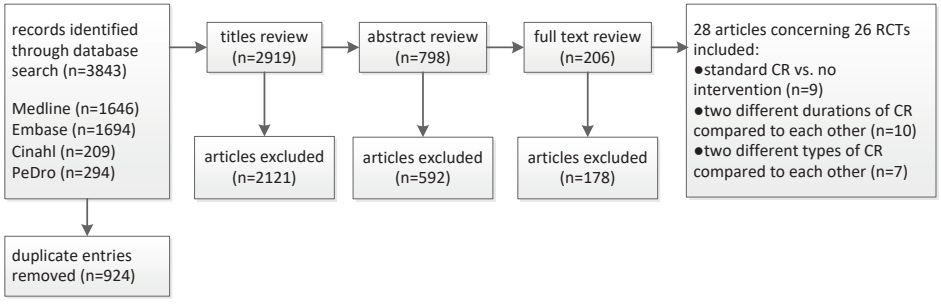

Figure 2.1 Selection of articles
RCT= randomized controlled trial; CR= cardiac rehabilitation.

Methodological quality of the 26 RCTs

The results of the methodological quality assessment are presented in Appendix 2B. Fourteen of the 26 RCTs scored 50% or more of the maximum score and were considered high quality. The most prevalent methodological flaws were: patients not blinded (100% of included RCTs); care provider not blinded (100% of RCTs); failure to report whether co-interventions were avoided (100% of RCTs); and failure to report whether treatment allocation was concealed (81% of RCTs).

Data extraction

Details of the characteristics and results of the included RCTs are presented in Appendix 2C.

Table 2.2 Treatment specifications for intervention group and control intervention in the 26 RCTs

			Intervention		Control intervention	
	RCT	Measurement tool	Home-based/ center-based	Duration	Home-based/ center-based	Duration
Standard CR vs. no intervention	Bertie 1992[16]	pedometer	center	4 weeks	no intervention	n.a.
	Higgins 2001[25]	self-reported	home	1 year	no intervention	n.a.
	Lidell 1996[19]	self-reported	center	6 months	no intervention	n.a.
	Naser 2008[21]	self-reported	center	2 years	no intervention	n.a.
	Oldenburg 1995[22]	self-reported	center	1 year	no intervention	n.a.
	Ornish 1990+1998*[23,24]	self-reported	home	1 year	no intervention	n.a.
	Otterstad 2003[20]	self-reported	center	2 years	no intervention	n.a.
	West 2012[17]	self-reported	center	6-8 weeks	no intervention	n.a.
	Engblom 1992[18]	self-reported	center	8 months	no intervention	n.a.
Two different durations of CR compared to each other	Arrigo 2008[29]	self-reported	center	1 year	center	1-3 months
	Hughes 2007[30]	self-reported/ accelerometer	center	1 year	center	3 months
	Carlsson 1997[33]	self-reported	center	1 year	center	5 weeks
	Mildestvedt 2008[32]	self-reported	center	2 years	center	4 weeks
	Giannuzzi 2008[34]	self-reported	center	3 years	center	6 months
	Janssen 2012[26]	pedometer	center	8 months	center	3 months
	Pinto 2011[27]	self-reported	center	9 months	center	3 months
	Reid 2005[31]	self-reported	center	1 year	center	3 months
	Lear 2006[35]	self-reported	center	4 years	center	4 months
	Moore 2006[28]	self-reported	center	5 months	center	3 months
Two different types of CR compared to each other	Carlson 2000[41]	self-reported	center	6 months	center	6 months
	Izawa 2005[42]	pedometer	center	6 months	center	6 months
	Tingström 2005[43]	self-reported/ accelerometer	center	1 year	center	1 year
	Jolly 2009[36]	self-reported	center	9-12 weeks	home	3 months
	Oerkild 2011[39]	self-reported	center	1 year	home	1 year
	Hansen 2008[40]	self-reported	center	3 months	center	3 months
	Smith 2004+2011*[37,38]	self-reported	center	6 months	home	6 months

RCT= randomized controlled trial; CR= cardiac rehabilitation; n.a.= not applicable.
**multiple publications on data of the same RCT and population are presented as originating from a single RCT.*

Effectiveness of CR on improving physical activity levels

We performed a best-evidence synthesis to summarize short-term effects (<6 months after completion of CR) and long-term effects (≥6 months after completion of CR). We

categorized RCTs into studies investigating 'center-based and home-based CR versus no intervention', 'comparison of CR programs of different durations' and 'comparison of 2 types of CR'. Duration of CR programs also varied greatly (4 weeks till 4 years) within the above categories. To further improve meaningful interpretation of results, we analysed and presented effects in every category in the following order: CR programs of short duration (1-3 months), CR programs of medium duration (4-11 months) and CR programs of long duration (≥12 months). Table 2.2 shows the treatment specifications and Tables 2.3, 2.4 and 2.5 show the results of the best-evidence synthesis per category.

Effectiveness of CR versus no intervention

Seven RCTs investigated the effectiveness of center-based CR, and 2 RCTs investigated the effects of home-based CR versus a control group. Controls visited the hospital only for routine check-ups or received oral or written information about cardiac disease (Table 2.2).

Center-based CR versus no intervention

For CR of short duration (1-3 months), Bertie et al.[16] (low quality, n=110) reported short-term effects of a 4-week CR program and showed that 3 months after completion of CR, the intervention group walked, on average, significantly more miles each day (8.2 miles) than the controls (6.6 miles) ($p<0.05$). West et al.[17] (high quality, n=1813) focused on long-term effectiveness and reported that 10 months after completion of CR, the percentage of active patients (>100kcal/day) was higher in controls (12%) than in patients randomized to 6-8 weeks CR (9%) ($p=0.05$). According to the best evidence synthesis, there is limited evidence that, in the short term (<6 months after completion of CR), center-based CR of short duration is effective in improving physical activity levels. In the long term (≥6 months after completion), there is moderate evidence in favor of controls (Table 2.3).

For CR of medium duration (4-11 months), Engblom et al.[18] (high quality, n=171) reported no short-term effects 4 months after completion of an 8-month CR program. Lidell and Fridlund[19] (low quality, n=116) performed 2 long-term measurement: at 6 months and at 4.5 years. Significant effects were found at the 6-month follow-up (66.7% of intervention group was active versus 27.6% of controls, $p<0.001$); these improvements were not maintained after 4.5 years. As defined in our methods, the measurement closest to 1 year after completion of CR was used in the best evidence synthesis (ie, the results at 6-month follow-up). The best evidence synthesis revealed that there is no evidence that center-based CR of medium duration is effective in the short term (<6 months after completion of CR) and limited evidence that it is effective in the long term (≥6 months after completion of CR). See Table 2.3.

For CR of long duration (≥12 months), Otterstad et al.[20] (high quality, n=197) found that upon completion of a 2-year CR program, 67% of patients exercised for more than 1 hour every week compared with 46% of controls (p<0.01). Naser et al.[21] (low quality, n=100) reported that upon completion of a 2-year CR program, 88% of patients were vigorously active at least 3 times per week for 20 minutes, whereas this figure was only 20% in controls (p<0.05). Oldenburg et al.[22] (low quality, n=86) investigated a 1-year CR program and found no effects upon completion. We conclude that there is conflicting evidence for the short-term effectiveness (<6 months after completion of CR) of center-based CR of long duration. No RCTs focused on long-term effects (Table 2.3).

Table 2.3 Evidence for effectiveness of CR interventions versus no intervention

Duration CR	RCT	Low/ high quality	Short-term effects < 6 mo after completion of CR	Long term-effects ≥6 mo after completion of CR
Center-based CR versus no intervention				
Short (1-3 mo)	Bertie 1992[16]	low	+	n.a.
	West 2012[17]	high	n.a.	-
	Best evidence synthesis:		***limited evidence***	***moderate evidence#***
Medium (4-11 mo)	Engblom 1992[18]	high	0	n.a.
	Lidell 1996[19]	low	n.a.	+
	Best evidence synthesis:		***no evidence***	***limited evidence***
Long (≥12 mo)	Otterstad 2003[20]	high	+	n.a.
	Naser 2008[21]	low	+	n.a.
	Oldenburg 1995[22]	low	0	n.a.
	Best evidence synthesis:		***conflicting evidence***	***no RCT***
Home-based CR versus no intervention				
Short (1- 3 mo)	***no RCT***			
Medium (4-11 mo)	***no RCT***			
Long (≥12 mo)	Ornish 1990+1998*[23,24]	high	+	0
	Higgins 2001[25]	low	+	n.a.
	Best evidence synthesis:		***moderate evidence***	***no evidence***

CR= cardiac rehabilitation; RCT= randomized controlled trial; mo=months; "+"= significant differences in favor of intervention; "-"= significant differences in favor of controls; "0"= no significant differences found; n.a.= not applicable.

#moderate evidence in favor of no intervention.

**multiple publications on data of the same RCT and population are presented as originating from a single RCT.*

Home-based CR versus no intervention

No RCTs were found for CR of short duration (1-3 months) or medium duration (4-11 months).

For CR of long duration (≥12 months), Ornish et al.[23] (high quality, n=48) reported that patients in the intervention group (1-year CR) increased from 0.26 exercise sessions/day at the start to 0.69 sessions/day on completion of the program; this increase was lower for controls (from 0.35 to 0.39 sessions/day) (p=0.0008). There were no significant differences at 4-year follow-up.[24] Higgins et al.[25] (low quality, n=105) reported that patients participating in a 1-year CR program increased from 35% being active before CR to 72% upon completion. This increase was larger than that in controls (53% to 61%) (p<0.001). In conclusion, there is moderate evidence that in the short term (<6 months after completion of CR) home-based CR of long duration is effective. There is no evidence for long-term effectiveness. See Table 2.3.

Comparison of CR programs of different durations

Ten of the 26 included RCTs compared 2 center-based CR programs of different duration. In this category, short-term effects were defined as results measured <6 months after completion of the CR program with the longer duration, and long-term effects were defined as results measured 6 months or more after completion of the program with the longer duration.

CR of medium duration (4-11 months) versus short duration (1-3 months)

Janssen et al.[26] (high quality, n=210) reported that upon completion of 8-month CR, patients had increased their daily step count by 1142 compared to the start of CR, whereas patients randomized to 3-month CR had decreased their daily step count by 522 by that time (p=0.001). The RCT of Pinto et al.[27] (high quality, n=130) showed an increased duration of moderate exercise per week 3 months after completion of a CR program of 9 months for patients randomized to this longer program compared with patients randomized to receive 3-month CR (difference 0.47, standardized values, p=0.008). Contrasting results were found by Moore et al.[28] (high quality, n=250) who did not find short-term differences between 3 and 5-month CR programs. Moore et al. also reported long-term effects, but again no differences were found. We conclude that there is conflicting evidence that, in the short term (<6 months after completion of the CR program of medium duration), CR of medium duration is more effective than CR of short duration for improving levels of physical activity. In the long term, there is no evidence of effectiveness. (Table 2.4).

CR of long duration (≥12 months) versus short duration (1-3 months)

Arrigo et al.[29] (low quality, n=261) reported that 73% of patients randomized to a 1-year CR program were physically active at least 3 times a week for 30 minutes upon completion of the program, compared with 40% of patients randomized to receive 1 to 3 months of CR (p<0.0005). Hughes et al.[30] (low quality, n=70) found that, upon

completion of a 1-year CR program, patients exercised on average 130 minutes per week more than patients who had participated in a 3-month CR program (significant, p-value not reported). In contrast, 3 other RCTs (1 high quality[31], 2 low quality[32,33]) showed no short-term differences between CR of long and short duration. Only 1 RCT also focused on long-term effects. Reid et al.[31] (high quality, n=392) did not find differences when comparing a 1-year program with a 3-month program. In conclusion, there is conflicting evidence that, in the short term (<6 months after completion of the CR program of long duration), CR of long duration is more effective than CR of short duration. In the long term there is no evidence of effectiveness (Table 2.4).

Table 2.4 Evidence for effectiveness of two different durations of CR compared with each other

RCT	Low/high quality	Short-term effects < 6mo after completion of CR	Long-term effects ≥6 mo after completion of CR
CR of medium duration (4-11 mo) versus CR of short duration (1-3 mo)			
Janssen 2012[26]	high	+	n.a.
Pinto 2011[27]	high	+	n.a.
Moore 2006[28]	high	0	0
Best evidence synthesis:		***conflicting evidence***	***no evidence***
CR of long term duration (≥12 mo) versus CR of short duration (1-3 mo)			
Arrigo 2008[29]	low	+	n.a.
Hughes 2007[30]	low	+	n.a.
Reid 2005[31]	high	0	0
Carlsson 1997[33]	low	0	n.a.
Mildestvedt 2008[32]	low	0	n.a.
Best evidence synthesis:		***conflicting evidence***	***no evidence***
CR of long term duration (≥12 mo) versus CR of medium duration (4-11 mo)			
Giannuzzi 2008[34]	high	+	n.a.
Lear 2006[35]	high	0	n.a.
Best evidence synthesis:		***conflicting evidence***	***no RCT***

CR= cardiac rehabilitation; RCT= randomized controlled trial; mo=month; "+"= significant differences in favor of CR of longer duration; "-"= significant differences in favor of CR of shorter duration; "0"= no significant differences found; n.a.= not applicable.

CR of long duration (≥12 months) versus medium duration (4-11 months)

Giannuzzi et al.[34] (high quality, n=3241) found that, upon completion of a 3-year CR program, patients had a higher physical activity score (23.8% on a self-report questionnaire) compared with patients randomized to a 6-month program (18.8%) (p=0.001). Lear et al.[35] (high quality, n=302) did not find significant differences in the short term when comparing a 4-year with a 4-month program. None of the RCTs looked at long-term differences. We conclude that there is conflicting evidence in the short term (<6

months after completion of the CR program of long duration) that CR of long duration is more effective than CR of medium duration. There were no RCTs investigating long-term differences (Table 2.4).

Comparison of two types of CR

Center-based CR versus home-based CR

For CR of short duration (1-3 months), Jolly et al.[36] (high quality, n=525) compared a 3-month center-based program with a 3-month home-based program and found no differences between the groups in the long term (7 months after completion). We conclude that there is no evidence for long-term differences (≥6 months after completion of CR) between center-based and home-based CR of short duration in effects on physical activity level. No RCTs investigated short-term differences (Table 2.5).

For CR of medium duration (4-11 months), Smith et al.[37,38] (high quality, n=242) performed 2 long-term measurements: at 1- and 6-year follow-ups. One year after completion of the 6-month intervention, patients randomized to home-based CR program had higher physical activity scores (Physical Activity Scale for the Elderly score= 232.6) than patients randomized to the center-based CR program (Physical Activity Scale for the Elderly score= 170.0) ($p \leq 0.0001$).[37] These differences were still significant at 6-year follow-up (166.7 for home-based CR versus 139.7 for center-based CR, $p \leq 0.001$).[38] As defined in our methods, the measurement closest to 1 year after completion of CR was used for the best-evidence synthesis (ie. the 1-year follow-up). We conclude that there is moderate evidence that home-based CR of medium duration is more effective in the long-term (≥6 months after completion of CR) than center-based CR. There were no RCTs investigating short-term differences (Table 2.5).

For CR of long duration (≥12 months), Oerkild et al.[39] (high quality, n=75) found no differences between a center-based CR and a home-based CR program of 1 year's duration upon completion of the programs. In conclusion, there is no evidence for a difference in effectiveness in the short term (<6 months after completion of CR). There were no RCTs investigating long-term differences (Table 2.5).

Low-volume center-based CR versus high volume center-based CR

For CR of short duration (1-3 months), Hansen et al.[40] (high quality, n=119) compared center-based CR that involved a low-volume training program (3x40min/week endurance exercise for 3 months) with center-based CR that involved a high-volume training program (3x60min/week endurance exercise for 3 months). No differences were found in the long term (15 months after completion). We conclude that there is no evidence in

favor of either a low-volume or a high-volume training program of short duration in the long term (≥6 months after completion of CR). There were no RCTs looking at short-term differences (Table 2.5).

No RCTs were found for CR programs of medium (4-11 months) and long duration (≥12 months).

Table 2.5 Evidence for effectiveness of two different types of CR compared to each other

Duration	RCT	Low/high quality	Short-term effects <6 mo after completion of CR	Long-term effects ≥6 mo after completion of CR
Center-based CR versus home-based CR				
Short (1-3 mo)	Jolly 2009[36]	high	n.a.	0
	Best evidence synthesis:		***no RCT***	***no evidence***
Medium (4-11 mo)	Smith 2004+2011*[37,38]	high	n.a.	-
	Best evidence synthesis:		***no RCT***	***moderate evidence***
Long (≥12 mo)	Oerkild 2011[39]	high	0	n.a.
	Best evidence synthesis:		**no evidence**	**no RCT**
Low-volume training group versus high-volume training group				
Short (1-3 mo)	Hansen 2008[40]	high	n.a.	0
	Best evidence synthesis:		***no RCT***	***no evidence***
Medium (4-11 mo)	*no RCT*			
Long (≥12 mo)	*no RCT*			
CR including a self-efficacy intervention to increase physical activity versus standard CR				
Short (1-3 mo)	*no RCT*			
Medium (4-11 mo)	Carlson 2000[41]	low	0	n.a.
	Best evidence synthesis:		***no evidence***	***no RCT***
Long (≥12 mo)	*no RCT*			
CR including self-monitoring to increase physical activity versus standard CR				
Short (1-3 mo)	*no RCT*			
Medium (4-11 mo)	Izawa 2005[42]	low	n.a.	+
	Best evidence synthesis:		***no RCT***	***limited evidence***
Long (≥12 mo)	*no RCT*			
CR including problem-based learning to increase physical activity versus standard CR				
Short (1-3 mo)	*no RCT*			
Medium (4-11 mo)	*no RCT*			
Long (≥12 mo)	Tingström 2005[43]	low	0	n.a.
	Best evidence synthesis:		***no evidence***	***No RCT***

*CR= cardiac rehabilitation; RCT= randomized controlled trial; mo=month; "+"= significant differences in favor of first-mentioned intervention;"-"= significant differences in favor of second-mentioned intervention;"0"= no significant differences found; n.a,= not applicable. *multiple publications on data of the same RCT and population are presented as originating from a single RCT.*

CR including a self-efficacy intervention to increase physical activity versus standard CR

No RCTs found were found for CR of short duration (1-3 months) and long duration (≥12 months).

For CR of medium duration (4-11 months), Carlson et al.[41] (low quality, n=80) reported no significant differences upon completion between a 6-month CR program based on Bandura's self-efficacy theory and designed to enhance confidence for independent exercise and a 6-month standard center-based CR program. The best-evidence synthesis revealed that, in the short term (<6 months after completion of CR), there is no evidence for the effectiveness of a self-efficacy CR intervention. There are no RCTs investigating long-term effects (Table 2.5).

CR including self-monitoring to increase physical activity versus standard CR

No RCTs were found for CR of short duration (1-3 months) and long duration (≥12 months).

For CR of medium duration (4-11 months), Izawa et al.[42] (low quality, n=45) compared a 6-month self-monitoring and goal-setting intervention aimed at increasing physical activity with a 6-month, standard, center-based CR program. Six months after completion, the step count in patients randomized to the intervention group was significantly higher (10458.7 steps/week) than in patients randomized to standard CR (6922.5 steps/week) (p-value not reported). In conclusion, in the long term (≥6 months after completion) there is limited evidence that the self-monitoring and goal-setting intervention is more effective than standard CR. There were no RCTs investigating short-term effects (Table 2.5).

CR including problem-based learning to increase physical activity versus standard CR

No RCTs were found for CR of short duration (1-3 months) and medium duration (4-11 months).

For CR of long duration (≥12 months), Tingström et al.[43] (n=207) reported no significant differences upon completion of center-based CR including a problem-based learning intervention and aimed at increasing physical activity (duration= 1 year) and standard center-based CR (also 1 year). The best-evidence synthesis revealed that in the short term (<6 months after completion of CR) there is no evidence for a problem-based learning intervention. There were no RCTs investigating long-term effects (Table 2.5).

DISCUSSION

This systematic review provides an overview of the evidence for the effectiveness of current standard CR compared with no intervention in improving physical activity levels in patients with ACS in the short term (<6 months after completion of CR) and in the long term (≥6 months). In addition, we focussed on the optimal duration and type of CR to achieve and maintain changes in physical activity level.

Center-based and home-based CR compared to no intervention

When center-based CR programs of different duration were compared with no intervention, both in the short-term (<6 months after completion of CR) and in the long-term (≥6 months after completion), at most limited evidence was found for the effectiveness of CR. In contrast to our expectations, there is even moderate evidence (based on one high-quality study) that controls are more active in the long-term than patients randomized to center-based CR of short duration. However, reported differences were small (12% active vs 9% active, P<0.005) and, according to the authors of this article, could be due to coincidence.[17] We conclude that it seems doubtful whether physical activity improvements are reached during center-based CR programs.

Only 2 RCTs focused on effectiveness of home-based CR compared with no intervention. Outcomes were more promising. In the short term, there was moderate evidence of effectiveness for programs of long duration (≥12 months). However, no evidence was found for long-term maintenance (≥6 months after completion) of these results. When directly comparing home-based CR with center-based CR, moderate evidence also was found that home-based programs of medium duration (4-11 months) are more effective in the long term. However, no differences were found for programs of short duration (1-3 months) or long duration (≥12 months). A possible explanation for the somewhat better results found after home-based CR may be that physical activity is better incorporated into daily routine. Two recent observational studies showed that although physical activity increased during center-based CR, patients nevertheless failed to reach recommended levels by the end of the intervention. This was primarily caused by patient non-activity on the days they did not attend CR.[44-46] These results may indicate that patients do not easily incorporate physical activity into daily life. Because there is limited research investigating the effectiveness of home-based CR, more research on this topic is needed before firm conclusions can be drawn.

Optimal duration of CR

Duration of CR programs investigated in this review ranged from 4 weeks to 4 years. It is possible that given more time and guidance, patients can further increase or better

maintain their physical activity level. However, conflicting evidence was found that patients completing a CR program of longer duration are more active shortly after the end of this program than patients who have followed a shorter program are at that time. For long-term maintenance of this higher activity level, no evidence was found. The optimal length of CR has not been studied extensively yet and might depend on the outcome of interest.[31,47] According to a previous study[47], mental health recovery is mainly achieved beyond 3 months of CR. However, physical activity and physical function improvements peak in the first 3 months of CR, and there is no further improvement after this period.[47] This finding is in line with the results of our review. We also found no clear evidence that greater improvements in physical activity are achieved when extending the length of CR to a duration beyond 3 months.

Type of CR

In addition to variation in location (home or center) and duration of CR, there is variability in type of CR. No evidence was found that a higher-training volume is more beneficial. There was also no evidence for the short-term effectiveness of performing a certain extra intervention during the standard CR period aimed at increasing physical activity levels. In the long-term there was limited evidence for the effectiveness of such an extra intervention, based on one low-quality study that studied the benefits of a behavioral self-monitoring approach as add-on therapy. Promising results were found in this study.[42]

It is essential that more research will focus on effective interventions to stimulate optimal activity levels, because it seems doubtful whether standard CR is sufficient to improve and maintain an active lifestyle. Having an active lifestyle is essential in managing cardiac risk factors. Previous research showed that patients fail to reach recommended activity levels mainly on the days they did not attend CR.[44-46] These results may indicate that patients do not easily incorporate physical activity into daily life. Therefore, we suggest that guidance on how to incorporate activity into daily life using behavioral techniques may increase physical activity on days patients do not attend CR and after completion of CR. Because the core of CR consists of exercise sessions led by physical therapists, they could play an important role in this guidance. Future research should focus on this role. Recently, 2 reviews examined what behavioral interventions aimed at increasing and maintaining physical activity are most effective for patients with cardiac conditions (both participating and not participating in CR). Behavioural interventions identified as promising were self-monitoring, goal setting, identifying barriers, and developing plans for relapse.[48,49]

Limitations

First, there are large differences between the included RCTs regarding the location, duration and type of the CR intervention and follow-up term. To minimize heterogeneity, we defined strict inclusion criteria based on international guidelines[2,6,12] to select only RCTs investigating CR programs that are currently considered to be standard. We also categorized RCTs based on location, type and duration to improve meaningful interpretation of our results. Despite this organization, categories in this review are still relatively broad. Furthermore, the amount of studies per category is low.

Second, two RCTs[19,37,38] included in this review performed 2 measurements in the long-term (≥6 months after completion) (ie, 6 months and 4.5 years[19], and 1 and 6 years[37,38]). As defined in our methods the measurement closest to 1 year after completion of CR was used in analysis. One-year was arbitrarily chosen. If we would have chosen a follow-up time closer to the 4- or 6-year follow-up, it would only have changed our conclusion for long-term effectiveness of center-based programs of medium duration as reported by Lidell and Fridlund.[19] from limited to no evidence; the conclusions based on the results of Smits et al.[37,38] remain the same.

Third, there was considerable variety in the measurement tools used to assess physical activity. In 21 of the 26 included RCTs, physical activity was self-reported using a wide variety of questionnaires or diaries. Therefore, we refrained from statistical pooling of the results. We used a best evidence synthesis, which is a next best solution and is a transparent method commonly applied when statistical pooling is not feasible or clinically viable.[15] In addition, it is known that self-report measures often fail to demonstrate adequate validity or reliability, making it difficult to draw firm conclusions about the magnitude and clinical meaning of improvements.[50-53]

Fourth, only 54% of the RCTs were considered to be of high quality according to the criteria in the Furlan list.[14] There is evidence that a threshold of less than 50% of the criteria on the Furlan list is associated with bias.[54] The quality of the RCTs was often considered as low because information was missing on avoidance of cointerventions and on concealment of treatment allocation. Furthermore, patients and care providers were not blinded in all RCTs. However, correct blinding is difficult due to the nature of the interventions.

CONCLUSIONS

Despite the fact that improving physical activity habits is an important goal of CR, it would appear that current standard center-based CR is not sufficient to improve and maintain physical activity habits. In this review it was shown that home-based programs might be more successful to improve physical activity habits. However, more research on this topic is needed before firm conclusions can be drawn. There is a wide variability in duration and type of CR programs offered. There is no clear evidence that increasing training volume, extending the duration of CR, or adding an extra intervention to CR leads to greater improvements in physical activity levels. Because having an active lifestyle is essential in managing cardiac risk factors and reducing mortality, future research should focus on finding successful interventions to achieve and maintain an active lifestyle.

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REFERENCES

1. World Health Organization *Top ten causes of death*. 2008. Factsheet 310.
2. Piepoli, M.F., U. Corra, W. Benzer, B. Bjarnason-Wehrens, et al., *Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 1-17.
3. Saczynski, J.S., D. Lessard, F.A. Spencer, J.H. Gurwitz, et al., *Declining length of stay for patients hospitalized with AMI: impact on mortality and readmissions.* Am J Med, 2010. **123**(11): p. 1007-15.
4. Giannuzzi, P., H. Saner, H. Bjornstad, P. Fioretti, et al., *Secondary prevention through cardiac rehabilitation: position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur Heart J, 2003. **24**(13): p. 1273-8.
5. Giannuzzi, P., A. Mezzani, H. Saner, H. Bjornstad, et al., *Physical activity for primary and secondary prevention. Position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur J Cardiovasc Prev Rehabil, 2003. **10**(5): p. 319-27.
6. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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.* J Cardiopulm Rehabil Prev, 2007. **27**(3): p. 121-9.
7. Warburton, D.E., P.T. Katzmarzyk, R.E. Rhodes, and R.J. Shephard, *Evidence-based guidelines for physical activity of adult Canadians.* Appl Physiol Nutr Metab, 2007. **32 Suppl 2F**: p. S17-74.
8. Taylor, R.S., A. Brown, S. Ebrahim, J. Jolliffe, et al., *Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials.* Am J Med, 2004. **116**(10): p. 682-92.
9. Lavie, C.J. and R.V. Milani, *Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention.* Prog Cardiovasc Dis, 2011. **53**(6): p. 397-403.
10. van den Berg-Emons, R.J., J.B. Bussmann, A.H. Balk, and H.J. Stam, *Factors associated with the level of movement-related everyday activity and quality of life in people with chronic heart failure.* Phys Ther, 2005. **85**(12): p. 1340-8.
11. Jolliffe J. and T. R., *Physical activity and cardiac rehabilitation: a critical review of the literature.* Coron Health Care, 1998. **2**: p. 179-86.
12. Revalidatiecommissie NVVC / NHS, *Multidisciplinaire Richtlijn Hartrevalidatie 2004 (multidisciplinaire guidelines cardiac rehabilitation)*. 2004, Den Haag: Nederlandse hartstichting.
13. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.
14. Furlan, A.D., V. Pennick, C. Bombardier, and M. van Tulder, *2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group.* Spine (Phila Pa 1976), 2009. **34**(18): p. 1929-41.
15. van Tulder, M., A. Furlan, C. Bombardier, and L. Bouter, *Updated method guidelines for systematic reviews in the cochrane collaboration back review group.* Spine (Phila Pa 1976), 2003. **28**(12): p. 1290-9.
16. Bertie, J., A. King, N. Reed, A.J. Marshall, et al., *Benefits and weaknesses of a cardiac rehabilitation programme.* J R Coll Physicians Lond, 1992. **26**(2): p. 147-51.

17. West, R.R., D.A. Jones, and A.H. Henderson, *Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction.* Heart, 2012. **98**(8): p. 637-44.
18. Engblom, E., E.K. Hietanen, H. Hamalainen, V. Kallio, et al., *Exercise habits and physical performance during comprehensive rehabilitation after coronary artery bypass surgery.* Eur Heart J, 1992. **13**(8): p. 1053-9.
19. Lidell, E. and B. Fridlund, *Long-term effects of a comprehensive rehabilitation programme after myocardial infarction.* Scand J Caring Sci, 1996. **10**(2): p. 67-74.
20. Otterstad, J.E., *Influence on lifestyle measures and five-year coronary risk by a comprehensive lifestyle intervention programme in patients with coronary heart disease.* Eur J Cardiovasc Prev Rehabil, 2003. **10**(6): p. 429-37.
21. Naser, A., J. Shahamfar, G.V. Kumar, M.K. Daga, et al., *Cardiac risk factor changes through an intensive multifactorial life style modification program in CHD patients: Results from a two year follow up.* J of Biol Sci, 2008. **8**(2): p. 248-257.
22. Oldenburg, B., A. Martin, J. Greenwood, L. Bernstein, et al., *A controlled trial of a behavioral and educational intervention following coronary artery bypass surgery.* J of Cardiopul Rehabil, 1995. **15**(1): p. 39-46.
23. Ornish, D., S.E. Brown, L.W. Scherwitz, J.H. Billings, et al., *Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial.* Lancet, 1990. **336**(8708): p. 129-33.
24. Ornish, D., L.W. Scherwitz, J.H. Billings, K. Lance Gould, et al., *Intensive lifestyle changes for reversal of coronary heart disease.* JAMA, 1998. **280**(23): p. 2001-2007.
25. Higgins, H.C., R.L. Hayes, and K.T. McKenna, *Rehabilitation outcomes following percutaneous coronary interventions (PCI).* Pat Educ Couns, 2001. **43**(3): p. 219-230.
26. Janssen, V., V. De Gucht, H.V. Exel, and S. Maes, *Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients.* Eur J Prev Cardiol, 2013. **20**(3): p. 431-41.
27. Pinto, B.M., M.G. Goldstein, G.D. Papandonatos, N. Farrell, et al., *Maintenance of exercise after phase II cardiac rehabilitation: a randomized controlled trial.* Am J Prev Med, 2011. **41**(3): p. 274-83.
28. Moore, S.M., J.M. Charvat, N.H. Gordon, F. Pashkow, et al., *Effects of a CHANGE intervention to increase exercise maintenance following cardiac events.* Ann of Behav Med, 2006. **31**(1): p. 53-62.
29. Arrigo, I., H. Brunner-Larocca, M. Lefkovits, M. Pfisterer, et al., *Comparative outcome one year after formal cardiac rehabilitation: The effects of a randomized intervention to improve exercise adherence.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(3): p. 306-311.
30. Hughes, A.R., N. Mutrie, and P.D. Macintyre, *Effect of an exercise consultation on maintenance of physical activity after completion of phase III exercise-based cardiac rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2007. **14**(1): p. 114-21.
31. Reid, R.D., W.A. Dafoe, L. Morrin, A. Mayhew, et al., *Impact of program duration and contact frequency on efficacy and cost of cardiac rehabilitation: Results of a randomized trial.* Am Heart J 2005. **149**(5): p. 862-868.
32. Mildestvedt, T., E. Meland, and E.G. Eide, *How important are individual counselling, expectancy beliefs and autonomy for the maintenance of exercise after cardiac rehabilitation?* Scand J Public Health, 2008. **36**(8): p. 832-840.
33. Carlsson, R., G. Lindberg, L. Westin, and B. Israelsson, *Influence of coronary nursing management follow up on lifestyle after acute myocardial infarction.* Heart, 1997. **77**(3): p. 256-9.
34. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: Results of the GOSPEL study, a multicenter,*

randomized controlled trial from the Italian Cardiac Rehabilitation Network. Arch of Int Med, 2008. **168**(20): p. 2194-2204.

35. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
36. Jolly, K., G.Y. Lip, R.S. Taylor, J. Raftery, et al., *The Birmingham Rehabilitation Uptake Maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation.* Heart, 2009. **95**(1): p. 36-42.
37. Smith, K.M., H.M. Arthur, R.S. McKelvie, and J. Kodis, *Differences in sustainability of exercise and health-related quality of life outcomes following home or hospital-based cardiac rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2004. **11**(4): p. 313-319.
38. Smith, K.M., R.S. McKelvie, K.E. Thorpe, and H.M. Arthur, *Six-year follow-up of a randomised controlled trial examining hospital versus home-based exercise training after coronary artery bypass graft surgery.* Heart, 2011. **97**(14): p. 1169-74.
39. Oerkild, B., M. Frederiksen, J.F. Hansen, L. Simonsen, et al., *Home-based cardiac rehabilitation is as effective as centre-based cardiac rehabilitation among elderly with coronary heart disease: results from a randomised clinical trial.* Age Ageing, 2011. **40**(1): p. 78-85.
40. Hansen, D., P. Dendale, J. Berger, S. Onkelinx, et al., *Importance of exercise training session duration in the rehabilitation of coronary artery disease patients.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(4): p. 453-459.
41. Carlson, J.J., J.A. Johnson, B.A. Franklin, and R.L. Vanderlaan, *Program participation, exercise adherence, cardiovascular outcomes, and program cost of traditional versus modified cardiac rehabilitation.* Am J Cardiol 2000. **86**(1): p. 17-23.
42. Izawa, K.P., S. Watanabe, K. Omiya, Y. Hirano, et al., *Effect of the self-monitoring approach on exercise maintenance during cardiac rehabilitation: A randomized, controlled trial.* Am J Phys Med Rehabil, 2005. **84**(5): p. 313-321.
43. Tingstrom, P.R., K. Kamwendo, and B. Bergdahl, *Effects of a problem-based learning rehabilitation programme on quality of life in patients with coronary artery disease.* Eur J Cardiovasc Nurs, 2005. **4**(4): p. 324-30.
44. Ayabe, M., P.H. Brubaker, D. Dobrosielski, H.S. Miller, et al., *The physical activity patterns of cardiac rehabilitation program participants.* J Cardiopulm Rehabil Prev, 2004. **24**(2): p. 80-6.
45. Jones, N.L., P.L. Schneider, L.A. Kaminsky, K. Riggin, et al., *An assessment of the total amount of physical activity of patients participating in a phase III cardiac rehabilitation program.* J Cardiopulm Rehabil Prev, 2007. **27**(2): p. 81-5.
46. Stevenson, T.G., K. Riggin, P.R. Nagelkirk, T.A. Hargens, et al., *Physical activity habits of cardiac patients participating in an early outpatient rehabilitation program.* J Cardiopulm Rehabil Prev, 2009. **29**(5): p. 299-303.
47. Morrin, L., S. Black, and R. Reid, *Impact of duration in a cardiac rehabilitation program on coronary risk profile and health-related quality of life outcomes.* J Cardiopulm Rehabil, 2000. **20**(2): p. 115-21.
48. Chase, J.A., *Systematic review of physical activity intervention studies after cardiac rehabilitation.* J Cardiovasc Nurs, 2011. **26**(5): p. 351-8.
49. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
50. Craig, C.L., A.L. Marshall, M. Sjostrom, A.E. Bauman, et al., *International physical activity questionnaire: 12-country reliability and validity.* Med Sci Sports Exerc, 2003. **35**(8): p. 1381-95.

51. van den Berg-Emons, R.J., A.A. L'Ortye, L.M. Buffart, C. Nieuwenhuijsen, et al., *Validation of the Physical Activity Scale for individuals with physical disabilities.* Arch Phys Med Rehabil, 2011. **92**(6): p. 923-8.
52. Richardson, M.T., B.E. Ainsworth, D.R. Jacobs, and A.S. Leon, *Validation of the Stanford 7-day recall to assess habitual physical activity.* Ann Epidemiol, 2001. **11**(2): p. 145-53.
53. Le Grande, M.R., P.C. Elliott, M.U. Worcester, B.M. Murphy, et al., *An evaluation of self-report physical activity instruments used in studies involving cardiac patients.* J Cardiopulm Rehabil Prev, 2008. **28**(6): p. 358-69.
54. van Tulder, M.W., M. Suttorp, S. Morton, L.M. Bouter, et al., *Empirical evidence of an association between internal validity and effect size in randomized controlled trials of low-back pain.* Spine (Phila Pa 1976), 2009. **34**(16): p. 1685-92.

APPENDIXES

Appendix 2A

Search strings

PubMed

Heart disease - Heart diseases [Mesh]
Rehabilitation - Rehabilitation[tiab] OR Lifestyle intervention[tiab] OR lifestyle program[tiab] OR life-style intervention[tiab] OR life-style program[tiab] OR exercise training[tiab] OR aerobic training[tiab] OR physical training[tiab] OR exercise therapy[tiab]) OR physical therapy[tiab] OR exercise intervention[tiab]
Cardiac rehabilitation - Cardiac rehabilitation[tiab] OR cardio rehabilitation[tiab] OR heart rehabilitation[tiab]
RCT - ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials[mh] OR randomly[tiab] OR trial [ti]) NOT (animals[mh] NOT humans[mh]))
Complete search string: ((Heart disease AND Rehabilitation) OR Cardiac Rehabilitation) AND RCT

Embase

Heart disease - 'Heart disease'/exp
Rehabilitation - (Rehabilitation OR ((lifestyle OR life-style OR 'life style') NEAR/2 (intervention OR program OR therapy)):ti,ab OR ((exercise OR aerobic OR physical) NEAR/2 (training OR intervention OR therapy))):ti,ab
Cardiac rehabilitation - 'Cardiac rehabilitation':ti,ab OR 'heart rehabilitation'/exp
RCT - ('randomized controlled trial':it OR 'controlled clinical trial':it OR 'clinical trial':it OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti NOT ([animals]/lim NOT [humans]/lim))
Complete search string: ((Heart disease AND Rehabilitation) OR Cardiac Rehabilitation) AND RCT

Cinahl

Heart disease -MH "Heart diseases"
Rehabilitation - SU (Rehabilitation OR "lifestyle intervention" OR "lifestyle program" OR "life-style intervention" OR "life-style program" OR "exercise training" OR "aerobic training" OR "physical training" OR "exercise therapy" OR "physical therapy" OR "exercise intervention")
Cardiac rehabilitation - SU ("Cardiac rehabilitation" OR "heart rehabilitation") OR MH "cardiac rehabilitation"
RCT - (PT "randomized controlled trial" OR PT "controlled clinical trial" OR SU (randomized OR placebo OR randomly) OR TI trial) NOT MH (animals NOT humans)

Pedro

Cardiac rehabilitation - "cardiac rehabilitation"

Appendix 2B Methodological quality scores of the 26 RCTs

		Adequate randomization?	Concealed treatment allocation?	Patient blinded?	Care provider blinded?	Outcome assessor blinded?	Drop-out rate described?	Patients analysed in allocated group?	No selective outcome reporting?	Similar at baseline?	Co interventions avoided?	Compliance acceptable?	Timing assessment similar?		
	RCT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total score**	**Percentage of max score**
Standard CR versus no intervention	Bertie 1992[16]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Higgins 2001[25]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Lidell 1996[19]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Naser 2008[21]	+	+	-	-	+/-	-	+	-	+	+/-	+/-	+	5	42%
	Oldenburg 1995[22]	+/-	+/-	-	-	+/-	+	+	+/-	+	+/-	+	+	5	42%
	Ornish 1990&1998[23,24]*	+/-	+/-	-	-	+	+	+	+	-	+/-	+	+	6	50%
	Otterstad 2003[20]	+	+/-	-	-	+/-	-	+	+	+	+/-	+	+	6	50%
	West 2012[17]	+	+/-	-	-	-	+	+	+	-	-	+	+	6	50%
	Engblom 1992[18]	+/-	+/-	-	-	+	+	+	+	+	+/-	+	+	7	58%
Two different durations of CR compared to each other	Arrigo 2008[29]	+/-	+/-	-	-	-	+	+	-	+	+/-	+/-	+	4	33%
	Hughes 2007[30]	+	+/-	-	-	+/-	-	+	+	+/-	+/-	+/-	+	4	33%
	Carlsson 1997[33]	+/-	+/-	-	-	+/-	+	+	+	+	-	+/-	+	5	42%
	Mildestvedt 2008[32]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Giannuzzi 2008[34]	+	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	6	50%
	Janssen 2012[26]	+	+/-	-	-	+/-	+	+	+	+/-	+/-	+	+	6	50%
	Pinto 2011[27]	+	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	6	50%
	Reid 2005[31]	+	+	-	-	+	+/-	+	-	-	+/-	+	+	6	50%
	Lear 2006[35]	+	+	-	-	+/-	+	+	+	+	+/-	+	+	8	67%
	Moore 2006[28]	+	+/-	-	-	+	+	+	+	+	+/-	+	+	8	67%

Appendix 2B Methodological quality scores of the 26 RCTs (*continued*)

		Adequate randomization?	Concealed treatment allocation?	Patient blinded?	Care provider blinded?	Outcome assessor blinded?	Drop-out rate described?	Patients analysed in allocated group?	No selective outcome reporting?	Similar at baseline?	Co interventions avoided?	Compliance acceptable?	Timing assessment similar?		
	RCT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total score**	**Percentage of max score**
Two different types of CR compared to each other	Carlson 2000[41]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Izawa 2005[42]	+/-	+/-	-	-	+/-	+	+	+	+	+/-	+/-	+	5	42%
	Tingström 2005[43]	+	+/-	-	-	+/-	+	+	+	+/-	+/-	+/-	+	5	42%
	Jolly 2009[36]	+	+	-	-	+/-	+	+	+/-	+	+/-	-	+	6	50%
	Oerkild 2011[39]	+	+/-	-	-	-	+	+	+	+	+/-	+/-	+	6	50%
	Hansen 2008[40]	+	+/-	-	-	-	+	+	+	+	+/-	+	+	7	58%
	Smith 2004+2011[37,38]*	+	+	-	-	+	+	+	+	+	+/-	+	+	9	75%

RCT= randomized controlled trial; CR= cardiac rehabilitation.

Appendix 2C Characteristics and outcomes of included studies

Study	Intervention	Control treatment	Outcomes	P-value	Results
Bertie et al.1992[16]	Center-based CR **total duration**: 4 weeks *n=57*	Standard care *n=53*	Pedometer daily km walked (7 days)		Between group effects intervention vs. control *mean daily km walked* baseline: 5.1 vs. 4.5
Participants: •AMI AGE *(mean)* Intervention: 52.7 Control: 52.1	*week 1-4*: 2x/week supervised group session: •exercise training (circuit training and relaxation) •reinforcement health measures (stop smoking, diet advice etc.) patients received a video recording of the exercise program and were encouraged to undertake daily exercises at home	not described		p not reported p not reported **p<0.05**	4 weeks: 6.0 , not measured for controls **4 months: 8.2 vs. 6.6**

Study	Intervention	Control treatment	Outcomes	P-value	Results
West et al. 2012[17]	Center-based CR **total duration**:6-8 weeks *n=903*	Standard care *n=910*	Self-report questionnaire for the assessment of leisure time		Between group effects intervention vs. control *% of patients exercising >100 kcal/day*
Participants: •AMI AGE *(mean +/- SD)* Intervention: 64.2 +/- 11.2 Control: 64.7 +/- 10.9	standard care (same as controls) *week 1-6/8*: (weekly or biweekly sessions, on average 20 hours in total) •exercise training (warm-up, cool-down, exercise equipment) •health education about heart, heart disease, risk factors and	explanatory booklet advice to see general practitioner routine outpatient follow-up	physical activities (Taylor et al. 1978)	n.s (p not reported) **p=0.05**	baseline: 11 vs. 13 **1 year: 9 vs. 12 (in favour of control group!)**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	treatment •counselling for recovery and advice for long-term secondary prevention				
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Engblom et al. 1992[18]	Center-based CR **total duration**: 8 months	Standard care	Self-report: questionnaire that		Between group effect intervention vs. control
	n=93	*n=78*	divides exercise habits in scale 1-3	no differences (p not reported)	*scale 1-3* data not shown
Participants:	standard care (same as controls)	*month 2,6,12:* hospital visits	(no exercise-regular exercise)		*frequency (% of patients being active 1-2x/week)*
•CABG	*2-3 weeks before surgery:*				
	information about surgery	written information	questionnaire	no differences	baseline: 2 vs. 1
AGE *(mean+/- SD)*	& recovery	(care at home, exercise,	about frequency	(p not reported)	6 months: 13 vs. 9
Intervention:		diet and medication)	and duration of		12 months: 11 vs. 10
54 +/- 6	*6-8 weeks after surgery:*		exercise periods		
Control: 54 +/- 6	•21h supervised exercise training (floor- and swimming-pool gymnastics, ergo meter cycling, swimming, ball games)				*frequency (% of patients being active >3x/week)*
				no differences (p not reported)	baseline: 20 vs. 9 6 months: 29 vs. 29 12 months: 31 vs. 25
	•5h upper extremity exercise •3h relaxation training •3h group discussion (daily life hobbies, physical exercise)				*duration exercise period (% of patients exercising 15-29min)*
	•2 group discussions (symptoms, risk factors, CHD treatment) •dietary advices			no differences (p not reported)	baseline: 4 vs. 3 6 months: 10 vs. 6 12 months: 8 vs. 6
	•group therapy sessions led by a psychologist				*duration exercise period (% of patients exercising >60 min)*
				no differences (p not reported)	baseline: 9 vs. 3 6 months: 10 vs. 10 12 months: 15 vs. 15
	8 months after surgery: 2 day refresher course (exchange				

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	experiences)				
					Within group effect intervention *scale 1-3 (% of patients who exercise regular)*
				p<0.01	**Δbaseline-6 months: data not shown**
				p<0.01	**Δbaseline-12 months: data not shown**
					control *scale 1-3 (% of patients who exercise regular)*
				p<0.001	**Δbaseline-6 months: data not shown**
				p<0.001	**Δbaseline-12 months: data not shown**
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Lidell et al. 1996[19]	Center-based CR **total duration**: 6 months	Standard care	Self-report started to exercise		Between group effects intervention vs. control
	n=53	*n=63*	after MI/ did not		*% exercising*
Participants:			start to exercise	n.s.	baseline: 28.3 vs. 27.0
	week 1-3: 1-hour visit to nurse	routine medical care	after MI	(p not reported)	
		information (cardiac		**p<0.001**	**1 year: 66.7 vs. 27.6**
•AMI	*month 2-6:*	risk factors,		p=0.112	5 years: 40.9 vs. 27.5
	•1 hour/week group physical	medication, return to			
AGE *(mean)*	exercise sessions (bicycle	work, leisure			
Intervention: 55.0	ergometer, calisthenics, fitness)	activities, medical			
Control: 57.6	•1 hour/week group meeting	planning on			
	(discuss lifestyle & health risks,	discharge)			
	psychosocial consequences of				
	MI)	routine follow-up			

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	•home-training program •phone calls •home visits •weekly forum/ support meetings (facilitate independent off-site exercise, cardiovascular risk reducing behaviours)	out-patient department & general practitioner			
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Otterstad et al. 2003[20] **Participants:** •AMI •unstable AP •PCI •CABG AGE *(mean +/- SD)* Intervention: 54 +/- 8 Control: 55 +/- 8	Center-based CR **total duration**: 2 years *n=98* *week 1-6:* •2x/week 1 hour exercise group training (warming-up, endurance training, cool-down, stretching and relaxation) •2x/week two hour group education sessions (diet,smoking cessation, physical activity counselling, risk factor management, psychosocial management, health education) •individual psychosocial support •encouraged to exercise at home *week 7-15:* •2x/week exercise group (increased intensity)	Standard care *n=99* •standard nurse-based information (CHD in general, lifestyle measures) •routine follow-up	Self-reported Food Frequency Questionnaire (items exercise habits)	n.s(p not reported) **p<0.01** **p<0.01** **p<0.01**	Between group effects intervention vs. control *% of participants who exercise more than 1 hour/week* baseline: values not reported **6 months: 93 vs. 72** **24 months: 67 vs. 46** % of participant who did not exercise at all **24 months: 7 vs. 22**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	every third month thereafter (until two years): group meetings on life style measures				
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Naser et al. 2008[21]	Center-based CR **total duration**: 2 years	Standard care	Self-report questionnaire		Between group effects intervention vs. control
	n=50	*n=50*	about physical activity level		*% of patients who exercise vigorously for 20 min 3x/week*
Participants:					
	month 1: 2 exercise sessions (60 minutes: warm-up, aerobic exercise, giving a manual with home-based exercises, information on adhering to lifestyle modification)	no intervention		p not reported	**baseline: 20 vs. 22**
•CHD				**p<0.05**	**24 months : 88 vs. 20**
AGE *(mean)* Intervention: 53.2 Control: 54.8	*month 2-6*:1 exercise sessions/ month *month 4,9,10,11, 14,15,17,18*: telephone follow-up (assessment program progress, spotting new symptoms, overall consultation lifestyle behaviours) *month 8,10,12,13,16*: lifestyle and risk factor counselling (consultation risk factors based on risk factor profile: stress, weight, alcohol, diet)				
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Oldenburg et al. 1995[22]	Center-based CR **total duration**: 1 year	Standard care	Self-report inventory adapted		Between group effects intervention vs. control
	n=43	*n=43*	from the National	**time effect:**	**Δ baseline-4 months: no**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

			Heart Foundation 1986 Risk Factor Prevalence Survey inventory adapted from the National Heart Foundation's	**p<0.001** group effect: p not reported interaction: p not reported **time effect: p<0.001** group effect: p not reported Interaction: p not reported	**values reported** **Δ baseline-12 months: no values reported**
Participants: •CABG AGE *(mean +/- SD)* Intervention: 60 +/- 7.1 Control: 59 +/- 8.1	*week 1-6*: weekly meeting •behavioural education (goal setting, skill training, feedback, reinforcement, modelling, self-monitoring, social support tailored at personal risk factors) •supervised exercise (stretching, different activities, cycle ergometer, walking) *month 8+12*: 3 hour booster sessions on CHD risk and quality of life	standard medical and nursing care			

Study	Intervention	Control treatment	Outcomes	P-value	Results
Ornish et al. 1990[23] & Ornish et al. 1998[24]*	Home-based CR **total duration**: 1 year *n=28* *week 1:* residential stay with lifestyle education	Standard care *n=20* general advise from personal physician	Self-report questionnaire about type, frequency and duration of exercise	p not reported	Between group effects intervention vs. control *times/day exercise (mean+/- SD)* baseline: 0.26 +/-0.37 vs. 0.35 +/- 0.39
Participants: •CHD AGE *(mean +/- SD)* Intervention: 56.1 +/- 7.5 Control: 59.8 +/- 9.1	*year0-1:* intensive lifestyle program: •low fat vegetarian diet •1 hour/day stress management techniques •3hour/week: prescribed moderate aerobic exercise •2x/week: 4 hour support meeting with group lifestyle			p not reported **p=0.0008** p=0.64* p not reported	1 year: 0.69 +/- 0.20 vs. 0.39 +/- 0.37 **Δ baseline-1 year: values not reported** Δ baseline-5 years: values not reported *min/day exercise (mean +/- SD)* baseline:11.0+/-17.7 vs. 18.4

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	discussions (strategies of adherence, communication skills, expression of feelings)			p not reported **p=0.0004** p=0.50* *based on a subsample n=20 (intervention) and n=15 (control)	+/-27.7 1 year: 38.1 +/- 17.4 vs. 20.6 +/- 27.7 **Δ baseline-1 year: values not reported** Δ baseline-5 years: values not reported
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Higgins et al. 2001[25] **Participants:** •PCI AGE *(mean (range))* Intervention: 48 (31-63) Control: 47 (26-63)	Home-based CR **total duration**: 1 year *n=54* standard care (same as controls) individualized plan for goal-setting (e.g. moderate-intensity walking, vocational counselling) *month 0-2*: • 3x home visit (reinforce CHD knowledge, include spouses, monitor exercise, and diet, reinforce risk factor modification strategies) *month 0-12*: •monthly telephone calls (guidance and support to adhere to program)	Standard care *n=51* educational session pre-PCI (information PCI procedure) education sessions post-PCI (information pathology, risk factors,instruction wound and medication management) 3-monthly telephone follow-up (CHD information focused)	Self-report frequency & duration of participation in activities in last three months (walking, active sporting etc.) patients were classified as exercising(>20min once per week) or sedentary	**p<0.01** p not reported **p<0.001** **p<0.001** n.s. (p not reported) n.s. p not reported)	Between group effects intervention vs. control *% currently exercising* **Δ baseline-2 months: data not shown** Δ baseline-12 months: data not shown Within-group effect intervention *% currently exercising* **Δbaseline-2 months: 35 to 88** **Δbaseline-12 months:35 to 72** control *% currently exercising* Δ baseline-2 months: 53 to 59 Δbaseline-12 months: 53 to 61

Appendix 2C Characteristics and outcomes of included studies (*continued*)

Study	Intervention	Control treatment	Outcomes	P-value	Results
Janssen et al. 2012[26]	Center-based CR **total duration**: 8 months *n=112*	Center-based CR **total duration**: 3 months *n=98*	Pedometer (Yamax, 7 days)		Between group effects intervention vs. control *nr steps/day (mean+/- SD)*
Participants: •CHD •AMI AGE *(mean+/- SD)* Intervention: 56.6 +/- 9.2 Control: 58.8 +/- 9.3	*month 1-3*: same as controls *week 1:*1 hour personal motivation interviewing session (goal setting) *week 3,5,7,9,11,15,19*: 7x 2 hour group session in week (self-regulation skills for goals, self-monitoring, developing action plans, obtain feedback, problem- solving strategies)	*month 1-3*: •3x/week exercise training (cycling and weight training) •4x 2 hour psycho-educational sessions (pathophysiology, healthy eating, exercise, psychological adjustment) •2 hour practical session on progressive relaxation •optional consultation (weight reduction, smoking cessation, stress reduction and management) *month 3*: • 1 hour personal interview (goal setting)		p not reported p not reported **p=0.001**	month 3: 8093 +/- 3508 vs. 8156+/- 4280 month 9: 9235 +/- 3852 vs. 7634 +/- 3844 *nr steps/day (mean(95% CI))* **Δ 3-9 months: 1142 (338 to 1947) vs. -522 (-1039 to -545)**

Study	Intervention	Control treatment	Outcomes	P-value	Results
Pinto et al. 2011[27]	Center-based CR **total duration**:9 months *n=64*	Center-based CR **total duration**:3 months *n=66*	Self-report 7-day activity recall: min moderate		Between group effects intervention vs. control *min/week moderate intensity exercise (mean +/-SD)*
Participants: • AMI • stable AP • CABG	*week 1-12*: same as controls *month 3-9*: • activity counselling phone	*week 1-12*: •3x 90 min/week exercise training •education on nutrition,	intensity exercise Accelerometer (Biotrainer-pro),	p=0.25	3 months : 233 +/- 199 vs. 199 +/- 138 *differences between groups*

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	calls, weekly over first 2	medication use, risk factors	exercise counts		*min/week moderate intensity*
AGE *(mean+/- SD)*	months, biweekly for next 2		(3 days)		*exercise (standardized values*
Intervention: 62.9	months, monthly for last 2	*month 3-9:*			*+/- SE)*
+/- 9.3	months (promote adherence,	• phone calls, weekly over		p=0.26	6 months: 0.19 +/-0.16
Control: 64.3	feedback on pedometer home	first 2 months, biweekly for		**p=0.008**	**12 months: 0.47 +/- 0.08**
	log)	next 2 months, monthly			
+/- 10.0	• feedback letter at 4,5,6,7,8	last 2 months (general			*METs (kcal/week) (mean +/-*
	months (exercise progress,	health)			*SD)*
				p=0.42	3 months : 234 +/- 13 vs. 233
					+/- 11
					differences between groups
					METs (standardized values
					+/- SE)
				p=0.08	6 months: 0.23 +/- 0.13
				p=0.003	**12 months: 0.43 +/- 0.14**
					differences between groups
					in probability to meet
					guidelines of >150 min
					activity/week (AOR (95% CI))
				p=0.31	6 months: 1.50 (0.69, 3.26)
				p=0.09	12 months: 2.23 (0.89, 5.60)

Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Moore	Center-based CR	Center-based CR	Self-report:		Between group effects
et al. 2006[28]	**total duration**: 5 months	**total duration**: 3 months	exercise amount,		intervention vs. control
	n=119	*n=131*	frequency &		*monthly hours of exercise*
Participants:			intensity over		*(mean+/- SD)*
	week 1-12: same as controls	*week 1-12* (several	study period	n.s.	month 1: 9.5+/- 7.4 vs. 8.5 +/-
		times/week):		(p not reported)	8.9
•AMI	*week 10-12:*	•medical evaluation		n.s.	month 12: 7.0 +/- 7.2 vs. 6.4
•CABG	•3x 1.5 hours group counselling	•prescribed exercise		(p not reported)	+/- 9.2

Appendix 2C Characteristics and outcomes of included studies (*continued*)

•PCI AGE *(mean+/- SD)* Intervention: 62.5 +/- 11.4 Control: 62.3 +/- 10.8	and behaviour modification sessions (self-efficacy enhancement, problem solving skills, relapse prevention, exercise maintenance) *month 4 & 5:* •2x 1.5 hours group counselling and behaviour modification sessions	•cardiac risk factor modification counselling (diet modification, stress reduction)		n.s. (p not reported) n.s. p not reported)	*monthly exercise sessions (mean+/- SD)* month 1: 11.5 +/- 7.8 vs. 10.6 +/- 9.2 month 12: 7.6 +/- 7.0 vs. 7.1 +/- 8.2

Study	Intervention	Control treatment	Outcomes	P-value	Results
Arrigo et al. 2008[29] **Participants:** • non-fatal cardiac event • PCI • CABG • other reasons for referral to CR AGE *(mean+/- SD)* Intervention: 61 +/- 10 Control: 61 +/- 9	Center-based CR **total duration**:1 year *n=129* *month 1-3*: same as controls *month 3,6,9,12 after completion of CR:* •group exercise sessions (diary sheets discussed at individual and group level)	Center-based CR **total duration**:1-3 months *n= 132* *month 1-3*: *1 month* inpatient CR ***OR*** *3 months* outpatient CR mandatory content: •medical evaluation •controlled physical activity •cardiac risk factor modification • instructions for a heart-healthy lifestyle • stress management • psycho-social support & practical advice for social and professional reintegration	Self-report diary sheets, being active was defined as increasing pulse rate and breathing >3 times per week for >30 min	**p<0.0005** **p=1.48E-07** **p= 2.41E-05**	Between group effects (patients that participated in inpatient & outpatient CR together) intervention vs. control *% physical active* **1 year: 73 vs. 40** Between group effects (only patient that participated in inpatient CR)* intervention vs. control *% physical active* **1 year: 88 vs. 38** Between group effects (only patient that participated in) outpatient CR)** intervention vs. control *% physical active* **1 year: 67 vs. 41**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

*based on intervention *n=36*, controls *n=49*
**based on intervention *n=69*, controls *n=74*

Study	Intervention	Control treatment	Outcomes	P-value	Results
Hughes et al. 2007[30]	Center-based CR **total duration**: 1 year *n=35*	Center-based CR **total duration**: 3 months *n=35*	Self-report 7-day activity recall: min moderate, hard & very hard activity		Between group effects intervention vs. control *min/week total activity (median (98% CI))* **difference between groups: 130 (-295,-20)**
Participants: • AMI • CABG • PCI • unstable AP AGE *(mean+/- SD)* Intervention: 59.0 +/- 9.7 Control: 60.9 +/- 11.3	*week 1-12*: same as controls *month 3 & 9*: •phone call (exercise consultation: assessing activity status, exploring pros and cons, problem-solving, social support, exploring activity options, setting goals, relapse prevention) *month 6 & 12*: •support phone call (barriers, achieving goals, remaining active)	*week 1-12*: •2x 60 min/week exercise training •medical evaluation •education •psychological support •exercise leaflet *month 6 & 12:* •phone call unrelated to subject	Accelerometer (MTI) activity counts (7 days)	**significant** **p not reported** n.s. (p not reported) n.s. (p not reported) **significant** **p not reported** **significant** **p not reported** n.s. (p not reported)	Within group effects intervention *min/week total activity (mean (98% CI))* Δ 3-9 months: 47 (-43,191) Δ 9-15 months: 23 (-63, 154) controls *min/week total activity (mean (98% CI))* **Δ 3-9 months: -115 (-228, -28)** **Δ 9-15 months: -63(-126, -5)** Within group effects intervention *total activity counts (98% CI)* Δ 3-9 months: -381927, 504719

Appendix 2C Characteristics and outcomes of included studies (*continued*)

				n.s. (p not reported)	Δ 3-15 months: -381927, 504719
					Within group effects controls *total activity counts (98% CI)*
				n.s. (p not reported)	Δ 3-9 months: 47 (-43,191), 5.2% decrease
				n.s. (p not reported)	Δ 3-15 months: 23 (-63, 154), 8% decrease
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Reid et al. 2005[31]	Center-based CR **total duration**:1 year *n=196*	Center-based CR **total duration**: 3 months *n=196*	Self-report 7-day activity recall: kcal/week		Between group effects intervention vs. control *kcal/week (mean +/- SD)*
Participants:				program effect:	baseline: 1940 +/- 2001 vs. 2129
	months 1-12:	*months 1-3:*		p=0.53	+/-2226
•AMI	•2x3 hour education (behaviour	•2x3 hour education		**time effect:**	12 months: 2419 +/- 3127 vs.
•CABG	change, nutrition, psychosocial	(behaviour change,		**p<0.01**	
•PCI	and vocational recovery) (week	nutrition, psychosocial and		interaction:	2441 +/-2446
•AP	1-2)	vocational recovery, week		p=0.92	24 months: 2484 +/- 2248 vs.
	•2 case manager visits (week	1-2)			2647 +/-2533
	2+26)	•2 case manager visits			
AGE *(mean +/- SD)*	•telephone contact (week 8)	(week 2+8)			
Intervention:	•physician visit (week 7)	•telephone contact (week			
58+/- 10	•27 exercise classes	4)			
Control: 58+/-	•home exercise prescription	•physician visit (week 7)			
11	•optional program (smoking	•27 exercise classes			
	cessation, stress management,	•home exercise			
	vocational-, psychosocial- or	prescription			
	nutrition counselling)	•optional program			
		(smoking cessation, stress			
		management, vocational-,			
		psychosocial- or nutrition			

Appendix 2C Characteristics and outcomes of included studies (*continued*)

		counselling)			
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Carlsson et al. 1997[33]	Center-based CR **total duration**: 1 year *n=87*	Center-based CR **total duration**: 5 weeks *n=81*	Self-report questionnaire that assessed level of physical activity in 5 levels: sedentary-vigorous physical training		Between group effect intervention vs. control *% regular active* (minimal 30 min/day walking or biking or minimal 1x/week sport activities) baseline: 69 vs. 78 1 year: 77 vs. 70
Participants: •AMI AGE *(mean)* Intervention: 62.2 Control: 61.9	*week 1-5*: same as controls *months 2-4*: 2-3x40min/week exercise training sessions (cycling, jogging) *months 2,3,4,5,6,9,12*: group+ individual lifestyle education (smoking cessation, diet, physical activity)	*week 1-5:* •visits to nurse and cardiologist •supervised exercise (45min easy interval training) •education on risk factors+ lifestyle (smoking cessation, diet, physical activity) *months 2-12*: general visits to general practitioner		p not reported p not reported p= 0.43 p=0.50	*%stopped physical training After 1 year* 12 vs. 17 *% started physical training after 1 year* 78 vs. 67

Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Mildestvedt et al. 2008[32]	Center-based CR **total duration:** 2 years *n=90*	Center-based CR **total duration:** 4 weeks *n=86*	Self-report four question to determine exercise composite score (1- 5, higher better) & exercise intensity (1-4,higher more intense)		Between group effects intervention vs. control *exercise composite score* **baseline: 3.2 +/- 0.9 vs. 3.3 +/- 0.8** 6 months: 3.6 +/- 0.7 vs. 3.5 +/- 0.7 24 months: 3.4 +/- 0.8 vs. 3.4 +/- 0.8
Participants: •CHD AGE *(mean +/- SD)* Intervention: 55.6 +/- 8.5 Control: 56.4	*week 1-4:* same as controls individualized self-efficacy and autonomy supportive intervention focussing on personal goals •*week 1-4*: 2 x 1 hour individual sessions	*week 1-4:* •group-based daily exercise sessions •information about benefits exercise		**time effect: p<0.001** group effect: p<0.79 interaction: p=0.66 **time effect:**	*exercise intensity* **baseline: 2.7 +/- 0.9 vs.2.6 +/-**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

+/- 10.3	•*month 6 +24*: follow-up telephone calls			**p<0.001** group effect: p=0.60 Interaction: p=0.67	**0.9** 6 months: 3.1 +/- 0.9 vs. 3.0 +/- 0.9 24 months: 3.1 +/- 1.0 vs. 3.0 +/- 1.0
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Giannuzzi et al. 2008[34] **Participants:** •AMI AGE *(mean +/- SD)* Intervention: 57.8 +/- 9.1 Control: 58.0 +/- 9.3	Center-based CR **total duration**: 3 years *n=1620* *week 1-3/6:* same as controls *month 2-7*: monthly one-to-one support sessions (described below) *months 7-36*: 1-to-1 support sessions every 6 months 1-to-1 support session: •30 min aerobic exercise •1 hour lifestyle and risk factor counselling •reinforcement preventive interventions •booklet lifestyle modifications	Center-based CR **total duration**: 6 months *n=1621* *week 1-3/6:* •exercise sessions •lifestyle and risk factor management •optimization medical therapy *month 6, 12, 24, 36 and then yearly till end study*: follow-up visits	Self-report questionnaire, score: 3 (most unfit)-12 (≥ 3h/week of exercise)	p=0.06 **p=0.005** p=0.20 **p=0.01** **p=0.01** **p<0.01** **p=0.01**	Between group effects intervention vs. control *physical activity score , range 3-12 (mean +/- SD)* baseline: 6.7 +/- 2.5 vs. 6.6 +/- 2.4 **6 months: 7.5 vs. 7.1** 12 months: 7.5 vs. 7.2 **24 months: 7.5 vs. 7.1** **36 months: 7.5 vs. 7.1** **Δ baseline-6 months: 24.3% vs. 18.2%, difference 6.1%** **Δ baseline-36 months: 23.8% vs. 18.8%, difference 5%**
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Lear et al. 2006[35] **Participants:** •CHD	Center-based CR **total duration**: 4 years *n=151* *week 1-16:* same as controls	Center-based CR **total duration**: 4 months *n=151* *week 1-16:* •supervised exercise	Self-report: Minnesota Leisure Time Physical Activity Questionnaire	p=0.574	Between group effects intervention vs. control *kcal/week (mean +/- SD)* 48 months: 2099 +/- 2074 vs. 2349 +/- 2018

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	year 1:	(2x/week)			Within group effects
	•6 cardiac rehabilitation	•regular nurse and dietary			intervention
AGE *(mean +/- SD)*	exercise sessions	reviews			*kcal/week (mean +/- SD)*
Intervention: 64.8	•6 telephone sessions (assess			**p<0.001**	**Δ baseline-48 months: 2907**
+/- 8.8	progress, provide counselling,				**+/- 1812 to 2099 +/- 2074**
Control: 63.4 +/-	identify symptoms, answer				
10.2	questions)				Within group effects
	•3 lifestyle & risk factor				controls
	counselling sessions				*kcal/week (mean +/- SD)*
				p<0.01	**Δ baseline-48 months: 3009**
	year 2:				**+/- 2204 to 2349 +/- 2018**
	•4 telephone sessions				
	•2 lifestyle & risk factor				
	counselling sessions				
	year 3 & year 4: same as year 2				

Study	Intervention	Control treatment	Outcomes	P-value	Results
Jolly	Center-based CR	Home-based CR	Self-report		Between group effects
et al. 2009[36]	**total duration:** 9-12 weeks	**total duration:** 3 months	Godin		intervention vs. control
	(depending on hospital)		questionnaire		*physical activity score*
Participants:	*n=262*	*n=263*	(higher score		*(mean+/- SD)*
			means more	n.s	baseline: 6.08 +/- 3.80 vs. 6.24
•AMI	standard CR provided by 4	*week 1-6*: manual for	active)	(p not reported)	+/- 3.75
•PCI	different hospitals, exact	home-based program		p=0.4	12 months:6.83+/- 4.1(median
•CABG	programs differed but all	(education, home- based			7.0, IQR 3.9) vs. 7.11 +/- 4.0
	included:	exercise program, a			(median 7.0, IQR 3.9)
AGE *(mean +/- SD)*	•supervised exercise sessions	tape-based relaxation and			
Intervention: 60.3	•relaxation	stress management			*hours of self-reported activity*
+/- 10.5	•lifestyle counselling	program			*weighted for intensity*
Control: 61.8		*week 1,6,12*:home-visit		p=0.3	12 months: 15.91 +/- 16.7
+/- 11.0		nurse			(median 10.5, IQR 5,20.6) vs.
		week 3: telephone contact			19.24 +/- 20.8 (median 12, IQR
		subjects home visits and			5.5,27)

Appendix 2C Characteristics and outcomes of included studies (*continued*)

		telephone calls: •content of the manual •goal setting for smoking, diet and exercise			
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Smith et al. 2004[37] & Smith et al. 2011[38]*	Center-based CR **total duration**: 6 months *n=122* *months 1-6*:	Home-based CR **total duration:** 6 months *n=120* *months 1-6*:	Self-report PASE (Physical Activity Scale for the Elderly)		Between group effects intervention vs. control *mean score PASE +/- SD, median (range)*
Participants: •CABG AGE *(mean +/- SD)* Intervention: 62.5 +/- 8.8 Control: 62.2 +/- 9.4	•3x/week 1 hour group exercise sessions (aerobic exercise: cycle ergometer, arm cycle ergometer, treadmill, track walking and stair climbing) •advise to train 5x/week and keep an exercise log (monthly reviewed)	•baseline+ month 3: 1 hour individual exercise session+ consultation (same program as the group sessions for center-based group) •advise to train 5x/week+ keep an exercise log (discussed on phone every 2 weeks from month 1-6) •optional program offered by dietician, nurse, psychologist	0 (very limited physical exercise)-360 (very high level physical exercise)	**p=0.05** **P≤0.001** **p≤0.01** **p=0.042**	**18 months: 170.0+/- 89.2 vs. 232.6 +/- 99.4** **18 months*: 171.8 +/- 87.9 vs. 228.2+/-102.1** **based on a sub sample still participating in the study at the 6-year follow op* **6 years: 139.7 +/-66.5 vs. 166.7 +/- 90.2** **Δ 18 months-6 years:-26vs.-19**
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Oerkild et al. 2011[39] **Participants:** •AMI •PCI •CABG	Center-based CR **total duration**: 1 year *n=39* *week 1-6*: •2x60min/week supervised group exercise training (encouraged to exercise at	Home-based CR **total duration**: 1 year *n=36* *week 1-6:* •2 home-visits & 1 phone call to develop a training program aimed at 6x30	Self-report four levels (no details reported)	 n.s. (p not reported) n.s. (p not reported)	Between group effects intervention vs. control *% of patients having an active lifestyle* baseline: 52.6 vs. 60.0 Δ baseline-3 months: 23.5 vs. 14.7, difference 8.8

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	home)	min/week exercise		n.s.	Δ baseline-12 months: 0 vs. -13.3, difference 13.3
AGE *(mean +/- SD)*	•6 life style education sessions,	(recommended was brisk		(p not reported)	
Intervention: 74.4	2 dietary counselling,	walking and stationary			
+/- 5.8	3 cooking classes,	bicycling)			Within group effects
Control: 74.7+/-	smoking cessation counselling	•optional dietary			intervention
5.9		counselling and smoking			*% of patients having an active lifestyle*
	baseline, month 3,6 &12: risk	cessation sessions			
	factor and medical adjustment			**p<0.05**	**Δ baseline-3 months: 23.5**
	counselling	*baseline, month 3,6 &12:*		n.s.	Δ baseline-12 months: 0
		risk factor and medical		(p not reported)	
		adjustment counselling			
					Within group effects
		month 4+5: telephone call			control
		for questions			*% of patients having an active lifestyle*
				n.s.	Δ baseline-3 months: 14.7
				(p not reported)	
				n.s.	Δ baseline-12 months: -13.3
				(p not reported)	

Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Hansen	Center-based CR	Center-based CR	Self-report		Between group effects
et al. 2008[40]	(low training volume)	(high training volume)	International		intervention vs. control
	total duration: 3 months	**total duration**: 3 months	Physical Activity		*min/week moderate intensity*
Participants:	*n=61*	*n=58*	Questionnaire		*physical activity (mean+/-SD)*
				p=0.36	18 months: 107+/-204 vs.
•CHD	*week 1-7:*	*week 1-7:*			77+/-131
	• 3x 40min/week endurance	• 3x 60min/week			
AGE *(mean +/- SD)*	training (treadmill, cycle	endurance training (same			*min/week vigorous intensity*
Intervention: 63	ergometer,arm cranking device)	program as			*physical activity (mean+/-SD)*
+/- 8	• educational sessions about	intervention group)		p=0.96	18 months: 30 +/-96 vs. 29 +/-108
Control: 66 +/- 9	healthy diet and cardiovascular	• educational sessions			
	disease risk factor management	(same as intervention			
		group)			*total min/week physical*
	week 8-12: possibility to prolong				*activity (mean+/-SD)*

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	exercise sessions	*week 8-12*: possibility to prolong exercise sessions		p=0.40	18 months: 137 +/- 226 vs. 106 +/- 158
					% of patients achieving minimal 150 min exercise/week
				p=0.66	18 months: 29.5 vs. 25.8
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**
Carlson et al. 2000[41] **Participants:** •cardiovascular surgery or event AGE *(mean +/- SD)* Intervention:59 +/- 9 Control: 59+/- 10	Center-based CR (modified protocol, based on Bandura's self-efficacy theory) **total duration**: 6 months *n=42* *month 1:* same as controls *months 2-6:* •gradually weaned from supervised exercise & ECG (independent exercise stimulated) •education (health behaviours, overcoming barriers to independent exercise and diet) •weekly forum/ support meetings (facilitate independent off-site exercise, cardiovascular risk reducing behaviours)	Center-based CR (traditional protocol) **total duration**: 6 months *n=38* *month 1*: •3x/week exercise sessions with ECG monitoring (aerobic exercises) •3 group education sessions (diet and cardiovascular risk factors) *months 2-3*: same month 1 *months 4-6*: encouraged to follow a phase 3 maintenance program (3x/week exercise without ECG monitoring)	Self-report weekly exercise log books for frequency of exercise	n.s. (p not reported) n.s. (p not reported) **p=0.03** n.s. (p not reported)	Between group effect intervention vs. control *weekly average amount of exercise sessions (≥30min aerobic activity/day) +/- SD* week 1-6:4.6+/-1.3 vs. 4.9+/-1.3 week7-12:4.4+/-1.4vs.4.8+/-1.4 **weeks 13-25:3.4+/-1.6 vs.4.2+/-1.5** 6 month average 3.8 +/- 1.3 vs. 4.3 +/-1.2
Study	**Intervention**	**Control treatment**	**Outcomes**	**P-value**	**Results**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

Izawa et al. 2005[42]	Center-based CR + self-monitoring approach **total duration**: 6 months *n=24*	Center-based CR (traditional protocol) **total duration**: 6 months *n=21*	Pedometer (Kenz Life recorder) (7 days)		Between group effects intervention vs. control *mean nr of steps+/- SD* baseline: 6564.9 +/- 1114.6 vs. 6282.6 +/- 1985.9 **12 months: 10458.7 +/- 3310.1 vs. 6922.5 +/- 3192.9** **Δ baseline-12 months: data not shown**
Participants: • MI AGE *(mean +/- SD)* Intervention: 63.9 +/- 9.7 Control: 64.5 +/- 10.1	comprehensive CR (same as controls) self-monitoring approach (based on Bandura's self-efficacy theory) *month 1-6*: • self-monitoring physical activity (pedometer), blood pressure and heart rate • goal setting • verbal and written feedback	*end of acute phase:* • diet & medication instructions • individual education sessions (diet, medication, risk factors, smoking cessation) • low intensity treadmill walking with upper and lower limb exercises and body stretches *start recovery phase-6 months:* 2x 60min/week supervised combined aerobic and resistance exercise (treadmill walking, upper+ lower limb exercises, stretches)		n.s. (p not reported) **significant (p not reported)** **p<0.001**	

Study	Intervention	Control treatment	Outcomes	P-value	Results
Tingström et al. 2005[43]	Center-based CR (+ problem based learning program) **total duration**: 1 year *n=104*	Center-based CR (traditional protocol) **total duration**: 1 year *n=103*	Self-report interview about amount and intensity of exercise over last 3-4 weeks	**p-values are based on mean Δbaseline-12 months**	Between group effects intervention vs. control *interview* *not warm and out of breath (mean score min/day +/- SD)* baseline: 18 +/- 38 vs. .33 +/- 55
Participants: • AMI • PCI • CABG	*month 1-12:* •same program as controls	*month 1-12:* • visits to rehabilitation	Activity monitor	**p=0.003**	**12 months: 13 +/- 40 vs. 6 +/-**

Appendix 2C Characteristics and outcomes of included studies (*continued*)

	•13x1.5 hour group meetings (problem based learning: symptoms, psychological reactions, psychosocial factors, risk factors, goal setting etc.)	nurse and cardiologist • weekly 1-hour group exercise • individual counselling (smoking cessation, diet)	counts/minute (8 days)		**20**
AGE *(mean +/- SD)* Intervention: 59.1 +/- 7.1 Control: 59.4 +/- 7.2				p=0.106	*warm and out of breath (mean score min/day +/- SD)* baseline: 57 +/- 64 vs .48+/- 66 12 months: 66 +/- 71 vs. 80 +/- 120
				p=0.916	*total activity reported (mean score min/day +/- SD)* baseline: 75 +/- 76 vs. 81 +/- 73 12 months: 79 +/- 73vs 86 +/- 120
				p-values based on mean 12 months values	Between group effects intervention vs. control *activity monitor* *no activity (mean min+/-SD)*
				p=0.672	12 months: 650 +/- 112 vs. 644 +/- 78 *sitting standing (mean min +/- SD)*
				p=0.421	12 months: 470+/-95 vs. 459+/-80 *low activity (mean min +/- SD)*
				p=0.165	12 months:262+/-69 vs.262+/- 1 *moderate activity (mean minutes +/- SD)*
				p =0.131	12 months:44 +/-25 vs.50+/-30 *vigorous activity (mean min +/-SD)*
				p=0.050	12 months:14+/- 16vs.10+/- 10 *continued periods of >10min*

Appendix 2C Characteristics and outcomes of included studies (*continued*)

		at moderate and vigorous levels (mean min +/- SD)
	p=0.481	12 months: 0.8 +/-0.9vs.0.7+/-0.7*counts per min (mean+/-SD)*
	p=0.979	12 months: 330 +/- 136 vs. 330 +/- 134
	p-values are based on mean Δbaseline-12 months	*activity monitor (based on subsample of 34 intervention, 35 in control that did wear activity monitor at both baseline and 12 months*
		no activity(mean minutes+/SD)
	p=0.478	baseline:646+/-102vs.669+/-78 12 months:653+/-104 vs.653+/-78
		sitting standing(mean minutes +/-SD)
	p=0.216	baseline: 486+/-77vs.470 +/-99 12 months: 502 +/- 91 vs. 456 +/-80
		low activity (mean minutes +/-SD)
	p=0.548	baseline:251+/- 66 vs.255+/-60 12 months: 262+/-69 vs.277+/-71
		moderate activity (mean minutes+/- SD)
	p=0.458	baseline: 45 +/- 33 vs.40 +/- 22 12 months:47 +/-29 vs.48+/-27
		vigorous activity (mean min +/-SD)
	p=0.478	baseline: 11 +/- 13 vs. 8 +/- 10 12 months:15 +/- 15vs.10+/-12

Appendix 2C Characteristics and outcomes of included studies (*continued*)

		continued periods of >10min at moderate and vigorous levels (mean min +/-SD) baseline:0.8 +/- 0.8 vs0.7+/-0.7
	p=0.908	12 months:0.8 +/- 1.0 vs. 0.7 +/- 0.7
		counts per minute (mean+/SD) baseline: 306 +/- 134 vs. 291 +/- 131
	p=0.816	12 months: 331 +/- 144 vs. 323 +/- 128

CR= Cardiac Rehabilitation; AMI= Acute Myocardial Infarction; PCI= Percutaneous Coronary Intervention; CHD= Coronary Heart Disease; CABG= Coronary Artery Bypass Grafting; AP= Angina Pectoris.

**multiple publications on data of the same RCT and population are extracted and presented as originating from a single RCT.*

Chapter 3

Changes in physical activity and sedentary behavior during cardiac rehabilitation

Nienke ter Hoeve
Madoka Sunamura
Myrna E. van Geffen
Malou H. Fanchamps
Herwin L. Horemans
Johannes B. Bussmann
Henk J. Stam
Ron T. van Domburg
Rita J. G. van den Berg-Emons

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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+). 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 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.[32] The program was terminated when individual physical and psychosocial goals were met, as evaluated by an exercise stress test and consultation by a multi-

disciplinary 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 3.1. 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 3.1). ActiGraph[a] wear time increased between T0 and T1 and between T0 and T2 (Table 3.2). 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.

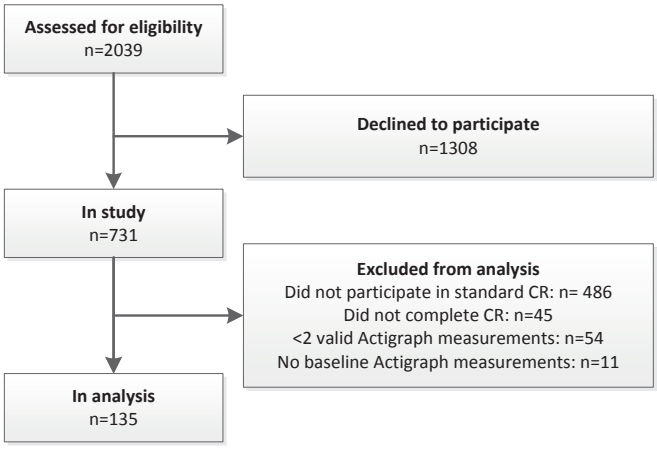

Figure 3.1 Flow diagram of participants
CR= cardiac rehabilitation

Table 3.1 Baseline characteristics of the study population (n=135)

Characteristics	
Men , %	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

Changes in physical behavior during cardiac rehabilitation

Table 3.2 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 3.2).

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).

Table 3.2 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

MVPA= moderate-to-vigorous physical activity; SB= sedentary behavior.
** t-tests.*

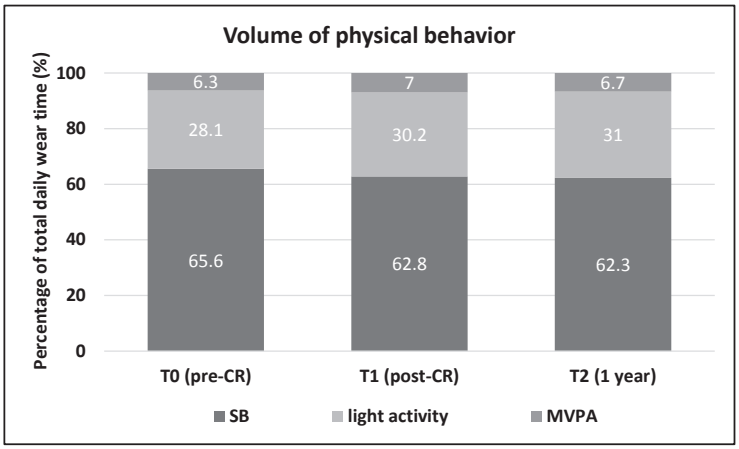

Figure 3.2 Percentage of waking hours spent in SB, light activities, and MVPA
CR= cardiac rehabilitation; SB= sedentary behavior; MVPA= moderate-to-vigorous physical activity.

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

Table 3.3 Distribution of 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***
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

MVPA= moderate-to-vigorous physical activity; SB= sedentary behavior.

** 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.

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 differ-

ence=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.

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 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+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.

REFERENCES

1. Bussmann, J.B. and R.J. van den Berg-Emons, *To total amount of activity..... and beyond: perspectives on measuring physical behavior.* Front Psychol, 2013. **4**: p. 463.
2. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.
3. Wilmot, E.G., C.L. Edwardson, F.A. Achana, M.J. Davies, et al., *Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis.* Diabetologia, 2012. **55**(11): p. 2895-905.
4. Biswas, A., P.I. Oh, G.E. Faulkner, R.R. Bajaj, et al., *Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis.* Ann Intern Med, 2015. **162**(2): p. 123-32.
5. Chau, J.Y., A.C. Grunseit, T. Chey, E. Stamatakis, et al., *Daily sitting time and all-cause mortality: a meta-analysis.* Plos One, 2013. **8**(11): p. e80000.
6. World Health Organization, *Global Recommendations on Physical Activity for Health.* 2010.
7. Healy, G.N., K. Wijndaele, D.W. Dunstan, J.E. Shaw, et al., *Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).* Diabetes Care, 2008. **31**(2): p. 369-71.
8. Strath, S.J., R.G. Holleman, D.L. Ronis, A.M. Swartz, et al., *Objective physical activity accumulation in bouts and nonbouts and relation to markers of obesity in US adults.* Prev Chronic Dis, 2008. **5**(4): p. A131.
9. Murphy, M., A. Nevill, C. Neville, S. Biddle, et al., *Accumulating brisk walking for fitness, cardiovascular risk, and psychological health.* Med Sci Sports Exerc, 2002. **34**(9): p. 1468-74.
10. Healy, G.N., D.W. Dunstan, J. Salmon, E. Cerin, et al., *Breaks in sedentary time: beneficial associations with metabolic risk.* Diabetes Care, 2008. **31**(4): p. 661-6.
11. Kim, Y., G.J. Welk, S.I. Braun, and M. Kang, *Extracting objective estimates of sedentary behavior from accelerometer data: measurement considerations for surveillance and research applications.* Plos One, 2015. **10**(2): e0118078.
12. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
13. Warburton, D.E., P.T. Katzmarzyk, R.E. Rhodes, and R.J. Shephard, *Evidence-informed physical activity guidelines for Canadian adults.* Can J Public Health, 2007. **98 Suppl 2**: p. S16-68.
14. Giannuzzi, P., A. Mezzani, H. Saner, H. Bjornstad, et al., *Physical activity for primary and secondary prevention. Position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur J Cardiovasc Prev Rehabil, 2003. **10**(5): p. 319-27.
15. Evenson, K.R., E.N. Butler, and W.D. Rosamond, *Prevalence of physical activity and sedentary behavior among adults with cardiovascular disease in the United States.* J Cardiopulm Rehabil Prev, 2014. **34**(6): p. 406-19.
16. Prince, S.A., C.M. Blanchard, S.L. Grace, and R.D. Reid, *Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates.* Eur J Prev Cardiol, 2015.

17. Sasaki, J.E., D. John, and P.S. Freedson, *Validation and comparison of ActiGraph activity monitors.* Journal of Science and Medicine in Sport, 2011. **14**(5): p. 411-6.
18. Carr, L.J. and M.T. Mahar, *Accuracy of intensity and inclinometer output of three activity monitors for identification of sedentary behavior and light-intensity activity.* J Obes, 2012. **2012**: p. 460271.
19. Tieges, Z., G. Mead, M. Allerhand, F. Duncan, et al., *Sedentary behavior in the first year after stroke: a longitudinal cohort study with objective measures.* Arch Phys Med Rehabil, 2015. **96**(1): p. 15-23.
20. Blikman, L.J., J. van Meeteren, H.L. Horemans, I.C. Kortenhorst, et al., *Is physical behavior affected in fatigued persons with multiple sclerosis?* Arch Phys Med Rehabil, 2015. **96**(1): p. 24-9.
21. Masse, L.C., B.F. Fuemmeler, C.B. Anderson, C.E. Matthews, et al., *Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables.* Med Sci Sports Exerc, 2005. **37**(11 Suppl): p. S544-54.
22. Troiano, R.P., D. Berrigan, K.W. Dodd, L.C. Masse, et al., *Physical activity in the United States measured by accelerometer.* Med Sci Sports Exerc, 2008. **40**(1): p. 181-8.
23. Chastin, S.F., P.M. Dall, W.W. Tigbe, M.P. Grant, et al., *Compliance with physical activity guidelines in a group of UK-based postal workers using an objective monitoring technique.* Eur J Appl Physiol, 2009. **106**(6): p. 893-9.
24. Keadle, S.K., E.J. Shiroma, P.S. Freedson, and I.M. Lee, *Impact of accelerometer data processing decisions on the sample size, wear time and physical activity level of a large cohort study.* BMC Public Health, 2014. **14**: p. 1210.
25. Ayabe, M., H. Kumahara, K. Morimura, and H. Tanaka, *Epoch length and the physical activity bout analysis: an accelerometry research issue.* BMC Res Notes, 2013. **6**: p. 20.
26. Lee, J.A., S.M. Williams, D.D. Brown, and K.R. Laurson, *Concurrent validation of the Actigraph gt3x+, Polar Active accelerometer, Omron HJ-720 and Yamax Digiwalker SW-701 pedometer step counts in lab-based and free-living settings.* J Sports Sci, 2015. **33**(10): p. 991-1000.
27. Ayabe, M., P.H. Brubaker, D. Dobrosielski, H.S. Miller, et al., *Target step count for the secondary prevention of cardiovascular disease.* Circ J, 2008. **72**(2): p. 299-303.
28. Tudor-Locke, C., C.L. Craig, Y. Aoyagi, R.C. Bell, et al., *How many steps/day are enough? For older adults and special populations.* Int J Behav Nutr Phys Act, 2011. **8**: p. 80.
29. Hamm, L.F., B.K. Sanderson, P.A. Ades, K. Berra, et al., *Core competencies for cardiac rehabilitation/ secondary prevention professionals: 2010 update: position statement of the American Association of Cardiovascular and Pulmonary Rehabilitation.* J Cardiopulm Rehabil Prev, 2011. **31**(1): p. 2-10.
30. Pate, R.R., M. Pratt, S.N. Blair, W.L. Haskell, et al., *Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.* JAMA, 1995. **273**(5): p. 402-7.
31. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
32. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
33. Prince, S.A., T.J. Saunders, K. Gresty, and R.D. Reid, *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): p. 905-19.
34. Byun, W., C. Ozemek, K. Riggin, S. Strath, et al., *Correlates of objectively measured physical activity in cardiac patients.* Cardiovasc Diagn Ther, 2014. **4**(5): p. 406-10.

35. Guiraud, T., R. Granger, V. Gremeaux, M. Bousquet, et al., *Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program.* Ann Phys Rehabil Med, 2012. **55**(5): p. 312-21.
36. Ribeiro, F., N.L. Oliveira, G. Silva, L. Campos, et al., *Exercise-based cardiac rehabilitation increases daily physical activity of patients following myocardial infarction: subanalysis of two randomised controlled trials.* Physiotherapy, 2017. **103**(1):59-65.
37. Gorman, E., H.M. Hanson, P.H. Yang, K.M. Khan, et al., *Accelerometry analysis of physical activity and sedentary behavior in older adults: a systematic review and data analysis.* European Review of Aging and Physical Activity, 2014. **11**(1): p. 35-49.
38. Orme, M., K. Wijndaele, S.J. Sharp, K. Westgate, et al., *Combined influence of epoch length, cut-point and bout duration on accelerometry-derived physical activity.* Int J Behav Nutr Phys Act, 2014. **11**(1): p. 34.
39. Gardner, B., L. Smith, F. Lorencatto, M. Hamer, et al., *How to reduce sitting time? A review of behaviour change strategies used in sedentary behaviour reduction interventions among adults.* Health Psychol Rev, 2016. **10**(1): p. 89-112.
40. Ozemek, C., H.L. Cochran, S.J. Strath, W. Byun, et al., *Estimating relative intensity using individualized accelerometer cutpoints: the importance of fitness level.* BMC Med Res Methodol, 2013. **13**: p. 53.

Chapter 4

Fatigue during and after cardiac rehabilitation

Myrna E. van Geffen
Nienke ter Hoeve
Madoka Sunamura
Henk J. Stam
Ron T. van Domburg
Rita J. G. van den Berg-Emons

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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.

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 (Figure 4.1). Reasons given by patients (n=17) for not participating in the follow-up measurements were: (I) lack of time, (II) immobility; and (III) unwillingness.

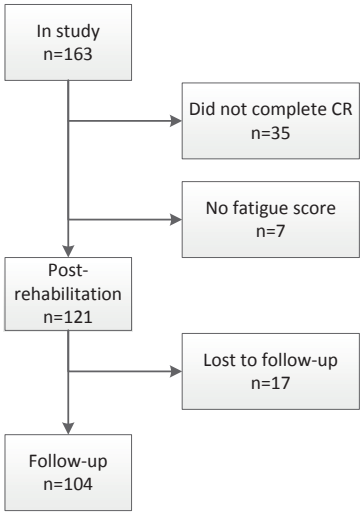

Figure 4.1 Patient inclusion in study
CR= cardiac rehabilitation.

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 χ2 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 4.1). The main diagnosis for referral to CR was myocardial infarction (75%). The mean number of training sessions was 22 (Table 4.1). 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.

Table 4.1 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)

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

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 4.2 and Figure 4.2). 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) (Figure 4.2). 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.

Table 4.2 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.

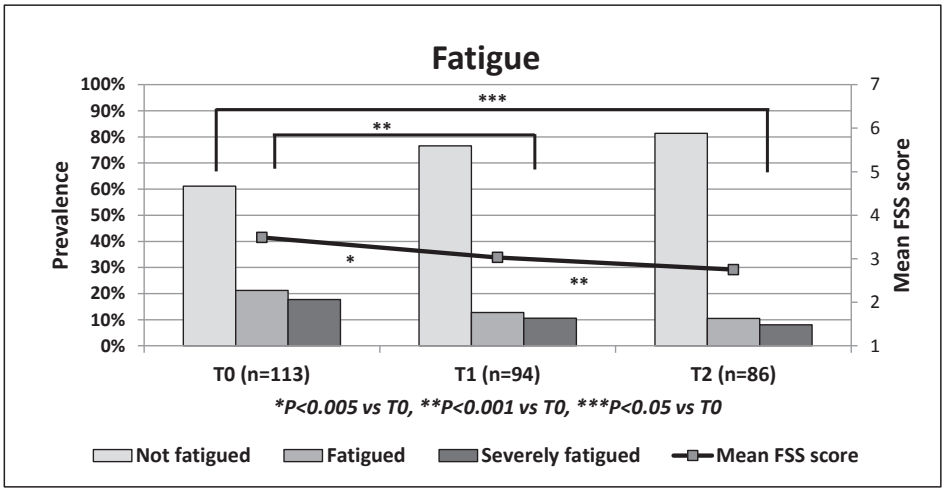

Figure 4.2 Prevalence and level of fatigue
FSS= fatigue severity scale.

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 4.3). 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 4.3 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, %	14.3	23.0	0.597
Diabetes, %	57.1	10.1	0.001

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 4.4), 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 4.4).

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 4.4). An association was also found between depression and changes in fatigue (B=0.203, p<0.001) (Table 4.4). 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 4.4 Generalized estimating equation model for changes in 6-min walk 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-min 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 fure 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.

REFERENCES

1. World Health Organization, *Media centre, cardiovascular diseases*. [[website]] 2013 [cited 2014 17 july]; Available from: www.who.int.
2. Roger, V.L., A.S. Go, D.M. Lloyd-Jones, E.J. Benjamin, et al., *Heart disease and stroke statistics--2012 update: a report from the American Heart Association.* Circulation, 2012. **125**(1): e2-e220.
3. Goto, Y., H. Sumida, K. Ueshima, H. Adachi, et al., *Safety and implementation of exercise testing and training after coronary stenting in patients with acute myocardial infarction.* Circ J, 2002. **66**(10): p. 930-6.
4. Marchionni, N., F. Fattirolli, S. Fumagalli, N. Oldridge, et al., *Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: results of a randomized, controlled trial.* Circulation, 2003. **107**(17): p. 2201-6.
5. Bunevicius, A., A. Stankus, J. Brozaitiene, S.S. Girdler, et al., *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**(2): p. 310-6.
6. Alsen, P. and E. Brink, *Fatigue after myocardial infarction - a two-year follow-up study.* J Clin Nurs, 2013. **22**(11-12): p. 1647-52.
7. Prescott, E., R. Hjardem-Hansen, F. Dela, B. Orkild, et al., *Effects of a 14-month low-cost maintenance training program in patients with chronic systolic heart failure: a randomized study.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(4): p. 430-7.
8. Pozehl, B., K. Duncan, and M. Hertzog, *The effects of exercise training on fatigue and dyspnea in heart failure.* Eur J Cardiovasc Nurs, 2008. **7**(2): p. 127-32.
9. Swardfager, W., N. Herrmann, Y. Dowlati, P. Oh, et al., *Relationship between cardiopulmonary fitness and depressive symptoms in cardiac rehabilitation patients with coronary artery disease.* J Rehabil Med, 2008. **40**(3): p. 213-8.
10. Johansson, I., B.W. Karlson, G. Grankvist, and E. Brink, *Disturbed sleep, fatigue, anxiety and depression in myocardial infarction patients.* Eur J Cardiovasc Nurs, 2010. **9**(3): p. 175-80.
11. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
12. Valko, P.O., C.L. Bassetti, K.E. Bloch, U. Held, et al., *Validation of the fatigue severity scale in a Swiss cohort.* Sleep, 2008. **31**(11): p. 1601-7.
13. Merkies, I.S., P.I. Schmitz, J.P. Samijn, F.G. van der Meche, et al., *Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group.* Neurology, 1999. **53**(8): p. 1648-54.
14. Armutlu, K., N.C. Korkmaz, I. Keser, V. Sumbuloglu, et al., *The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients.* Int J Rehabil Res, 2007. **30**(1): p. 81-5.
15. Andersson, E.A., G. Lundahl, L. Wecke, I. Lindblom, et al., *Maximal aerobic power versus performance in two aerobic endurance tests among young and old adults.* Gerontology, 2011. **57**(6): p. 502-12.
16. Bellet, R.N., L. Adams, and N.R. Morris, *The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review.* Physiotherapy, 2012. **98**(4): p. 277-86.
17. Doyle, F., H.M. McGee, D. De La Harpe, E. Shelley, et al., *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**(5): p. 461-7.

18. Krannich, J.H., P. Weyers, S. Lueger, M. Herzog, et al., *Presence of depression and anxiety before and after coronary artery bypass graft surgery and their relationship to age.* BMC Psychiatry, 2007. **7**: p. 47.
19. Stafford, L., M. Berk, and H.J. Jackson, *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**(5): p. 417-24.
20. Twisk, J.W., *Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis.* Eur J Epidemiol, 2004. **19**(8): p. 769-76.
21. Bunevicius, A., M. Staniute, J. Brozaitiene, and R. Bunevicius, *Diagnostic accuracy of self-rating scales for screening of depression in coronary artery disease patients.* J Psychosom Res, 2012. **72**(1): p. 22-5.
22. Appels, A., *Mental precursors of myocardial infarction.* Br J Psychiatry, 1990. **156**: p. 465-71.
23. Saeidi, M., S. Mostafavi, H. Heidari, and S. Masoudi, *Effects of a comprehensive cardiac rehabilitation program on quality of life in patients with coronary artery disease.* ARYA Atheroscler, 2013. **9**(3): p. 179-85.
24. Gupta, R., B.K. Sanderson, and V. Bittner, *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**(1): p. 11-8;.

Chapter 5

Participation in society in patients with coronary artery disease before and after cardiac rehabilitation

Nienke ter Hoeve
Myrna E. van Geffen
Marcel W. Post
Henk J. Stam
Madoka Sunamura
Ron T. van Domburg
Rita J. G. van den Berg-Emons

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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

BMI= body mass index.

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 5.2 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.*

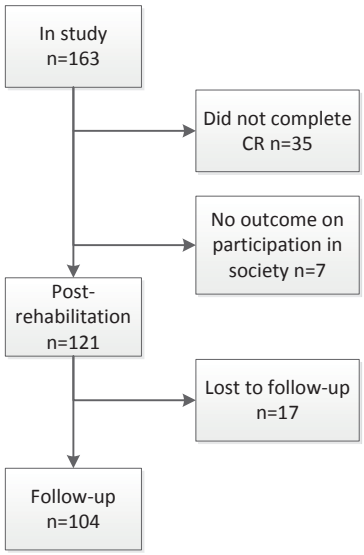

Figure 5.1 Patient flowchart
CR= cardiac rehabilitation.

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.

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).

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

	Not participating (%)		
Frequency scale	**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.*

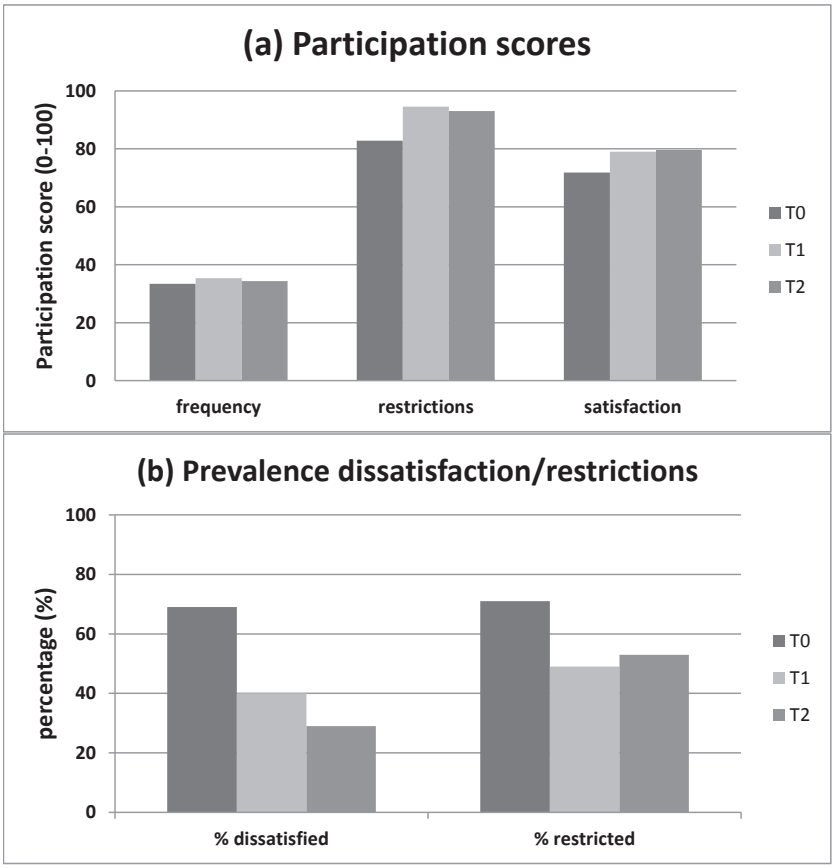

Figure 5.2 (A) Improvements in mean score for frequency, restrictions, and satisfaction scale during and after CR; **(B)** Improvements in prevalence of restrictions and dissatisfaction during and after CR

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).

Table 5.4 Mediating effects of physical capacity and depressive mood on changes in participation in society[*]

	Participation in society	
Mediating variable	**Satisfaction**	**Restrictions**
Physical capacity (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.

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 5.5 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%

HRQOL= health related quality of life.
[*]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 capacity, depressive mood and smoking status.
[2]GEE model corrected for confounding effect of physical capacity, depressive mood, smoking status and body mass index.
[3]GEE model corrected for confounding effect of physical capacity, depressive mood, age, sex, smoking status and marital status.
[4]GEE model corrected for confounding effect of physical capacity, 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.

REFERENCES

1. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
2. Piepoli, M.F., U. Corra, W. Benzer, B. Bjarnason-Wehrens, et al., *Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 1-17.
3. Nieuwenburg-van Tilborg, E.M., A.M. Horstman, B. Zwarts, and S. de Groot, *Physical strain during activities of daily living of patients with coronary artery disease.* Clinical Physiology and Functional Imaging, 2014. **34**(2): p. 83-89.
4. Britton, A., E. Brunner, M. Kivimaki, and M.J. Shipley, *Limitations to functioning and independent living after the onset of coronary heart disease: what is the role of lifestyle factors and obesity?* European Journal of Public Health, 2012. **22**(6): p. 831-835.
5. Soderman, E., J. Lisspers, and O. Sundin, *Depression as a predictor of return to work in patients with coronary artery disease.* Soc Sci Med, 2003. **56**(1): p. 193-202.
6. O'Neil, A., K. Sanderson, and B. Oldenburg, *Depression as a predictor of work resumption following myocardial infarction (MI): a review of recent research evidence.* Health and Quality of Life Outcomes, 2010. **8**: p. 95.
7. Swardfager, W., N. Herrmann, S. Marzolini, M. Saleem, et al., *Major Depressive Disorder Predicts Completion, Adherence, and Outcomes in Cardiac Rehabilitation: A Prospective Cohort Study of 195 Patients With Coronary Artery Disease.* Journal of Clinical Psychiatry, 2011. **72**(9): p. 1181-1188.
8. Boudrez, H. and G. de Backer, *Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting.* Acta Cardiologica, 2000. **55**(6): p. 341-349.
9. Dijkers, M.P., *Issues in the conceptualization and measurement of participation: an overview.* Archives of Physical Medicine & Rehabilitation, 2010. **91**(9 Suppl): S5-16.
10. Whiteneck, G. and M.P. Dijkers, *Difficult to measure constructs: conceptual and methodological issues concerning participation and environmental factors.* Arch Phys Med Rehabil, 2009. **90**(11 Suppl): p. S22-35.
11. Post, M.W.M., C.H. van der Zee, J. Hennink, C.G. Schafrat, et al., *Validity of the Utrecht Scale for Evaluation of Rehabilitation-Participation.* Disabil Rehabil 2012. **34**(6): p. 478-485.
12. van der Zee, C.H., J.M.A. Visser-Meily, E. Lindeman, L.J. Kappelle, et al., *Participation in the Chronic Phase of Stroke.* Natural Resources and Sustainable Development Ii, Pts 1-4, 2012. **524-527**: p. 52-61.
13. Thraen-Borowski, K.M., A. Trentham-Dietz, D.F. Edwards, K.F. Koltyn, et al., *Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors.* Journal of Cancer Survivorship, 2013. **7**(3): p. 369-378.
14. Levasseur, M., J. Desrosiers, and L. Noreau, *Is social participation associated with quality of life of older adults with physical disabilities?* Disability and Rehabilitation, 2004. **26**(20): p. 1206-1213.
15. McLean, A.M., T. Jarus, A.M. Hubley, and L. Jongbloed, *Associations between social participation and subjective quality of life for adults with moderate to severe traumatic brain injury.* Disabil Rehabil, 2014. **36**(17): p. 1409-18.

16. Speziale, G., G. Ruvolo, and B. Marino, *Quality of life following coronary bypass surgery.* J Cardiovasc Surg (Torino), 1996. **37**(1): p. 75-8.
17. Kimble, L.P., *Impact of cardiac symptoms on self-reported household task performance in women with coronary artery disease.* Journal of Cardiopulmonary Rehabilitation, 2001. **21**(1): p. 18-23.
18. Maes, S., V. De Gucht, R. Goud, I. Hellemans, et al., *Is the MacNew quality of life questionnaire a useful diagnostic and evaluation instrument for cardiac rehabilitation?* European Journal of Cardiovascular Prevention and Rehabilitation, 2008. **15**(5): p. 516-20.
19. van der Zee, C.H., A. Kap, R.R. Mishre, E.J. Schouten, et al., *Responsiveness of Four Participation Measures to Changes during and after Outpatient Rehabilitation.* Journal of Rehabilitation Medicine, 2011. **43**(11): p. 1003-1009.
20. van der Zee, C.H., A.R. Priesterbach, L. van der Dussen, A. Kap, et al., *Reproducibility of Three Self-Report Participation Measures: The Icf Measure of Participation and Activities Screener, the Participation Scale, and the Utrecht Scale for Evaluation of Rehabilitation-Participation.* Journal of Rehabilitation Medicine, 2010. **42**(8): p. 752-757.
21. ter Hoeve, N., M.W.M. Post, R.T. van Domburg, C.H. van der Zee, et al., *USER-Participatie omreken-procedure.* Nederlands Tijdschrift Revalidatiegeneeskunde, 2014. **1**: p. 40-41.
22. Bellet, R.N., L. Adams, and N.R. Morris, *The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review.* Physiotherapy, 2012. **98**(4): p. 277-86.
23. Doyle, F., H.M. McGee, D. De La Harpe, E. Shelley, et al., *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**(5): p. 461-7.
24. Stafford, L., M. Berk, and H.J. Jackson, *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**(5): p. 417-24.
25. De Gucht, V., T. Van Elderen, L. Van der Kamp, and N. Oldridge, *Quality of life after myocardial infarction: Translation and validation of the MacNew Questionnaire for a Dutch population.* Quality of Life Research, 2004. **13**(8): p. 1483-1488.
26. Twisk, J.W.R., *Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis.* European Journal of Epidemiology, 2004. **19**(8): p. 769-776.
27. Yohannes, A.M., A. Yalfani, P. Doherty, and C. Bundy, *Predictors of drop-out from an outpatient cardiac rehabilitation programme.* Clinical Rehabilitation, 2007. **21**(3): p. 222-229.
28. Worcester, M.U.C., B.M. Murphy, V.K. Mee, S.B. Roberts, et al., *Cardiac rehabilitation programmes: predictors of non-attendance and drop-out.* European Journal of Cardiovascular Prevention & Rehabilitation, 2004. **11**(4): p. 328-335.
29. Sandercock, G., V. Hurtado, and F. Cardoso, *Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis.* International Journal of Cardiology, 2013. **167**(3): p. 894-902.
30. Rutledge, T., L.S. Redwine, S.E. Linke, and P.J. Mills, *A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease.* Psychosom Med, 2013. **75**(4): p. 335-49.
31. Froelicher, E.S., L.L. Kee, K.M. Newton, B. Lindskog, et al., *Return to Work, Sexual-Activity, and Other Activities after Acute Myocardial-Infarction.* Heart & Lung, 1994. **23**(5): p. 423-435.
32. Shen, B.J., C.P. McCreary, and H.F. Myers, *Independent and mediated contributions of personality, coping, social support, and depressive symptoms to physical functioning outcome among patients in cardiac rehabilitation.* Journal of Behavioural Medicine, 2004. **27**(1): p. 39-62.
33. Orth-Gomer, K. and A.L. Unden, *Type A behavior, social support, and coronary risk: interaction and significance for mortality in cardiac patients.* Psychosom Med, 1990. **52**(1): p. 59-72.

34. Barefoot, J.C., M.M. Burg, R.M. Carney, C.E. Cornell, et al., *Aspects of social support associated with depression at hospitalization and follow-up assessment among cardiac patients.* Journal of Cardiopulmonary Rehabilitation, 2003. **23**(6): p. 404-12.
35. Magasi, S. and M.W. Post, *A comparative review of contemporary participation measures' psychometric properties and content coverage.* Arch Phys Med Rehabil, 2010. **91**(9 Suppl): p. S17-28.

Part 2

Behavioural interventions added to cardiac rehabilitation

Chapter 6

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

Madoka Sunamura
Nienke ter Hoeve
Rita J. G. van den Berg-Emons
Mirjam Haverkamp
Ken Redekop
Marcel L. Geleijnse
Henk J. Stam
Eric Boersma
Ron T. van Domburg

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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 objective

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 6.1), following inclusion and exclusion criteria as mentioned in Table 6.2. 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.

Table 6.1 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; SBP= systolic blood pressure.

Table 6.2 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.

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 disease 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.

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 6.3).

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.

Table 6.3 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]

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.

Cost effectiveness analysis

A cost-effectiveness analysis will be performed in accordance with the current Dutch guidelines (Guidelines for Pharmacoeconomic 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]

REFERENCES

1. Berghofer, A., T. Pischon, T. Reinhold, C.M. Apovian, et al., *Obesity prevalence from a European perspective: a systematic review.* BMC Public Health, 2008. **8**: p. 200.
2. Kearney, P.M., M. Whelton, K. Reynolds, P.K. Whelton, et al., *Worldwide prevalence of hypertension: a systematic review.* J Hypertens, 2004. **22**(1): p. 11-9.
3. *IDF Diabetes Atlas* 3rd ed, ed. I.d. federation. 2006, Brussels.
4. *Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk*. 2007: Geneva.
5. Yusuf, S., S. Hawken, S. Ounpuu, T. Dans, et al., *Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study.* Lancet, 2004. **364**(9438): p. 937-52.
6. Iestra, J.A., D. Kromhout, Y.T. van der Schouw, D.E. Grobbee, et al., *Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review.* Circulation, 2005. **112**(6): p. 924-34.
7. O'Connor, G.T., J.E. Buring, S. Yusuf, S.Z. Goldhaber, et al., *An overview of randomized trials of rehabilitation with exercise after myocardial infarction.* Circulation, 1989. **80**(2): p. 234-44.
8. Jolliffe, J.A., K. Rees, R.S. Taylor, D. Thompson, et al., *Exercise-based rehabilitation for coronary heart disease.* Cochrane Database Syst Rev, 2000(4): CD001800.
9. Gupta, R., B.K. Sanderson, and V. Bittner, *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**(1): p. 11-8.
10. van der Vlugt, M.J., H. Boersma, C.M. Leenders, G.A. Pop, et al., *Prospective study of early discharge after acute myocardial infarction (SHORT).* Eur Heart J, 2000. **21**(12): p. 992-9.
11. Euroaspire, I., I.I. Group, and E. European Action on Secondary Prevention by Intervention to Reduce, *Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events.* Lancet, 2001. **357**(9261): p. 995-1001.
12. Saczynski, J.S., D. Lessard, F.A. Spencer, J.H. Gurwitz, et al., *Declining length of stay for patients hospitalized with AMI: impact on mortality and readmissions.* Am J Med, 2010. **123**(11): p. 1007-15.
13. Galaszek, M., Z. Eysmontt, B. Choromanska-Matera, and E. Blaszczak, *Results of the residential cardiac rehabilitation in patients after myocardial infarction treated with percutaneous coronary intervention (PCI).* Pol Arch Med Wewn, 2006. **116**(1): p. 627-39.
14. Piestrzeniewicz, K., N. Navarro-Kuczborska, H. Bolinska, A. Jegier, et al., *The impact of comprehensive cardiac rehabilitation in patients up to 55 years old after acute myocardial infarction treated with primary coronary intervention.* Pol Arch Med Wewn, 2004. **111**(3): p. 309-17.
15. Goel, K., R.J. Lennon, R.T. Tilbury, R.W. Squires, et al., *Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community.* Circulation, 2011. **123**(21): p. 2344-52.
16. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network.* Arch Intern Med, 2008. **168**(20): p. 2194-204.
17. Pluss, C.E., E. Billing, C. Held, P. Henriksson, et al., *Long-term effects of an expanded cardiac rehabilitation programme after myocardial infarction or coronary artery bypass surgery: a five-year follow-up of a randomized controlled study.* Clin Rehabil, 2011. **25**(1): p. 79-87.

18. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
19. Bock, B.C., R.E. Carmona-Barros, J.L. Esler, and P.L. Tilkemeier, *Program participation and physical activity maintenance after cardiac rehabilitation.* Behav Modif, 2003. **27**(1): p. 37-53.
20. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.
21. Conroy, R.M., K. Pyorala, A.P. Fitzgerald, S. Sans, et al., *Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.* Eur Heart J, 2003. **24**(11): p. 987-1003.
22. Hansson, L., T. Hedner, and B. Dahlof, *Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point.* Blood Press, 1992. **1**(2): p. 113-9.
23. van Engen-Verheul, M.M., H.M. Kemps, N.F. de Keizer, I.M. Hellemans, 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**(3): p. 504-14.
24. Kemps, H.M., M.M. van Engen-Verheul, R.A. Kraaijenhagen, R. Goud, et al., *Improving guideline adherence for cardiac rehabilitation in the Netherlands.* Neth Heart J, 2011. **19**(6): p. 285-9.
25. Bennett, J.A., K.S. Lyons, K. Winters-Stone, L.M. Nail, et al., *Motivational interviewing to increase physical activity in long-term cancer survivors: a randomized controlled trial.* Nurs Res, 2007. **56**(1): p. 18-27.
26. Reid, R.D., L.I. Morrin, L.A. Higginson, A. Wielgosz, et al., *Motivational counselling for physical activity in patients with coronary artery disease not participating in cardiac rehabilitation.* Eur J Prev Cardiol, 2012. **19**(2): p. 161-6.
27. Schneider, P.L., S.E. Crouter, O. Lukajic, and D.R. Bassett, Jr., *Accuracy and reliability of 10 pedometers for measuring steps over a 400-m walk.* Med Sci Sports Exerc, 2003. **35**(10): p. 1779-84.
28. Plasqui, G. and K.R. Westerterp, *Physical activity assessment with accelerometers: an evaluation against doubly labeled water.* Obesity (Silver Spring), 2007. **15**(10): p. 2371-9.
29. Peters, R.J., *Nurses can significantly reduce the risk of recurrent complications in heart patients: results from the RESPONSE trial.* . European Society of Cardiology Conference Stockholm, 2010.
30. Vegter, S., C. Boersma, M. Rozenbaum, B. Wilffert, et al., *Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines.* Pharmacoeconomics, 2008. **26**(7): p. 569-87.
31. Yu, C.M., C.P. Lau, J. Chau, S. McGhee, et al., *A short course of cardiac rehabilitation program is highly cost effective in improving long-term quality of life in patients with recent myocardial infarction or percutaneous coronary intervention.* Arch Phys Med Rehabil, 2004. **85**(12): p. 1915-22.
32. Warburton, D.E., C.W. Nicol, and S.S. Bredin, *Health benefits of physical activity: the evidence.* CMAJ, 2006. **174**(6): p. 801-9.
33. Taylor, R.S., A. Brown, S. Ebrahim, J. Jolliffe, et al., *Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials.* Am J Med, 2004. **116**(10): p. 682-92.
34. Ades, P.A., *Cardiac rehabilitation and secondary prevention of coronary heart disease.* N Engl J Med, 2001. **345**(12): p. 892-902.
35. Moore, S.M., C.M. Ruland, F.J. Pashkow, and G.G. Blackburn, *Women's patterns of exercise following cardiac rehabilitation.* Nurs Res, 1998. **47**(6): p. 318-24.

36. van den Berg-Emons, R.J., J.B. Bussmann, A.H. Balk, and H.J. Stam, *Factors associated with the level of movement-related everyday activity and quality of life in people with chronic heart failure.* Phys Ther, 2005. **85**(12): p. 1340-8.
37. Cohen, D.J. and M.R. Reynolds, *Interpreting the results of cost-effectiveness studies.* J Am Coll Cardiol, 2008. **52**(25): p. 2119-26.
38. De Gucht, V., T. Van Elderen, L. van der Kamp, and N. Oldridge, *Quality of life after myocardial infarction: translation and validation of the MacNew Questionnaire for a Dutch population.* Qual Life Res, 2004. **13**(8): p. 1483-8.
39. Spinhoven, P., J. Ormel, P.P. Sloekers, G.I. Kempen, et al., *A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects.* Psychol Med, 1997. **27**(2): p. 363-70.
40. de Raaij, E.J., C. Schroder, F.J. Maissan, J.J. Pool, et al., *Cross-cultural adaptation and measurement properties of the Brief Illness Perception Questionnaire-Dutch Language Version.* Man Ther, 2012. **17**(4): p. 330-5.
41. Craig, C.L., A.L. Marshall, M. Sjöström, A.E. Bauman, et al. *International physical activity questionnaire: 12-country reliability and validity.* Med Sci Sports Exerc, 2003. **35**(8): p. 1381-95.
42. Krupp, L.B., N.G. LaRocca, J. Muir-Nash, and A.D. Steinberg, *The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.* Arch Neurol, 1989. **46**(10): p. 1121-3.
43. Denollet, J., J. Vaes, and D.L. Brutsaert, *Inadequate response to treatment in coronary heart disease : adverse effects of type D personality and younger age on 5-year prognosis and quality of life.* Circulation, 2000. **102**(6): p. 630-5.
44. van der Zee, C.H., A.R. Priesterbach, L. van der Dussen, A. Kap, et al., *Reproducibility of three self-report participation measures: The ICF Measure of Participation and Activities Screener, the Participation Scale, and the Utrecht Scale for Evaluation of Rehabilitation-Participation.* J Rehabil Med, 2010. **42**(8): p. 752-7.
45. Brooks, R., *EuroQol: the current state of play.* Health Policy, 1996. **37**(1): p. 53-72.
46. Scholz, R., Gutierrez-Dona ,B., Sud, S., Schwarzer, R. *Is General Self-Efficacy a universal construct?* Eur J Psychol Assess, 2002. **18**(3): p. 242-251.

Chapter 7

Effects of two behavioral cardiac rehabilitation interventions on physical activity: A randomized controlled trial

Nienke ter Hoeve
Madoka Sunamura
Henk J. Stam
Eric Boersma
Marcel L. Geleijnse
Ron T. van Domburg
Rita J. G. van den Berg-Emons

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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 7A):

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 7A). 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 day[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 7.1), 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 7.1).

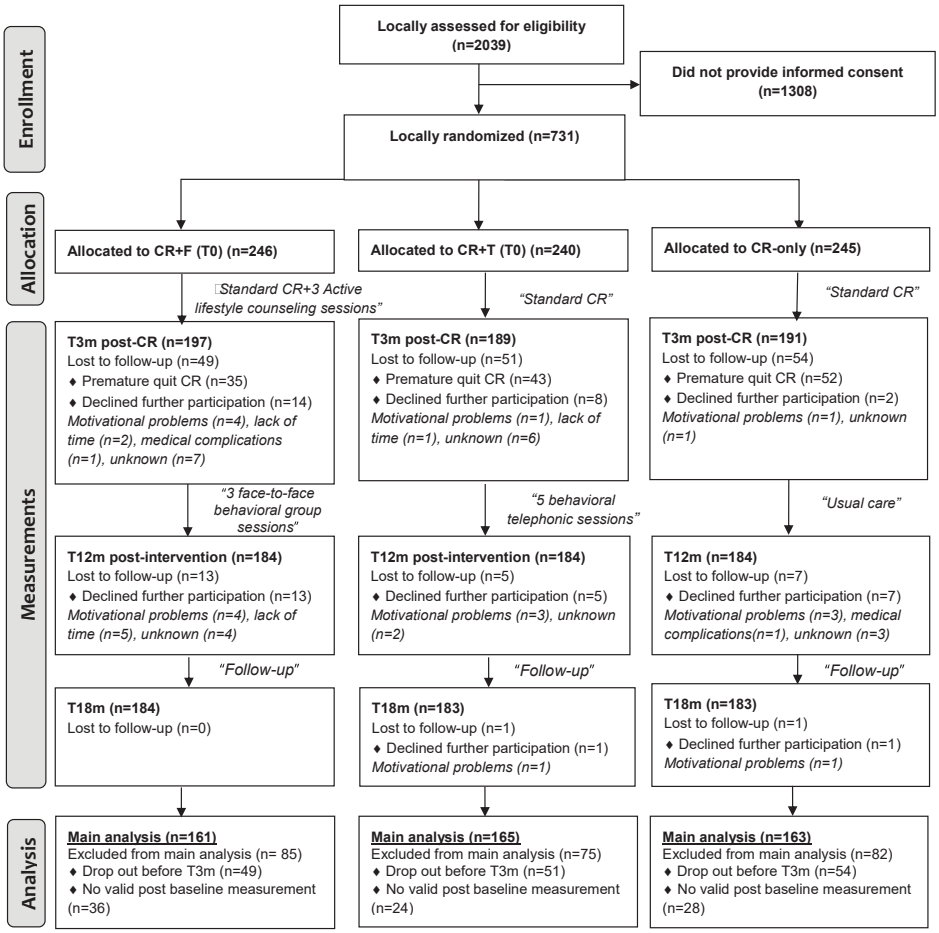

Figure 7.1 Consort flow diagram
CR= cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m=month.

Outcomes

At each time point, 69% to 86% of patients provided usable physical behavior measurements (Appendix 7B). 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.

Table 7.1 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+F), n=31 (CR+T), and n=14 (CR-only).

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

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

Intervention effects of CR+F compared to CR-only

Figure 7.2 displays observed study endpoints over time (for exact values see Appendix 7C). 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 7.2). Overall effects were also noted for achieving ≥6500 steps/day (OR=1.77; 95% CI=1.20 to 2.60; *P*=.004; Table 7.2).

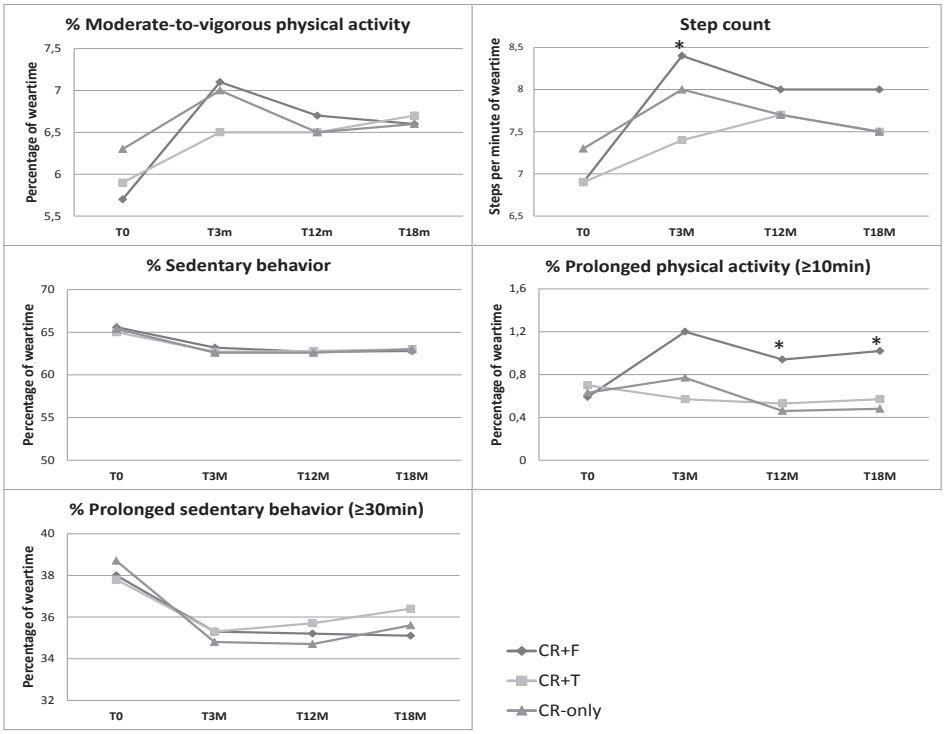

Figure 7.2 Volume of physical behavior and distribution over time
CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus telephonic counseling; CR-only= standard cardiac rehabilitation; m=month.
**Significant intervention effect for CR+F compared to CR-only.*

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 7.2).

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 7D and 7E).

Table 7.2 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; CI=confidence interval; 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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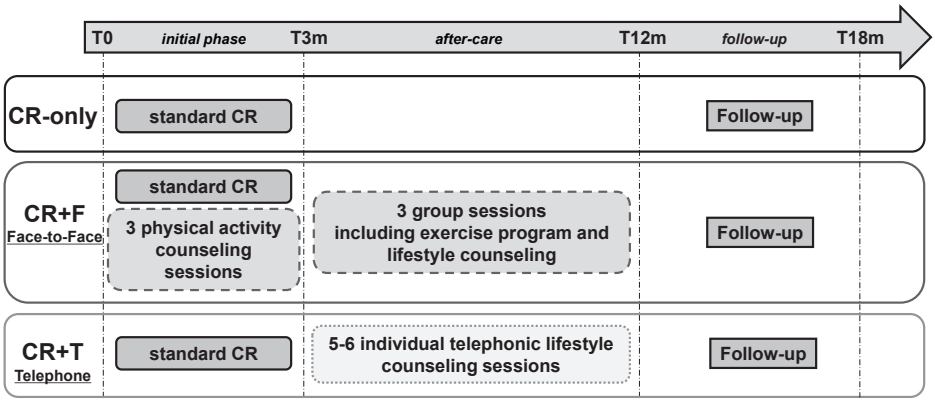
REFERENCES

1. Bussmann, J.B. and R.J. van den Berg-Emons, *To total amount of activity..... and beyond: perspectives on measuring physical behavior.* Front Psychol, 2013. **4**: p. 463.
2. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
3. Giannuzzi, P., A. Mezzani, H. Saner, H. Bjornstad, et al., *Physical activity for primary and secondary prevention. Position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur J Cardiovasc Prev Rehabil, 2003. **10**(5): p. 319-27.
4. Prince, S.A., C.M. Blanchard, S.L. Grace, and R.D. Reid, *Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates.* Eur J Prev Cardiol, 2016. **23** (8): 818-25.
5. Biswas, A., P.I. Oh, G.E. Faulkner, R.R. Bajaj, et al., *Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis.* Ann Intern Med, 2015. **162**(2): p. 123-32.
6. Strath, S.J., R.G. Holleman, D.L. Ronis, A.M. Swartz, et al., *Objective physical activity accumulation in bouts and nonbouts and relation to markers of obesity in US adults.* Prev Chronic Dis, 2008. **5**(4): A131.
7. Murphy, M., A. Nevill, C. Neville, S. Biddle, et al., *Accumulating brisk walking for fitness, cardiovascular risk, and psychological health.* Med Sci Sports Exerc, 2002. **34**(9): p. 1468-74.
8. Haskell, W.L., I.M. Lee, R.R. Pate, K.E. Powell, et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association.* Med Sci Sports Exerc, 2007. **39**(8): p. 1423-34.
9. Healy, G.N., D.W. Dunstan, J. Salmon, E. Cerin, et al., *Breaks in sedentary time: beneficial associations with metabolic risk.* Diabetes Care, 2008. **31**(4): p. 661-6.
10. Taylor, R.S., A. Brown, S. Ebrahim, J. Jolliffe, et al., *Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials.* Am J Med, 2004. **116**(10): p. 682-92.
11. Lavie, C.J. and R.V. Milani, *Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention.* Prog Cardiovasc Dis, 2011. **53**(6): p. 397-403.
12. ter Hoeve, N., B.M. Huisstede, H.J. Stam, R.T. van Domburg, et al., *Does cardiac rehabilitation after an acute cardiac syndrome lead to changes in physical activity habits? Systematic review.* Phys Ther, 2015. **95**(2): p. 167-79.
13. ter Hoeve, N., S. Sunamura, M.E. van Geffen, M.H.J. Fanchamps, et al., *Changes in Physical Activity and Sedentary Behavior during Cardiac Rehabilitation* Arch Phys Med Rehabil, 2017. **98** (12): 2378-84.
14. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
15. Prince, S.A., T.J. Saunders, K. Gresty, and R.D. Reid, *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): p. 905-19.

16. Butler, L., S. Furber, P. Phongsavan, A. Mark, et al., *Effects of a pedometer-based intervention on physical activity levels after cardiac rehabilitation: a randomized controlled trial.* J Cardiopulm Rehabil Prev, 2009. **29**(2): p. 105-14.
17. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network.* Arch Intern Med, 2008. **168**(20): p. 2194-204.
18. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
19. Le Grande, M.R., P.C. Elliott, M.U. Worcester, B.M. Murphy, et al., *An evaluation of self-report physical activity instruments used in studies involving cardiac patients.* J Cardiopulm Rehabil Prev, 2008. **28**(6): p. 358-69.
20. Sunamura, M., N. Ter Hoeve, H.J. van den Berg-Emons, M. Haverkamp, 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): p. 324-30.
21. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
22. Hancock, K., P.M. Davidson, J. Daly, D. Webber, et al., *An exploration of the usefulness of motivational interviewing in facilitating secondary prevention gains in cardiac rehabilitation.* J Cardiopulm Rehabil, 2005. **25**(4): p. 200-6.
23. Chase, J.A., *Systematic review of physical activity intervention studies after cardiac rehabilitation.* J Cardiovasc Nurs, 2011. **26**(5): p. 351-8.
24. Janssen, V., V. De Gucht, E. Dusseldorp, and S. Maes, *Lifestyle modification programmes for patients with coronary heart disease: a systematic review and meta-analysis of randomized controlled trials.* Eur J Prev Cardiol, 2013. **20**(4): p. 620-40.
25. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.
26. Sasaki, J.E., D. John, and P.S. Freedson, *Validation and comparison of ActiGraph activity monitors.* Journal of Science and Medicine in Sport, 2011. **14**(5): p. 411-6.
27. Carr, L.J. and M.T. Mahar, *Accuracy of intensity and inclinometer output of three activity monitors for identification of sedentary behavior and light-intensity activity.* J Obes, 2012. **2012**: p. 460271.
28. Ayabe, M., P.H. Brubaker, D. Dobrosielski, H.S. Miller, et al., *Target step count for the secondary prevention of cardiovascular disease.* Circ J, 2008. **72**(2): p. 299-303.
29. Tudor-Locke, C., C.L. Craig, Y. Aoyagi, R.C. Bell, et al., *How many steps/day are enough? For older adults and special populations.* Int J Behav Nutr Phys Act, 2011. **8**: p. 80.
30. Pate, R.R., M. Pratt, S.N. Blair, W.L. Haskell, et al., *Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.* JAMA, 1995. **273**(5): p. 402-7.
31. Hamm, L.F., B.K. Sanderson, P.A. Ades, K. Berra, et al., *Core competencies for cardiac rehabilitation/secondary prevention professionals: 2010 update: position statement of the American Association of Cardiovascular and Pulmonary Rehabilitation.* J Cardiopulm Rehabil Prev, 2011. **31**(1): p. 2-10.
32. World Health Organization, *Global Recommendations on Physical Activity for Health.* 2010.

33. Oliveira, J., F. Ribeiro, and H. Gomes, *Effects of a home-based cardiac rehabilitation program on the physical activity levels of patients with coronary artery disease.* J Cardiopulm Rehabil Prev, 2008. **28**(6): p. 392-6.
34. Stevenson, T.G., K. Riggin, P.R. Nagelkirk, T.A. Hargens, et al., *Physical activity habits of cardiac patients participating in an early outpatient rehabilitation program.* J Cardiopulm Rehabil Prev, 2009. **29**(5): p. 299-303.
35. White, I.R., J. Carpenter, and N.J. Horton, *Including all individuals is not enough: lessons for intention-to-treat analysis.* Clin Trials, 2012. **9**(4): p. 396-407.
36. Twisk, J. and W. de Vente, *Attrition in longitudinal studies. How to deal with missing data.* J Clin Epidemiol, 2002. **55**(4): p. 329-37.
37. Conn, V.S., A.R. Hafdahl, and D.R. Mehr, *Interventions to increase physical activity among healthy adults: meta-analysis of outcomes.* Am J Public Health, 2011. **101**(4): p. 751-8.
38. Chastin, S.F., P.M. Dall, W.W. Tigbe, M.P. Grant, et al., *Compliance with physical activity guidelines in a group of UK-based postal workers using an objective monitoring technique.* Eur J Appl Physiol, 2009. **106**(6): p. 893-9.
39. Sunamura, M., N. Ter Hoeve, R.J.G. van den Berg-Emons, M.L. Geleijnse, et al., *Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes.* Heart, 2018; **104**(5): p. 430-7.
40. Warburton, D.E., C.W. Nicol, and S.S. Bredin, *Health benefits of physical activity: the evidence.* CMAJ, 2006. **174**(6): p. 801-9.
41. van den Berg-Emons, R., A. Balk, H. Bussmann, and H. Stam, *Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure?* Eur J Heart Fail, 2004. **6**(1): p. 95-100.
42. Janssen, V., V. De Gucht, H. van Exel, and S. Maes, *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence.* J Behav Med, 2014. **37**(2): p. 308-21.
43. Leemrijse, C.J., R.J. Peters, C. von Birgelen, L. van Dijk, et al., *The telephone lifestyle intervention 'Hartcoach' has modest impact on coronary risk factors: A randomised multicentre trial.* Eur J Prev Cardiol, 2016. **23**(15): p. 1658-68.
44. Conn, V.S., A.R. Hafdahl, S.M. Moore, P.J. Nielsen, et al., *Meta-analysis of interventions to increase physical activity among cardiac subjects.* Int J Cardiol, 2009. **133**(3): p. 307-20.
45. Hughes, A.R., N. Mutrie, and P.D. Macintyre, *Effect of an exercise consultation on maintenance of physical activity after completion of phase III exercise-based cardiac rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2007. **14**(1): p. 114-21.
46. Guiraud, T., R. Granger, V. Gremeaux, M. Bousquet, et al., *Telephone support oriented by accelerometric measurements enhances adherence to physical activity recommendations in noncompliant patients after a cardiac rehabilitation program.* Arch Phys Med Rehabil, 2012. **93**(12): p. 2141-7.
47. Frederix, I., L. Vanhees, P. Dendale, and K. Goetschalckx, *A review of telerehabilitation for cardiac patients.* J Telemed Telecare, 2015. **21**(1): p. 45-53.

APPENDIXES



Appendix 7A 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 7B 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 7C 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 (2.5)	7.1 (2.8)	6.7 (3.0)	6.6 (3.1)	5.9 (2.8)	6.5 (2.7)	6.5 (3.3)	6.7 (3.3)	6.3 (2.9)	7.0 (2.7)	6.5 (3.0)	6.6 (3.1)
Step count (nr of steps per min of wear time)	6.9 (2.2)	8.4 (2.6)	8.0 (2.6)	8.0 (2.8)	6.9 (2.6)	7.4 (2.7)	7.7 (3.3)	7.5 (2.8)	7.3 (2.9)	8.0 (2.5)	7.7 (2.8)	7.5 (2.9)
SB (% of wear time)	65.6 (8.3)	63.2 (7.4)	62.7 (8.1)	62.8 (7.7)	65.0 (8.3)	62.7 (8.4)	62.8 (10.0)	63.0 (8.5)	65.4 (8.2)	62.6 (7.3)	62.6 (8.2)	63.0 (9.0)
Counts/min	524.6 (148.6)	604.5 (163.8)	597.3 (170.7)	591.3 (171.7)	535.4 (165.4)	576.6 (164.6)	577.4 (210.8)	581.0 (183.8)	548.3 (167.5)	601.0 (150.3)	587.2 (165.5)	582.4 (178.5)
Distribution, mean (SD)												
Prolonged MVPA (≥ 10 min; % of wear time)	0.59† (0:5.2)	1.20† (0:7.1)	0.94† (0:6.6)	1.02† (0:10.3)	0.7† (0:8.3)	0.57† (0:8.9)	0.53† (0:5.6)	0.57† (0:10.8)	0.63† (0:8.3)	0.77† (0:7.8)	0.46† (0:6.9)	0.48† (0:8.2)
Prolonged SB (≥ 30 min; % of wear time)	38.0 (12.5)	35.3 (10.8)	35.2 (11.9)	35.1 (11.8)	37.8 (13.1)	35.3 (12.7)	35.7 (13.8)	36.4 (12.8)	38.7 (11.9)	34.8 (11.1)	34.7 (11.1)	35.6 (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/week	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 7D 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.

[§]For dichotomous variables odds ratios are displayed.

Appendix 7E 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 per	overall	**0.55**	**0.13:0.98**	**0.010***	-0.24	-0.70:0.22	0.307
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 (≥10min)	overall	**0.73**[§]	**0.28:1.19**	**0.002***	1.02[§]	0.67:1.54	0.941
(% of wear time)	ΔT0-T3m	0.73[§]	-0.08:1.54	0.079	0.76[§]	0.39:1.48	0.411
	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.

[§] For dichotomous variables odds ratios are displayed.

**P < .05.*

Chapter 8

Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes

Madoka Sunamura
Nienke ter Hoeve
Rita J. G. van den Berg-Emons
Marcel L. Geleijnse
Mirjam Haverkamp
Henk J. Stam
Eric Boersma
Ron T. van Domburg

Heart 2018; 104(5): p. 430-7

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 8A). 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 8A.

Treatment allocation

For a complete explanation of interventions, please see Appendix 8A.

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 8.1).[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.

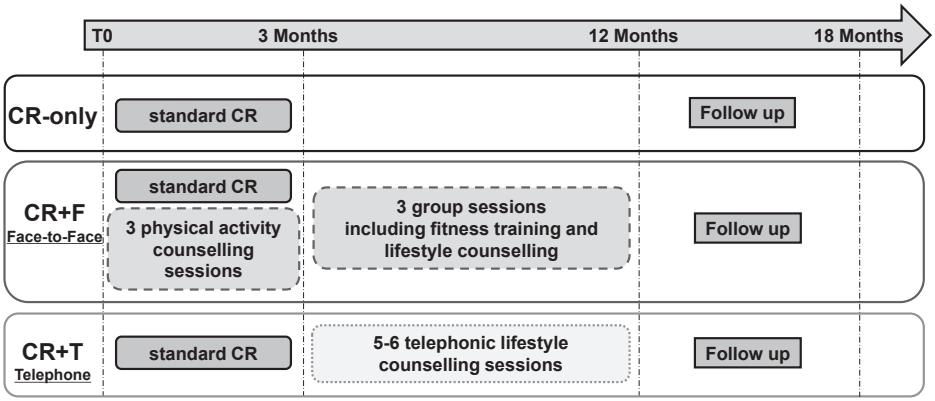


Figure 8.1 Study design and treatment allocation
CR= cardiac rehabilitation; CR-only= standard CR; CR+F = standard CR extended with face-to-face group counselling sessions; CR+T= standard CR extended with telephone counselling sessions; m=month.

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 8.1). 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 8.1). 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.

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 8A). 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 8.2). 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 8.1).

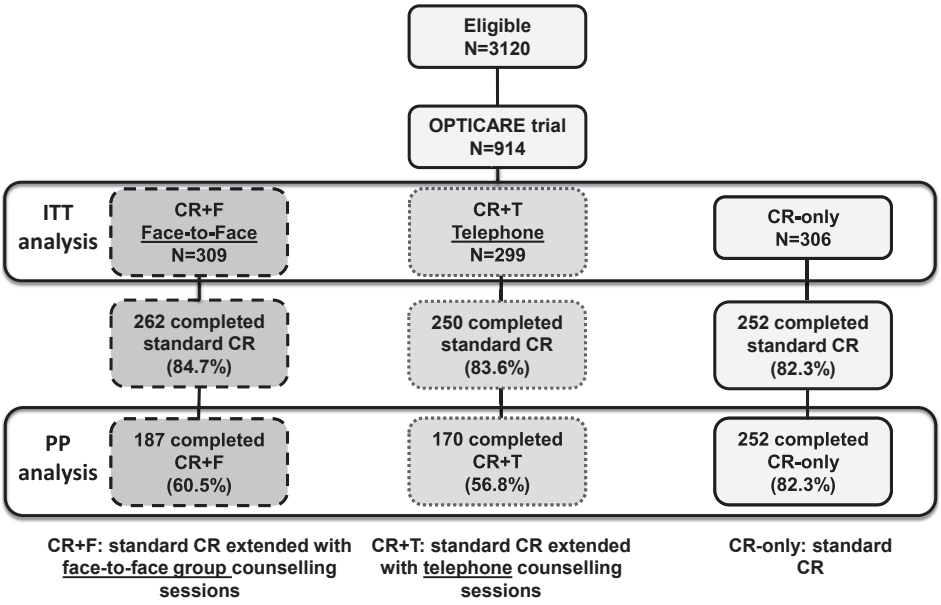


Figure 8.2 CONSORT (CONsolidated Standards Of Reporting Trials) flow diagram
CR= cardiac rehabilitation; CR+F = standard CR extended with face-to-face group counselling sessions; CR+T= standard CR extended with telephone counselling sessions; CR-only= standard CR; ITT= intention-to-treat; PP= per-protocol.

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.

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 8.3). 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 8.4). Changes to health-related quality of life (HRQL), anxiety and depression did not differ between groups (Appendix 8H).

Table 8.1 Patients characteristics by treatment group

	CR+F	CR+T	CR-only	P-values
	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.*

Per-protocol analyses

In the per-protocol analyses (CR+F: n=187; CR-only: n=252; Figure 8.2), the median SCORE results were similar to those from the ITT analyses (Figure 8.3). 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 8.4). Furthermore, total cholesterol at 18 months and Δ (18 months to baseline) favoured CR+F (both p<0.01).

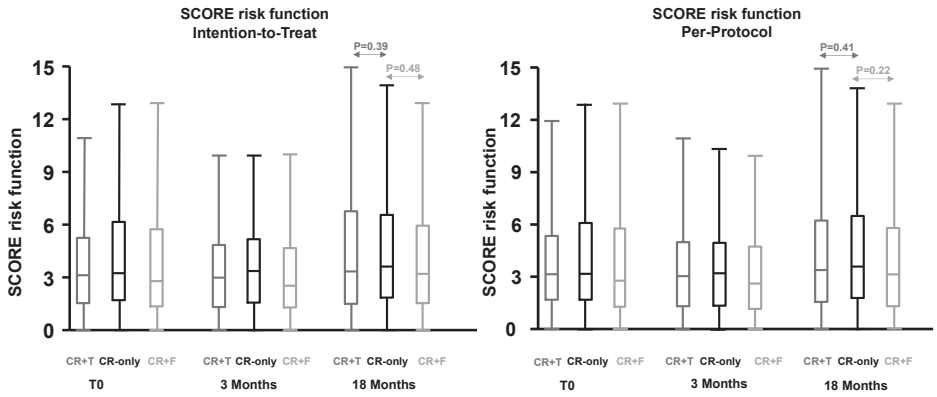


Figure 8.3 SCORE (Sytematic COronary Risk Evaluation) risk function (median, 25th-75th percentiles and minimum and maximum)

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.

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 8H). 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 8.3). 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 8I).

Per-protocol analyses

In the per-protocol analyses (CR+T: n=170; CR-only: n=252; Figure 8.2), the median SCORE results were similar to those from the ITT analyses (Figure 8.3). 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 8.4). 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).

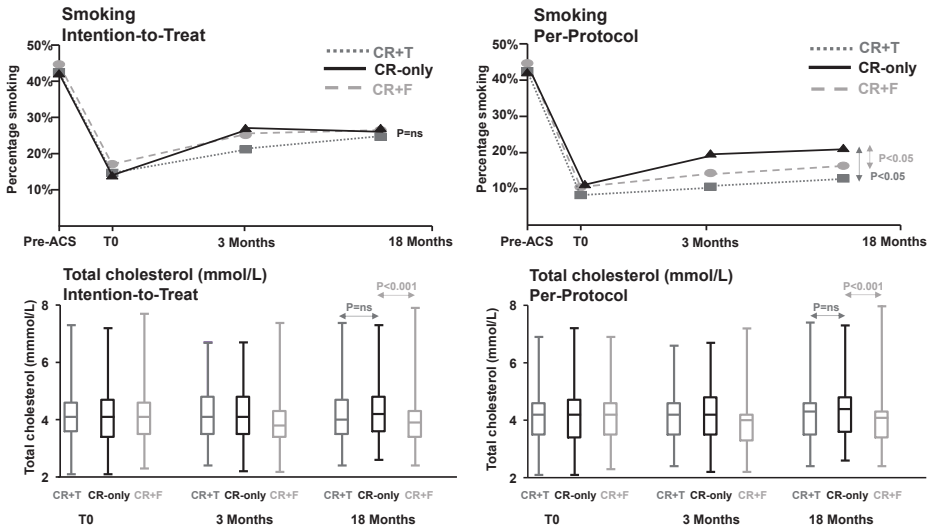


Figure 8.4 Smoking behaviour (percentages) and total cholesterol (median, 25th-75th percentiles and minimum and maximum)

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.

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 8I). 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 were on target in the CR+F group compared with 4.39 in the CR-only group (p=0.58), and 4.35 were 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 8B). 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 8C).

Appendix 8D and 8E (ITT), Appendix 8F and 8G (per-protocol) and Figure 8.5 show mean values for the measured cardiovascular risk factors at all time points.

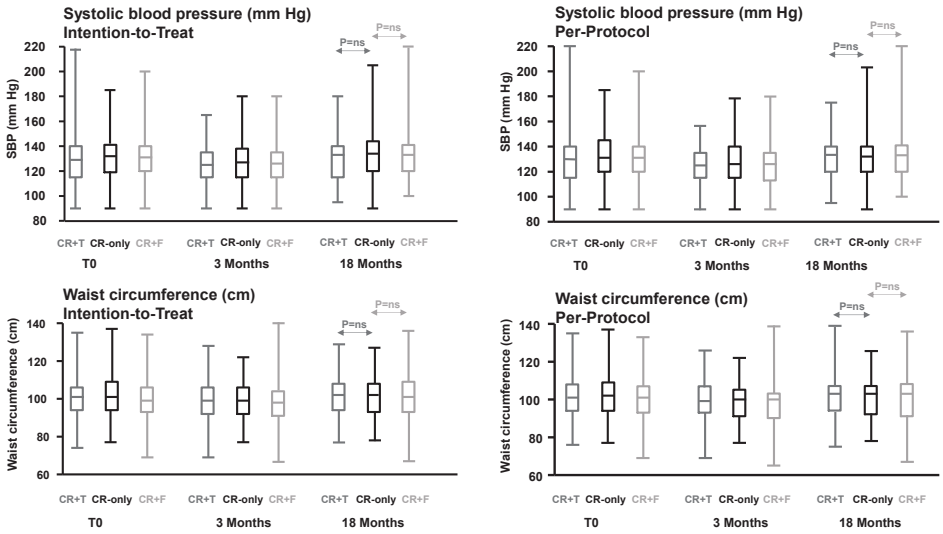


Figure 8.5 Systolic blood pressure and waist circumference (median, 25th-75th percentiles and minimum and maximum)

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.

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 8.2). 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.

Table 8.2 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 (22.9%)	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.

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REFERENCES

1. Euroaspire, I., I.I. Group, and E. European Action on Secondary Prevention by Intervention to Reduce, *Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events.* Lancet, 2001. **357**(9261): p. 995-1001.
2. Jolliffe, J.A., K. Rees, R.S. Taylor, D. Thompson, et al., *Exercise-based rehabilitation for coronary heart disease.* Cochrane Database Syst Rev, 2000(4): CD001800.
3. de Vries, H., H.M. Kemps, M.M. van Engen-Verheul, R.A. Kraaijenhagen, et al., *Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients.* Eur Heart J, 2015. **36**(24): p. 1519-28.
4. Gupta, R., B.K. Sanderson, and V. Bittner, *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**(1): p. 11-8.
5. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
6. Janssen, V., V. De Gucht, E. Dusseldorp, and S. Maes, *Lifestyle modification programmes for patients with coronary heart disease: a systematic review and meta-analysis of randomized controlled trials.* Eur J Prev Cardiol, 2013. **20**(4): p. 620-40.
7. Conroy, R.M., K. Pyorala, A.P. Fitzgerald, S. Sans, et al., *Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.* Eur Heart J, 2003. **24**(11): p. 987-1003.
8. Sunamura, M., N. Ter Hoeve, H.J. van den Berg-Emons, M. Haverkamp, 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): p. 324-30.
9. Hansson, L., T. Hedner, and B. Dahlof, *Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point.* Blood Press, 1992. **1**(2): p. 113-9.
10. Kemps, H.M., M.M. van Engen-Verheul, R.A. Kraaijenhagen, R. Goud, et al., *Improving guideline adherence for cardiac rehabilitation in the Netherlands.* Neth Heart J, 2011. **19**(6): p. 285-9.
11. van Engen-Verheul, M.M., H.M. Kemps, N.F. de Keizer, I.M. Hellemans, 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**(3): p. 504-14.
12. Selvarajah, S., G. Kaur, J. Haniff, K.C. Cheong, et al., *Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population.* Int J Cardiol, 2014. **176**(1): p. 211-8.
13. De Gucht, V., T. Van Elderen, L. van der Kamp, and N. Oldridge, *Quality of life after myocardial infarction: translation and validation of the MacNew Questionnaire for a Dutch population.* Qual Life Res, 2004. **13**(8): p. 1483-8.
14. Bjelland, I., A.A. Dahl, T.T. Haug, and D. Neckelmann, *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res, 2002. **52**(2): p. 69-77.
15. Jorstad, H.T., C. von Birgelen, A.M. Alings, A. Liem, et al., *Effect of a nurse-coordinated prevention programme on cardiovascular risk after an acute coronary syndrome: main results of the RESPONSE randomised trial.* Heart, 2013. **99**(19): p. 1421-30.

16. Bock, B.C., R.E. Carmona-Barros, J.L. Esler, and P.L. Tilkemeier, *Program participation and physical activity maintenance after cardiac rehabilitation.* Behav Modif, 2003. **27**(1): p. 37-53.
17. Leemrijse, C.J., R.J. Peters, C. von Birgelen, L. van Dijk, et al., *The telephone lifestyle intervention 'Hartcoach' has modest impact on coronary risk factors: A randomised multicentre trial.* Eur J Prev Cardiol, 2016. **23**(15): p. 1658-68.
18. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network.* Arch Intern Med, 2008. **168**(20): p. 2194-204.
19. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
20. Janssen, V., V. De Gucht, H. van Exel, and S. Maes, *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence.* J Behav Med, 2014. **37**(2): p. 308-21.
21. Kotseva, K., D. Wood, D. De Bacquer, G. De Backer, et al., *EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries.* Eur J Prev Cardiol, 2016. **23**(6): p. 636-48.
22. Kotseva, K., D. De Bacquer, C. Jennings, V. Gyberg, et al., *Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999-2013.* Glob Heart, 2017. **12**(4): p. 315-322.
23. Brown, T.M., A.F. Hernandez, V. Bittner, C.P. Cannon, et al., *Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program.* J Am Coll Cardiol, 2009. **54**(6): p. 515-21.
24. Vernooij, J.W., H.A. Kaasjager, Y. van der Graaf, J. Wierdsma, et al., *Internet based vascular risk factor management for patients with clinically manifest vascular disease: randomised controlled trial.* BMJ, 2012. **344**: e3750.
25. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.
26. Hancock, K., P.M. Davidson, J. Daly, D. Webber, et al., *An exploration of the usefulness of motivational interviewing in facilitating secondary prevention gains in cardiac rehabilitation.* J Cardiopulm Rehabil, 2005. **25**(4): p. 200-6.

APPENDIXES

Appendix 8A

Detailed methods

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 8.1) 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 8.1). 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 develop-

ing 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 8.1). 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 kinease-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 8.1). 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 8B Cardiovascular risk factors on target. CR+F *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		3 months (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
Body mass index ≤ 25kg/m2, %	23	24	23	22	22	24	0.76	0.93	0.55
Waist circumference, men ≤ 102cm, females ≤ 88 cm, %	46	46	56	55	52	44	0.96	0.81	0.15
LDL cholesterol ≤ 1.8 mmol/L, %	27	26	31	26	31	21	0.87	0.23	0.012
Total cholesterol ≤4.5 mmol/L, %	70	67	81	68	77	64	0.45	0.002	0.002
HDL cholesterol ≥1.0 mmol/L, %	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 8C Cardiovascular risk factors on target. CR+T *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		3 months (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=249	n=235	n=248	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 8D Cardiovascular risk factors. CR+F *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)*:* ***Intention-to-treat analysis***

	Baseline (T0)		3 months (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	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 8E Cardiovascular risk factors. CR+T *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)*:* ***Intention-to-treat analysis***

	Baseline (T0)		3 months (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=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 8F Cardiovascular risk factors. CR+F *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)*:* ***Per-protocol analysis***

	Baseline (T0)		3 months (T1)		18 months (T2)		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 8G Cardiovascular risk factors. CR+T *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)*:* ***Per-protocol analysis***

	Baseline (T0)		3 months (T1)		18 months (T2)		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 8H Health related quality of life, anxiety and depression. CR+F *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		3 months (T1)		18 months (T2)		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)/ mean differ rence [95%CI]	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 [0.19, 0.54]	0.46 [0.31, 0.64]	0.39	0.25
Physical, mean score (SD)/ mean difference [95%CI]	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 [0.62, 0.98]	0.86 [0.65, 1.00]	0.84	0.19
Social, mean score (SD) / mean difference [95%CI]	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 [0.68, 1.02]	0.80 [0.63, 0.98]	0.72	0.65
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)/ mean difference [95%CI]	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 [0.27, 0.65]	0.47 [0.30, 0.65]	0.97	0.004
Physical, mean score (SD)/ mean difference [95%CI]	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 [0.64, 1.04]	0.83 [0.65, 1.01]	0.92	0.015
Social, mean score (SD) / mean difference [95%CI]	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 [0.71, 1.11]	0.82 [0.64, 0.99]	0.72	0.65
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) or percentages or mean difference [95% CI: 95% confidence interval]; p-values are Student's t-tests or Chi-squared tests.
HRQL= health related quality of life; CR+F= CR extended with face-to-face counselling sessions; CR-only= standard CR.

Appendix 8I Health related quality of life, anxiety and depression. CR+T *vs* CR-only pre CR (T0), post-CR (T1) and at 18 months (T2)

	Baseline (T0)		3 months (T1)		18 months (T2)		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)/ mean difference [95%CI]	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 [0.31, 0.83]	0.46 [0.31, 0.64]	0.98	0.56
Physical, mean score (SD)/ mean difference [95%CI]	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 [0.63, 0.92]	0.86 [0.65, 1.00]	0.65	0.15
Social, mean score (SD) / mean difference [95%CI]	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 [0.68, 1.02]	0.81 [0.63, 0.98]	0.79	0.33
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)/ mean difference [95%CI]	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 [0.23, 0.58]	0.47 [0.30, 0.63]	0.63	0.04
Physical, mean score (SD)/ mean difference [95%CI]	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 [0.54, 0.88]	0.83 [0.65, 1.01]	0.36	0.31
Social, mean score (SD) / mean difference [95%CI]	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 [0.50, 0.86]	0.82 [0.64, 0.99]	0.31	0.60
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

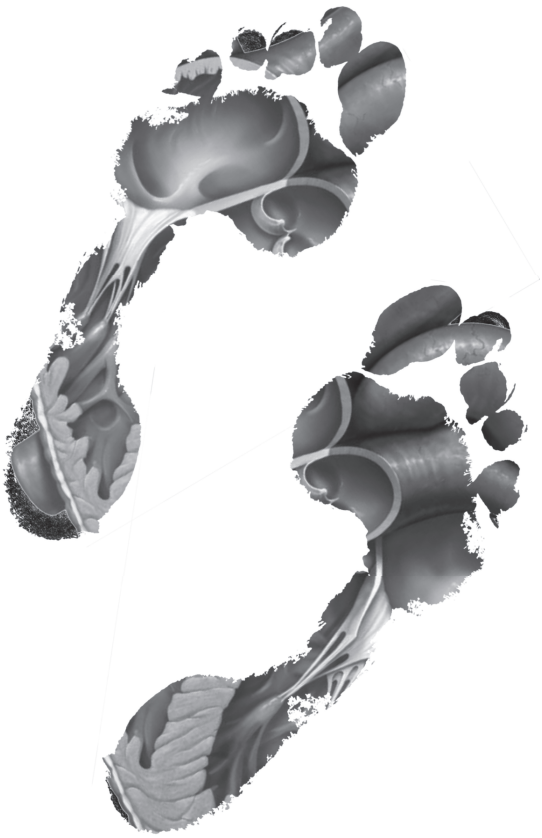
Data are mean (SD) or percentages or mean difference [95% CI: 95% confidence interval]; p-values are Student's t-tests or Chi-squared tests.
HRQL= health related quality of life; CR+T= CR extended with telephone counselling sessions; CR-only= standard CR.

Chapter 9

Extended cardiac rehabilitation improves aerobic capacity and fatigue: A randomized controlled trial

Nienke ter Hoeve
Madoka Sunamura
Henk J. Stam
Ron T. van Domburg
Rita J. G. van den Berg-Emons

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 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 9.1).

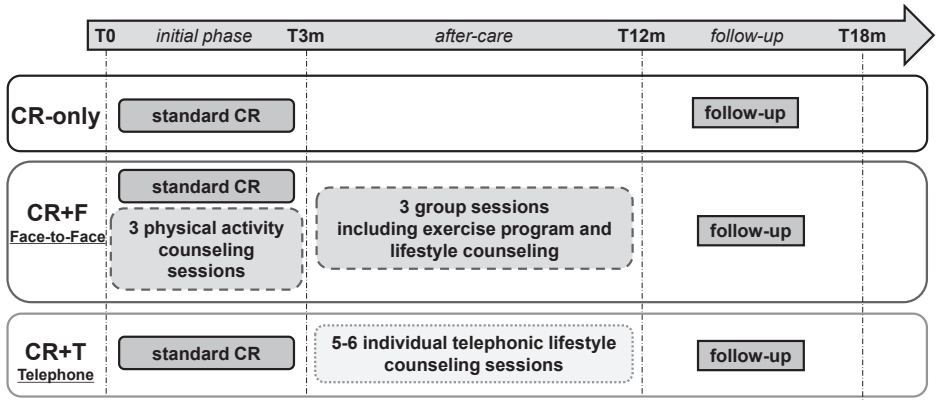


Figure 9.1 Treatment allocation and measurement time points
CR-only= standard cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus individual telephonic counseling; m= months.

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 9.1).

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 9.2). The remaining 740 patients were included in the analysis. The mean patient age was 57 years and 81% were male (Table 9.1). 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

Table 9.1 Participant baseline characteristics (n = 740)

Characteristic	CR+F (n = 251)	CR+T (n = 245)	CR-only (n = 244)
Male, %	80.5	82.4	80.3
Age, mean (SD)	57.5 (8.8)	56.7 (9.2)	57.5 (9.2)
Therapeutic intervention at index event, %			
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, %			
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, %[a]	80.5	84.0	83.4
Employed, %[b]	64.7	60.5	56.0

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).

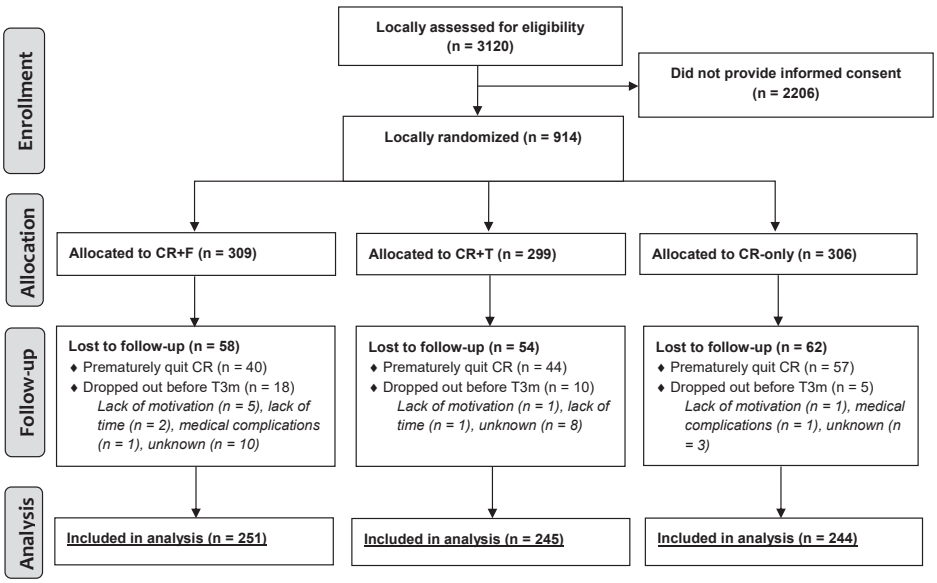


Figure 9.2 Consort flow diagram
CR= cardiac rehabilitation; CR+F= cardiac rehabilitation plus face-to-face group counseling; CR+T= cardiac rehabilitation plus individual telephonic counseling; CR-only= standard cardiac rehabilitation; m= months.

Intervention effects

Figure 9.3 shows the observed data for all outcomes measures. Outcomes of the GEE analyses are presented in Table 9.2.

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 9.2). This difference was no longer present at T18m. No intervention effects were found for CR+T (Table 9.2).

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 9.2). 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 9.2). 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 9.2).

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.

Table 9.2 General estimating equation model[ǂ] intervention effects

		CR+F vs CR-only			CR+T vs CR-only		
		B[†]	CI	P	B[†]	CI	P
Aerobic capacity (n= 674)							
6MWT, meters	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 score	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 score[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 score	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+T= cardiac rehabilitation plus individual telephonic counseling; CR-only= standard cardiac rehabilitation; m= months; FSS= Fatigue Severity Scale; n=number of patients that had at least 1 outcome post-baseline and were included in the GEE analysis.

[ǂ]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.

[†]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.

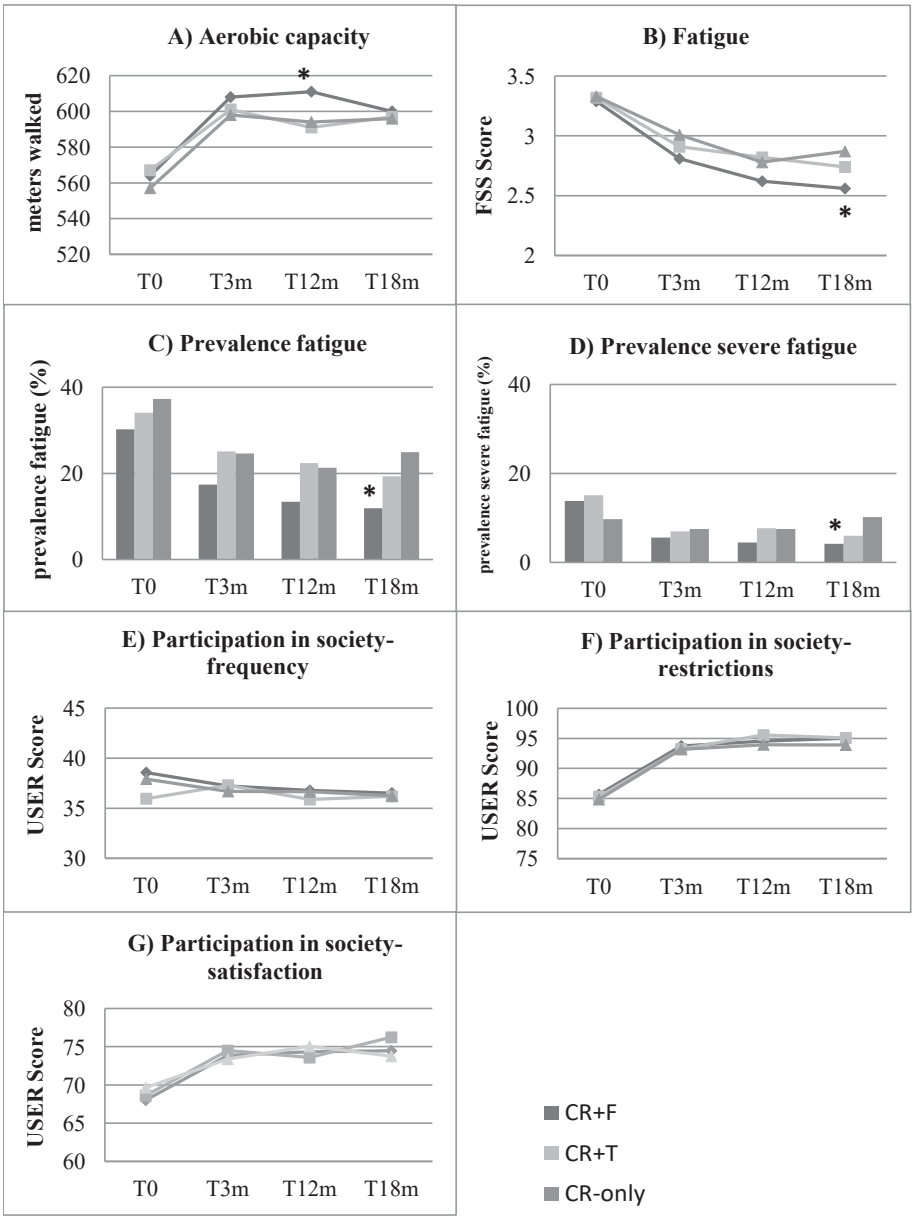


Figure 9.3 A) Aerobic capacity (meters walked on 6-minute walk test); **B)** FSS score, Fatigue severity scale score; **C)** Prevalence of fatigue (FSS > 4.0); **D)** Prevalence of severe fatigue (FSS > 5.2); **E)** Participation in society (frequency score of Utrecht Scale for Evaluation of Rehabilitation-Participation [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; FSS= fatigue severity score.

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

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 month period 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 publication 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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REFERENCES

1. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
2. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
3. Piepoli, M.F., U. Corra, W. Benzer, B. Bjarnason-Wehrens, et al., *Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 1-17.
4. de Vries, H., H.M. Kemps, M.M. van Engen-Verheul, R.A. Kraaijenhagen, et al., *Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients.* Eur Heart J, 2015. **36**(24): p. 1519-28.
5. Anderson, L., N. Oldridge, D.R. Thompson, A.D. Zwisler, et al., *Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis.* J Am Coll Cardiol, 2016. **67**(1): p. 1-12.
6. Ter Hoeve, N., M.E. van Geffen, M.W. Post, H.J. Stam, et al., *Participation in society in patients with coronary artery disease before and after cardiac rehabilitation.* Arch Phys Med Rehabil, 2015. **96**(6): p. 1110-6.
7. van Geffen, M.E., N. Ter Hoeve, M. Sunamura, H.J. Stam, et al., *Fatigue during and after cardiac rehabilitation.* J Rehabil Med, 2015. **47**(6): p. 569-74.
8. Sandercock, G., V. Hurtado, and F. Cardoso, *Changes in cardiorespiratory fitness in cardiac rehabilitation patients: a meta-analysis.* Int J Cardiol, 2013. **167**(3): p. 894-902.
9. Moholdt, T., I.L. Aamot, I. Granoien, L. Gjerde, 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): p. 388-90.
10. Beatty, A.L., N.B. Schiller, and M.A. Whooley, *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): p. 1096-102.
11. Taylor, C., C. Tsakirides, J. Moxon, J.W. Moxon, 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.
12. Brink, E., G. Grankvist, B.W. Karlson, and L.R. Hallberg, *Health-related quality of life in women and men one year after acute myocardial infarction.* Qual Life Res, 2005. **14**(3): p. 749-57.
13. Sunamura, M., N. Ter Hoeve, H.J. van den Berg-Emons, M. Haverkamp, 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): p. 324-30.
14. Sunamura, M., N. Ter Hoeve, R.J.G. van den Berg-Emons, M.L. Geleijnse, et al., *Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes.* Heart, 2018. **104**(5):p. 430-7.

15. Ter Hoeve, N., M. Sunamura, H. Stam, E. Boersma, et al., *Effects of two behavioral cardiac rehabilitation interventions on physical activity: A randomized controlled trial.* 2017.
16. Slaman, J., M. Roebroeck, W. van der Slot, J. Twisk, et al., *Can a lifestyle intervention improve physical fitness in adolescents and young adults with spastic cerebral palsy? A randomized controlled trial.* Arch Phys Med Rehabil, 2014. **95**(9): p. 1646-55.
17. Rogers, L.Q., K.S. Courneya, P.M. Anton, S. Verhulst, 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): p. 1901-6
18. Nooijen, C.F., H.J. Stam, T. Sluis, L. Valent, 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): p. 772-780.
19. Kulinski, J.P., A. Khera, C.R. Ayers, S.R. Das, et al., *Association between cardiorespiratory fitness and accelerometer-derived physical activity and sedentary time in the general population.* Mayo Clin Proc, 2014. **89**(8): p. 1063-71.
20. Prince, S.A., C.M. Blanchard, S.L. Grace, and R.D. Reid, *Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates.* Eur J Prev Cardiol, 2016. **23**(8): p. 818-25.
21. Puetz, T.W., *Physical activity and feelings of energy and fatigue: epidemiological evidence.* Sports Med, 2006. **36**(9): p. 767-80.
22. Hancock, K., P.M. Davidson, J. Daly, D. Webber, et al., *An exploration of the usefulness of motivational interviewing in facilitating secondary prevention gains in cardiac rehabilitation.* J Cardiopulm Rehabil, 2005. **25**(4): p. 200-6.
23. Prince, S.A., T.J. Saunders, K. Gresty, and R.D. Reid, *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): p. 905-19.
24. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
25. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.
26. Laboratories, A.T.S.C.o.P.S.f.C.P.F., *ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. **166**(1): p. 111-7.
27. Bellet, R.N., L. Adams, and N.R. Morris, *The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review.* Physiotherapy, 2012. **98**(4): p. 277-86.
28. Nadarajah, M., M. Mazlan, L. Abdul-Latif, and H.T. Goh, *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): p. 703-9.
29. Learmonth, Y.C., D. Dlugonski, L.A. Pilutti, B.M. Sandroff, et al., *Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale.* J Neurol Sci, 2013. **331**(1-2): p. 102-7.
30. Valko, P.O., C.L. Bassetti, K.E. Bloch, U. Held, et al., *Validation of the fatigue severity scale in a Swiss cohort.* Sleep, 2008. **31**(11): p. 1601-7.
31. Merkies, I.S., P.I. Schmitz, J.P. Samijn, F.G. van der Meche, et al., *Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group.* Neurology, 1999. **53**(8): p. 1648-54.

32. Post, M.W.M., C.H. van der Zee, J. Hennink, C.G. Schafrat, et al., *Validity of the Utrecht Scale for Evaluation of Rehabilitation-Participation.* Disabil Rehabil 2012. **34**(6): p. 478-485.
33. Sasaki, J.E., D. John, and P.S. Freedson, *Validation and comparison of ActiGraph activity monitors.* Journal of Science and Medicine in Sport, 2011. **14**(5): p. 411-6.
34. Carr, L.J. and M.T. Mahar, *Accuracy of intensity and inclinometer output of three activity monitors for identification of sedentary behavior and light-intensity activity.* J Obes, 2012. **2012**: p. 460271.
35. Twisk, J. and W. de Vente, *Attrition in longitudinal studies. How to deal with missing data.* J Clin Epidemiol, 2002. **55**(4): p. 329-37.
36. Barriga, S., F. Rodrigues, and C. Barbara, *Factors that influence physical activity in the daily life of male patients with chronic obstructive pulmonary disease.* Rev Port Pneumol, 2014. **20**(3): p. 131-7.
37. Bunevicius, A., A. Stankus, J. Brozaitiene, S.S. Girdler, et al., *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**(2): p. 310-6.
38. Mikkelsen, T., K. Korsgaard Thomsen, and O. Tchijevitch, *Non-attendance and drop-out in cardiac rehabilitation among patients with ischaemic heart disease.* Dan Med J, 2014. **61**(10): A4919.
39. Sunamura, M., N. Ter Hoeve, M.L. Geleijnse, R.V. Steenaard, 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): p. 618-28.

Chapter 10

General Discussion

In ***part I*** of this thesis we focused on changes in physical activity, sedentary behaviour, fatigue and participation in society during current standard cardiac rehabilitation (CR). In ***part II***, we focused on the main objective of this thesis: the added value of behavioural interventions integrated into CR on physical activity in patients with an acute coronary syndrome (ACS). Also, effects of the behavioural interventions on sedentary behaviour, cardiovascular health, aerobic capacity, fatigue and participation in society were studied. In the current chapter, the main findings of ***part I*** and ***part II*** are interpreted and discussed in the context of published literature. After that, methodological considerations, clinical implications and future directions are described.

PART I: STANDARD CARDIAC REHABILITATION

Main findings

CR programs focus on the promotion of a healthy lifestyle and optimization of cardiovascular risk factors and psychosocial status.[1-3] CR is essential for patients with coronary heart disease (CHD) and was shown to have substantial benefits on risk factors such as lipid profile and blood pressure, quality of life, aerobic capacity, mortality, and hospital readmissions.[4-7] Results of part I of this thesis showed that physical activity, sedentary behaviour, fatigue and participation in society also improved during CR in patients with CHD (see Figure 10.1). These benefits were maintained up till at least 12 months. Despite the favourable results, further improvements are warranted. Patients still spend relatively little time in physical activity and a long time sedentary post CR. Furthermore, prevalence of severe fatigue remained high and some restrictions and dissatisfaction with participation in society persisted. The results are discussed in more detail below.

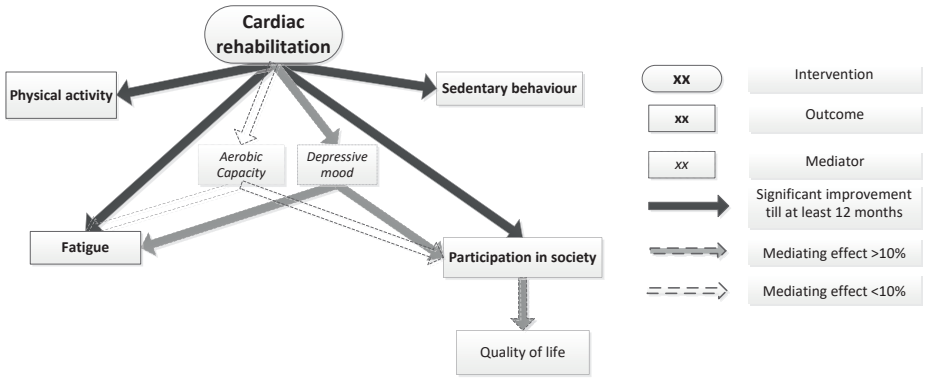

Figure 10.1 Schematic representation of the outcomes of part I of this thesis

Discussion

Improvements in physical activity and sedentary behaviour during CR are insufficient

An important goal of CR is to improve physical activity.[1] However, results of the systematic review presented in ***chapter 2***, revealed that standard CR seems insufficient to reach this goal in patients with ACS. The majority of randomized controlled trials (RCT's) that were included in this systematic review used self-reported outcome measures for physical activity, which are known to have limited validity and reliability.[8-11] Therefore, in ***chapter 3,*** we studied longitudinal changes in physical activity more in-depth using objective accelerometers in a cohort of 135 patients with ACS. During CR, improvements were found in moderate-to-vigorous intensity physical activity (MVPA; +5 min per day) and daily step count (+583 steps/day), which lasted up to at least 12 months. Magnitude of these improvements can be considered modest.[12] Similar improvements in physical activity during CR have been reported in a previous study[13] and a cross-sectional study showed comparable step counts and MVPA levels after CR.[14] Although the improvements reached during CR are encouraging, MVPA time remained low compared to healthy adults (7.0% of waking hours vs 10.2%).[15] With regard to step count, only half of the patients achieved a daily step target of 6500 steps, which is recommended to prevent cardiovascular disease progression.[16,17] In addition, we found that patients with ACS tend to break up physical activity into short bouts (<10 min), which is suggested to be detrimental for health.[18-20] This distribution did not change during CR. Our findings suggest that optimization of CR with regard to physical activity is needed. The RCT's selected for the systematic review ***(chapter 2)*** showed a variability in the investigated CR programmes. We performed an additional analysis to gain insight into the most successful strategy to improve physical activity. No evidence was found that extending CR duration or increasing the volume of the exercise programme leads to larger improvements. This is in line with outcomes of previous research that already suggested that aerobic interventions do not automatically translate into increases in physical activity.[21] Results did, however, suggest that home-based CR might be more successful compared to centre-based CR. Possibly, physical activity is better incorporated into the daily routine after home-based programmes. Furthermore, we found evidence for the effectiveness of interventions using self-monitoring of physical activity. This finding is supported by previous studies that confirmed the potential of interventions containing behavioural techniques to change physical activity such as self-monitoring, but also goal-setting and developing plans for relapse.[22-25] Although behavioural programmes focussing on lifestyle changes such as healthy diet and stress management are usually offered during CR, behavioural programmes focussing on physical activity are often lacking. There seems to exist a gap between the CR guidelines that recommend implementing physical activity counselling[1-3] and daily practice.

Independent of physical activity, increased sedentary time is also related to unfavourable health.[26-29] Outcomes of ***chapter 3*** revealed that patients had decreased sedentary time with nearly 22 min per day at the end of CR. In addition, sedentary time became more fragmented with more breaks and shorter sedentary periods, as is suggested to gain extra health benefits.[30,31] The magnitude of the found improvements is comparable to improvements in sedentary time reported in a large meta-analysis for healthy adults after participation in a lifestyle intervention.[32] Time in sedentary behaviour was mainly relocated to activities of light intensity. Although a previous study demonstrated that relocating time to MVPA yields greater reductions in risk factors, meaningful reductions in risk can also be achieved by relocating time in sedentary behaviour to light activity.[33] Regardless the promising improvements, sedentary time remained high at the end of CR with 62.8% of waking hours spent sedentary (approximately 9 hours), compared to 57.5% in healthy adults.[15] Outcomes of previous studies also suggest that cardiac patients tend to be sedentary and inactive.[34-36] Current CR programmes generally do not target sedentary behaviour. Our findings highlight the need to develop adjusted CR targets focusing not only on physical activity but also on sedentary behaviour.

CR should focus on severe fatigue and dissatisfaction with participation in society

In ***chapters 4 and 5***, we focused on fatigue and participation in society in a cohort of 121 patients with CHD. Results of ***chapter 4*** showed a high level of fatigue at the start of CR (21% experienced mild fatigue and 18% severe fatigue). The prevalence of mild fatigue decreased during CR and in the first year after CR to a level which is comparable to that of a healthy population.[37] However, standard CR appeared inadequate for a subgroup of patients that experienced more severe fatigue. Post CR and at 12 months follow-up, respectively 11% and 8% of patients remained severely fatigued, which is high when compared to a prevalence of 3.5% reported for healthy adults.[37] Patients with severe fatigue should probably be identified in an early stage of CR, so that additional interventions to relieve fatigue can be offered. An exploratory mediation analysis suggested that improvements in fatigue are mainly mediated by improvements in depressive mood, and only for a small amount by improvements in aerobic capacity. This suggests that interventions targeting severe fatigue should probably focus more on the mental, rather than the physical, component of fatigue. An association between depressive mood and fatigue has been reported before.[38]

With regard to participation in society, the focus in CR is often on return to work. Since a large proportion of CR patients are retired or unemployed (in our sample 35%), the focus in ***chapter 5*** was on domestic, occupational and recreational activities. Although our results did not show improvements in frequency of participation, considerable improvements were found in experienced restriction and satisfaction with participation

in society. In addition, results showed that satisfaction with participation and experienced restrictions are related to quality of life, whereas frequency of participation is not. These results are in line with previous studies[39,40] and confirm the relevance of the found improvements. Furthermore, these findings underline the importance of focussing on experienced restrictions and satisfaction, instead of focusing solely on frequency of participation. Despite the improvements, a large proportion of patients still reported experiencing restrictions (40%) and dissatisfaction (49%) at the end of CR in at least one activity of participation in society. A more individualized approach focusing on areas in which restrictions and dissatisfaction are experienced might help to optimize participation and, as a consequence, quality of life. In our study cohort, lasting restrictions were mainly experienced during exercising and lasting dissatisfaction during going out, exercising, outdoor activities, housekeeping and contact with friends. To gain more insight how to target these lasting restrictions and dissatisfaction, we performed an exploratory mediation analysis. We found indications that improvements in restrictions in participation were mediated by aerobic capacity (9%) and improvements in satisfaction by depressive mood (20%).

Additional interventions needed

Outcomes of Part I suggest that CR could be optimized with regard to physical activity, sedentary behaviour, fatigue and participation in society. Mainly for physical activity, there seems to be a large gap between guidelines and daily practice. In the OPTICARE trial, the additional effects of behavioural interventions added to standard CR were investigated (Part II). Primary aim was a further improvement in physical activity and cardiovascular health. Since the interventions had a broad focus on several aspects of behaviour and daily life, there could be an additional effect on sedentary behaviour, fatigue and participation in society.

PART II. BEHAVIOURAL INTERVENTIONS ADDED TO CARDIAC REHABILITATION

Main findings

Chapter 6 describes the design of the OPTICARE RCT. Patients were randomized to standard CR (CR-only) or one of the two novel behavioural interventions. The first novel intervention (CR+F) consisted of 3 months of standard CR with three pedometer-based, face-to-face physical activity group counselling sessions followed by 9 months of aftercare with three general lifestyle, face-to-face, group counselling sessions. The second novel intervention (CR+T) consisted of standard CR followed by 9 months of aftercare

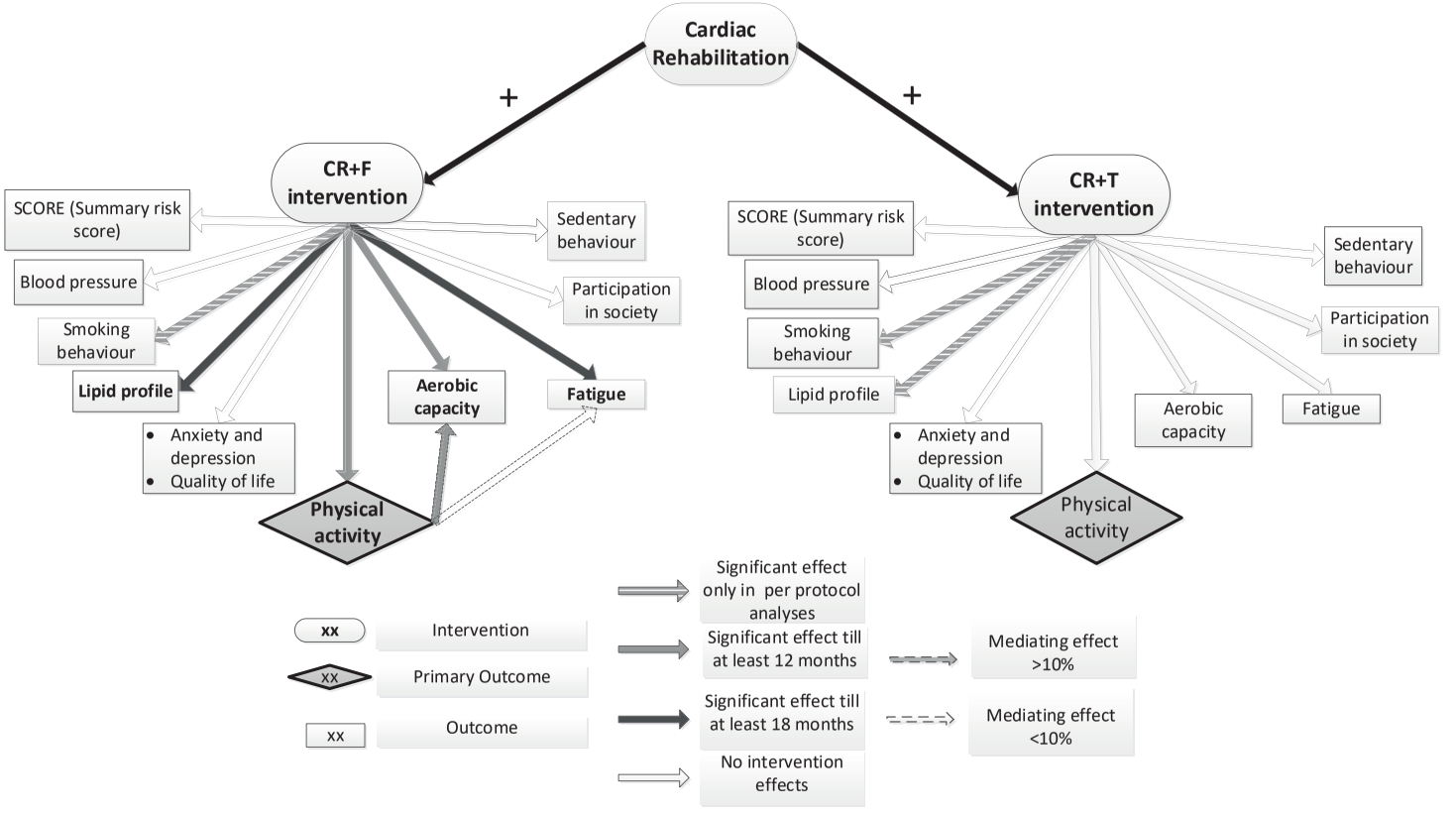

Figure 10.2 Schematic representation of the outcomes of the OPTICARE randomized controlled trial: intervention effects of novel interventions compared with standard CR only

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

with five to six general lifestyle, telephonic counselling sessions. Both novel behavioural interventions did not improve MVPA time as compared to CR-only. However, the physical activity counselling sessions offered in the CR+F intervention during the 3-month CR period were successful in increasing daily step count and increasing time spent in prolonged physical activity periods (>10 min). During the CR+F aftercare programme, improvements in step count partly diminished, while improvements in prolonged physical activity were maintained. Furthermore, the CR+F intervention resulted in an improved maintenance of aerobic capacity up to 12 months and in long-term improvements in fatigue. The CR+T intervention did not result in additional benefits. The outcomes are discussed in detail below. See also Figure 10.2.

Discussion

Pedometer-based behavioural group intervention increases physical activity

Our main results ***(chapter 7)*** showed that the pedometer-based physical activity counselling sessions that were integrated into the 3-month CR programme of the CR+F group resulted in an additional improvement of 513 steps/day as compared to CR-only. As a consequence, more patients were reaching a daily step target of 6500 (62% for CR+F vs 47% for CR-only), which is advised for prevention of cardiac disease progression. The magnitude of the improvements was similar to those reported in a large meta-analysis summarizing the effect of physical activity interventions among healthy subjects, which considered this a modest improvement.[12] Regardless the promising improvements in step count, there were no additional improvements in MVPA time. This indicates that an increase in step count does not automatically translate into increased MVPA time. Possibly, part of the walking activities was classified as light intensity or the extra walking activities were compensated for by decreasing other MVPA activities such as biking. Future research is needed to determine whether increasing step count or increasing MVPA time is more important for health. Our finding that patients mainly increased the activity on which they received objective feedback (in our study provided by pedometers) emphasizes the importance of self-monitoring for physical activity change, which is in line with results of other studies.[23] Unfortunately, during participation in the face-to-face aftercare programme offered to the CR+F group after the end of the initial CR phase, the improvements in step count partly diminished. This aftercare programme focused on several lifestyle changes simultaneously (eg. diet, physical activity and psychosocial functioning). In line with literature, we postulate that for more successful maintenance, the aftercare programme probably should have focused exclusively on physical activity.[12,41]

In addition to the improvements in step count, distribution of physical activity over time also improved in the CR+F group. MVPA was more often accumulated in prolonged periods of at least 10 minutes, which is recommended for optimal health benefits.[18-20] These additional improvements were maintained up to at least 18 months.

The CR+T group experienced no additional benefits with regard to physical activity. Since the CR+T aftercare programme also focused on several lifestyle changes, this is in line with our hypothesis that an exclusive focus on physical activity might be needed. The lack of effects could also be due to the mode of delivery (by telephone). A previous meta-analysis suggested that face-to-face contact is more successful for physical activity improvements.[42] In contrast to our findings, two previous studies investigating the effects of the COACH programme on which our telephonic aftercare programme (CR+T) was based, did show physical activity improvements.[43,44] These outcomes were, however, self-reported, and therefore less valid[8-11], which may explain the discrepancy with our results.

Both novel interventions did not lead to additional benefits with regard to sedentary behaviour ***(chapter 7)***. In the CR+F intervention, our primary aim was to improve physical activity. Only general advice was given about the health benefits of breaking up sedentary time. In the CR+T intervention, there was no specific attention for changing sedentary behaviour. Our results suggest that a focus on physical activity does not lead to changes in sedentary behaviour and that giving general information is insufficient. These results are in line with results of previous studies in healthy adults.[24,32]

Patients already achieve health outcome targets after standard CR

Results presented in ***chapter 8*** show that the novel interventions did not lead to additional improvements in SCORE, a risk function that estimates the 10 years risk of cardiovascular death based on age, gender and the modifiable components total cholesterol, systolic blood pressure and smoking status. In addition, there were no between-group differences in number of (cardiovascular) events. Although the individual risk factor total cholesterol did show some additional improvements in the CR+F group, the magnitude of this improvement seemed clinically irrelevant and was probably mainly caused by more strict titration of medication in the CR+F group, rather than by the behavioural group intervention. Further improvements were also not found for the individual risk factors blood pressure and smoking status. Patients randomized to standard CR without any additions (CR-only) were already successful; 75% of the patients were meeting guidelines for systolic blood pressure at 18 months, 64% for total cholesterol and 73% were not smoking. Since we did not include a control group that did not participate in CR, caution is required when attributing the success directly to CR. Since lipids and blood pressure

were already well-controlled at baseline, advances in medical treatment and cardio protective drugs seem to be at least partly responsible for the favourable results. With these well-controlled risk profiles, additional improvements with lifestyle modification will be more difficult to accomplish. An alternative explanation for the lack of additional health improvements is the poor adherence to the protocol. In an additional per-protocol analysis, we found that adherent patients participating in both novel interventions were more likely to permanently quit smoking compared to adherent patients participating in CR-only. Results of this per-protocol analysis should, however, be interpreted with caution. To be included in this analysis, patients needed to attend >75% of sessions. The CR-only group participated only in standard CR, whereas the extended groups had to attend additional sessions and therefore needed much greater engagement (and possibly motivation) over a much longer time period to be considered adherent, which could have caused a bias.

Studies that investigated CR aftercare programmes that differed in frequency and content of sessions, presented more successful outcomes regarding cardiovascular health in patient samples comparable to ours.[44-47] However, these studies all compared their interventions to usual care, generally not including CR. This difference in study design might explain the inconsistency with our results. A recent RCT that compared extended behavioural CR to standard CR reported outcomes comparable to ours.[48]

The lack of further improvements in cardiovascular health could suggest that the additional improvements in physical activity, found for the CR+F intervention, were insufficient to yield improvements in cardiovascular health. However, physical activity remains important. Physical activity can also influence mortality through other pathways (e.g. reducing chronic inflammation; improving coronary blood flow or augmenting cardiac function).[49] There are some alternative explanations why the improvements in physical activity did not translate to additional improvements in cardiovascular health. First, the majority of patients were using medications which could have masked effects on for instance blood pressure and cholesterol. Second, changes in physical activity possibly should be larger and sustained for a longer period to affect cardiovascular health. Finally, a large variation in physical activity was observed. Probably, patients with a low level of physical activity at baseline can profit more compared to patients with a high baseline level.

Secondary outcomes

In addition to the improvements in physical activity, the CR+F intervention was successful in preventing the commonly seen decline in aerobic capacity after ending CR.[50,51] An exploratory mediation analysis suggested that these benefits could partly be explained

by improvements in physical activity. In addition, the improved maintenance of aerobic capacity gains could be the result of the exercise component that was offered during the CR+F aftercare programme. Although the frequency of this exercise programme (three 1-hour sessions during a 9-month period) was insufficient to maintain aerobic capacity, these sessions may have encouraged patients to pursue activities that improve aerobic capacity. In line with previous studies[51-53], aerobic capacity started to decline in the CR+F group as soon as the aftercare programme ended. This suggests that ongoing attention is needed for permanent maintenance of gains.

The CR+F intervention was also successful in further improving fatigue up till at least 18 months. Prevalence of fatigue reached levels which are comparable or even lower than the prevalence reported for healthy people (11.9% vs 18% for mild-to-severe fatigue and 4.2% vs 3.5% for severe fatigue). This finding is of clinical relevance since outcomes of ***chapter 3*** revealed that prevalence of severe fatigue remained high after standard CR. Fatigue is known to influence quality of life.[54] The additional improvements in fatigue seemed unrelated to improvements in physical activity. The study design was not appropriate to detect what other factors could have caused the success. In ***chapter 3*** we described an association between depressive symptoms and fatigue. Since CR+F did not improve depression ***(chapter 7)***, improvements in depression are not expected to have mediated the improvements in fatigue.

No improvements in aerobic capacity and fatigue were seen for the CR+T group. Additionally, both novel interventions did not have secondary effects on participation in society, quality of life, anxiety, and depression ***(chapter 7 & 8)***. Even though lower anxiety and higher quality of life were seen at 18 months in adherent patients randomized to CR+F (visiting at least 75% of sessions), these improvements were mainly caused by baseline differences, rather than by the intervention. Patients with higher anxiety and lower quality of life were more likely to drop-out during the extended programme.

METHODOLOGICAL CONSIDERATIONS

Study design

In Part I of this thesis we investigated changes in several understudied outcomes in a longitudinal cohort of patients with CHD participating in CR. Since no control group was included and the study was performed in a single centre, caution is required when attributing changes directly to CR.

Outcomes of part II of this thesis are based on the OPTICARE randomized controlled trial. The OPTICARE was set up as a pragmatic trial. The design of the novel interventions makes it impossible to specify which elements of the programme contributed to the improvements. Due to the nature of the study, blinding was not feasible. Due to our strict measurement protocol, we believe that this did not result in relevant bias.

Although we did include the number of patients in the OPTICARE trial as intended after power calculation, the percentage of drop-outs was higher than expected. As a consequence, the number of patients in the main analysis for physical activity was lower than intended. However, since only one of the novel interventions showed significant benefits in physical activity as compared to CR-only, we decided to not directly compare the two novel interventions, thus no longer needing a Bonferroni correction. To be able to detect the hypothesized differences between each novel intervention and CR-only ($p<0.05$), only 57 patients in each arm were needed. So, we believe that we still had sufficient power to detect clinically meaningful differences.

Although we did not perform formal mediator analyses, our exploratory analyses performed in chapter 4, 5 and 9 do offer insight into possible mediators of results.

Generalizability

First, participants in our trial consisted of a relatively low-risk population. Included patients were young (on average 57 years) and had well-preserved cardiac function (left ventricular function >40%). The majority had no cardiac history. Our outcomes do not automatically generalize to a higher-risk population. In addition, our results do not generalize to women, who were underrepresented in our trial (19%). Second, Intention-to-treat analysis with full datasets is preferred to avoid bias in RCTs.[55] To answer our main question, patients had to visit the rehabilitation centre to have the accelerometer installed. Patients who dropped out before the second measurement and no longer visited the rehabilitation centre, as a consequence, had no follow-up physical activity measurement. Therefore, a full ITT analysis was not possible. We included only patients with at least 1 follow-up measurement in the analysis. The group that was excluded from analysis was on average older and had higher cardiovascular risk. Lastly, an additional bias could be caused by compliance to the intervention. Sensitivity analyses performed in **chapter 7**, showed that intervention effects were more pronounced for adherent patients who participated in at least 75% of interventions sessions.

In conclusion, our results are probably mainly valid for more compliant, lower-risk, male patients.

Outcome measures

Physical behaviour was objectively measured using accelerometers. Objective measurement is the method of choice, as it is more valid than self-reported measures.[11] In addition, accelerometers also estimate distribution and intensity of activities and not only volume of walking activities, which is a major strength when compared to pedometers. However, the use of accelerometers also has limitations. First, consensus in Actigraph accelerometer data processing is lacking. There is wide variability in the choices made for intensity cut-off points, which limits comparability between studies. Intensity cut-off points used in our study were originally developed for a healthy population. As a consequence, physical activity intensity may be underestimated for patients with lower aerobic capacity. An additional limitation is that the accelerometer we used is not water-resistant and could therefore not be worn during swimming activities. Finally, participants were aware that their physical activity was being measured, which may have influenced their behaviour. Since the accelerometers were blinded and the measurement period lasted at least 4 days, we expect this last limitation to only have a minimal effect on our results.

To estimate cardiovascular health, we used the SCORE risk function. We selected the SCORE risk function that was developed for primary prevention[7] because there is currently no validated risk score available for secondary prevention. Absolute scores (percentages) are therefore inaccurately reflecting 10-year mortality risk. However, the between-group differences in SCORE do provide an estimate of the relative overall impact of the investigated interventions.

Performing a maximal exercise stress test with measurement of oxygen consumption is preferred when measuring aerobic capacity. Unfortunately, this was not possible in the complex logistics of this study. Therefore we chose to use a 6-minute walk test (6MWT), which is an easy-to-administer and a frequently used test to measure functional aerobic capacity.[56] The 6MWT was found to be a valid and reliable test and responsive to clinically meaningful changes in a CR population.[57]

CLINICAL IMPLICATIONS

Based on our results, it is recommend to implement physical activity counselling into CR. The addition of three behavioural physical activity group counselling sessions (CR+F) was effective in improving step count and distribution of physical activity. Results suggested that objective feedback (in our intervention provided by pedometers) might be essential for behaviour change. During the CR+F aftercare programme, the benefits in

physical activity partly worn off. Long-lasting improvements were found in prevalence of mild and severe fatigue. Furthermore, the common decline in aerobic capacity after CR was prevented. These secondary outcomes increase the clinical relevance of the CR+F intervention. The intervention in its current form leaves room for further improvements, mainly with regard to MVPA time, long-term maintenance of physical activity benefits, and sedentary behaviour. Ideally, the interventions should first be optimized and then implemented into CR. Results of this thesis give several suggestions for optimization, which are discussed below in the 'future directions'. Since the CR+F intervention was imbedded in existing and reimbursed CR and consisted of a small number of additional group sessions, costs of the intervention are estimated to be relatively low. However, for successful implementation and reimbursement, a detailed economic evaluation is needed.

Telephonic aftercare (CR+T) did not result in additional benefits. Although this intervention requested a smaller effort (phone calls at home or at work), compliance was not higher than for the CR+F intervention. Since the phone calls were on individual basis, costs are not estimated to be much lower than for the CR+F group intervention. Implementation of the CR+T intervention is not recommended.

Usually, there is a great emphasis on cardiovascular risk profile and (cardiovascular) events when evaluating the success of CR. Our results showed very low event rates and well-controlled blood pressures and lipid profiles already at the start of CR. These favourable outcomes suggest that, both in clinical practice and when conducting research, there should be more emphasis on other goals and outcomes of CR that are less well-controlled by medication, such as directly measuring lifestyle behaviours.[58] Results of this thesis stress the importance of focussing on further improvements in physical activity habits. In addition, there is a need to develop additional CR targets for sedentary behaviour. Other important targets are experienced fatigue and participation in society. With regard to fatigue, main focus should be on patients that enter CR with severe fatigue complaints. Improving participation in society is already specified as a goal of CR. However, usually, the focus is on frequency of participation, while our results highlight the importance of focusing on areas of participation in society in which patients report to experience restrictions and dissatisfaction, such as going out, exercising, outdoor activities, housekeeping and contact with friends.

FUTURE DIRECTIONS

Further optimization of physical activity counselling

The CR+F intervention showed encouraging outcomes. For further improvements, a more in-depth understanding of barriers and facilitators for CR participants to become physically active is needed. Knowledge about common barriers and facilitators will help identify feasible and potentially more effective interventions to improve physical activity. Results of this thesis also provided several directions for optimization of the intervention with regard to physical activity. First, patients were most responsive to change the outcome on which they received objective feedback; in our case step count. A previous review also underlined the importance of objective self-monitoring.[23] The physical activity counselling sessions could possibly be improved by not only providing feedback on walking activities but also on total MVPA, which is possible with new technologies. Second, both aftercare programmes (CR+F and CR+T) had a focus on multiple lifestyle behaviours and were not successful with regard to physical activity, as opposed to physical activity counselling integrated into the initial phase of the CR+F intervention. An exclusive focus on physical activity might be needed also during aftercare. A meta-analysis in a general population confirmed that interventions focusing solely on physical activity were more successful than interventions addressing multiple behaviours.[42] Finally, to reach lasting changes, patients probably need ongoing attention, which could be feasible using E-health interventions.[59] 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. Furthermore, results of a meta-analysis also show the importance of, at least partly, face-to-face contact.[42]

Physical activity counselling could additionally be improved by adding a focus on sedentary behaviour, preferably including objective feedback. In line with previous studies[24,32], our results suggest that interventions with a main focus on physical activity do not automatically improve sedentary behaviour. Although more research into this area is needed, both for physical activity and sedentary behaviour it has been suggested that an exclusive focus on one of the behaviours is more successful than focussing on both components simultaneously.[24,32,42] Future studies should find a way to target sedentary behaviour, without replacing or diminishing the focus and effects on physical activity. Probably the focus could be divided over the day, for instance emphasize increasing physical activity during leisure time and reducing sedentary behaviour during working hours. The choice in focus could also be based on the motivation and baseline values of the patient. Future research should also investigate whether changing physical activity or sedentary behaviour yields larger health benefit. Most evidence on the association between physical behaviour (physical activity and sedentary behaviour) and health in

patients with CHD is based on outcomes of cross-sectional research. In addition, evidence is often based on self-reported outcomes, which are known to be less valid.[8-11] The exact magnitude of changes in objectively measured physical activity and sedentary behaviour required to gain health benefits are unclear. The longitudinal association between physical behaviour and health should be studied more extensively.

Which patients benefit most?

Probably not all patients need to prolong standard CR. Participation in aftercare programmes should perhaps be restricted to some specific groups who do not accomplish the target values for lifestyle recommendation or cardiovascular health after standard CR. Future studies should focus on selecting those patients that will benefit most from additional interventions.

Collaboration in the Netherlands

Over the last years, several large trials have been conducted in the Netherlands focussing on improving lifestyle habits in CR populations.[45,48,60,61] All trials strived to improve secondary prevention, but differed in content and in focus. Combining the outcomes of these trials, and discussing them in a multidisciplinary team, would give a unique opportunity to learn important lessons about secondary prevention in the Netherlands. This could lead to optimization of guidelines as well as opportunities for further research.

REFERENCES

1. Revalidatiecommissie NVVC / NHS en projectgroep PAAHR, *Multidisciplinaire Richtlijn Hartrevalidatie 2011 (multidisciplinaire guidelines cardiac rehabilitation)*. 2011, Utrecht: Nederlandse Vereniging Voor Cardiologie.
2. Balady, G.J., M.A. Williams, P.A. Ades, V. Bittner, 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): p. 2675-82.
3. Piepoli, M.F., U. Corra, W. Benzer, B. Bjarnason-Wehrens, et al., *Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 1-17.
4. Taylor, R.S., A. Brown, S. Ebrahim, J. Jolliffe, et al., *Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials.* Am J Med, 2004. **116**(10): p. 682-92.
5. Lavie, C.J. and R.V. Milani, *Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention.* Prog Cardiovasc Dis, 2011. **53**(6): p. 397-403.
6. Anderson, L., N. Oldridge, D.R. Thompson, A.D. Zwisler, et al., *Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis.* J Am Coll Cardiol, 2016. **67**(1): p. 1-12.
7. de Vries, H., H.M. Kemps, M.M. van Engen-Verheul, R.A. Kraaijenhagen, et al., *Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients.* Eur Heart J, 2015. **36**(24): p. 1519-28.
8. Craig, C.L., A.L. Marshall, M. Sjostrom, A.E. Bauman, et al., *International physical activity questionnaire: 12-country reliability and validity.* Med Sci Sports Exerc, 2003. **35**(8): p. 1381-95.
9. van den Berg-Emons, R.J., A.A. L'Ortye, L.M. Buffart, C. Nieuwenhuijsen, et al., *Validation of the Physical Activity Scale for individuals with physical disabilities.* Arch Phys Med Rehabil, 2011. **92**(6): p. 923-8.
10. Richardson, M.T., B.E. Ainsworth, D.R. Jacobs, and A.S. Leon, *Validation of the Stanford 7-day recall to assess habitual physical activity.* Ann Epidemiol, 2001. **11**(2): p. 145-53.
11. Le Grande, M.R., P.C. Elliott, M.U. Worcester, B.M. Murphy, et al., *An evaluation of self-report physical activity instruments used in studies involving cardiac patients.* J Cardiopulm Rehabil Prev, 2008. **28**(6): p. 358-69.
12. Conn, V.S., A.R. Hafdahl, and D.R. Mehr, *Interventions to increase physical activity among healthy adults: meta-analysis of outcomes.* Am J Public Health, 2011. **101**(4): p. 751-8.
13. Ribeiro, F., N.L. Oliveira, G. Silva, L. Campos, et al., *Exercise-based cardiac rehabilitation increases daily physical activity of patients following myocardial infarction: subanalysis of two randomised controlled trials.* Physiotherapy, 2017. **103**(1): p. 59-65.
14. Prince, S.A., C.M. Blanchard, S.L. Grace, and R.D. Reid, *Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates.* Eur J Prev Cardiol, 2016. **23**(8): p. 818-25.
15. Blikman, L.J., J. van Meeteren, H.L. Horemans, I.C. Kortenhorst, et al., *Is physical behavior affected in fatigued persons with multiple sclerosis?* Arch Phys Med Rehabil, 2015. **96**(1): p. 24-9.

16. Ayabe, M., P.H. Brubaker, D. Dobrosielski, H.S. Miller, et al., *Target step count for the secondary prevention of cardiovascular disease.* Circ J, 2008. **72**(2): p. 299-303.
17. Tudor-Locke, C., C.L. Craig, Y. Aoyagi, R.C. Bell, et al., *How many steps/day are enough? For older adults and special populations.* Int J Behav Nutr Phys Act, 2011. **8**: p. 80.
18. Strath, S.J., R.G. Holleman, D.L. Ronis, A.M. Swartz, et al., *Objective physical activity accumulation in bouts and nonbouts and relation to markers of obesity in US adults.* Prev Chronic Dis, 2008. **5**(4): A131.
19. Murphy, M., A. Nevill, C. Neville, S. Biddle, et al., *Accumulating brisk walking for fitness, cardiovascular risk, and psychological health.* Med Sci Sports Exerc, 2002. **34**(9): p. 1468-74.
20. Haskell, W.L., I.M. Lee, R.R. Pate, K.E. Powell, et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association.* Med Sci Sports Exerc, 2007. **39**(8): p. 1423-34.
21. van den Berg-Emons, R., A. Balk, H. Bussmann, and H. Stam, *Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure?* Eur J Heart Fail, 2004. **6**(1): p. 95-100.
22. Gardner, B., L. Smith, F. Lorencatto, M. Hamer, et al., *How to reduce sitting time? A review of behaviour change strategies used in sedentary behaviour reduction interventions among adults.* Health Psychol Rev, 2016. **10**(1): p. 89-112.
23. Ferrier, S., C.M. Blanchard, M. Vallis, and N. Giacomantonio, *Behavioural interventions to increase the physical activity of cardiac patients: a review.* Eur J Cardiovasc Prev Rehabil, 2011. **18**(1): p. 15-32.
24. Prince, S.A., T.J. Saunders, K. Gresty, and R.D. Reid, *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): p. 905-19.
25. Chase, J.A., *Systematic review of physical activity intervention studies after cardiac rehabilitation.* J Cardiovasc Nurs, 2011. **26**(5): p. 351-8.
26. Chau, J.Y., A.C. Grunseit, T. Chey, E. Stamatakis, et al., *Daily sitting time and all-cause mortality: a meta-analysis.* Plos One, 2013. **8**(11): e80000.
27. Wilmot, E.G., C.L. Edwardson, F.A. Achana, M.J. Davies, et al., *Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis.* Diabetologia, 2012. **55**(11): p. 2895-905.
28. Healy, G.N., K. Wijndaele, D.W. Dunstan, J.E. Shaw, et al., *Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).* Diabetes Care, 2008. **31**(2): p. 369-71.
29. Biswas, A., P.I. Oh, G.E. Faulkner, R.R. Bajaj, et al., *Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis.* Ann Intern Med, 2015. **162**(2): p. 123-32.
30. Healy, G.N., D.W. Dunstan, J. Salmon, E. Cerin, et al., *Breaks in sedentary time: beneficial associations with metabolic risk.* Diabetes Care, 2008. **31**(4): p. 661-6.
31. Kim, Y., G.J. Welk, S.I. Braun, and M. Kang, *Extracting objective estimates of sedentary behavior from accelerometer data: measurement considerations for surveillance and research applications.* Plos One, 2015. **10**(2): e0118078.
32. Martin, A., C. Fitzsimons, R. Jepson, D.H. Saunders, et al., *Interventions with potential to reduce sedentary time in adults: systematic review and meta-analysis.* Br J Sports Med, 2015. **49**(16): p. 1056-63.

33. Buman, M.P., E.A. Winkler, J.M. Kurka, E.B. Hekler, et al., *Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005-2006.* Am J Epidemiol, 2014. **179**(3): p. 323-34.
34. Byun, W., C. Ozemek, K. Riggin, S. Strath, et al., *Correlates of objectively measured physical activity in cardiac patients.* Cardiovasc Diagn Ther, 2014. **4**(5): p. 406-10.
35. Guiraud, T., R. Granger, V. Gremeaux, M. Bousquet, et al., *Accelerometer as a tool to assess sedentarity and adherence to physical activity recommendations after cardiac rehabilitation program.* Ann Phys Rehabil Med, 2012. **55**(5): p. 312-21.
36. Evenson, K.R., E.N. Butler, and W.D. Rosamond, *Prevalence of Physical Activity and Sedentary Behavior Among Adults With Cardiovascular Disease in the United States.* Journal of Cardiopulmonary Rehabilitation and Prevention, 2014. **34**(6): p. 406-419.
37. Valko, P.O., C.L. Bassetti, K.E. Bloch, U. Held, et al., *Validation of the fatigue severity scale in a Swiss cohort.* Sleep, 2008. **31**(11): p. 1601-7.
38. Bunevicius, A., A. Stankus, J. Brozaitiene, S.S. Girdler, et al., *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**(2): p. 310-6.
39. Levasseur, M., J. Desrosiers, and L. Noreau, *Is social participation associated with quality of life of older adults with physical disabilities?* Disability and Rehabilitation, 2004. **26**(20): p. 1206-1213.
40. McLean, A.M., T. Jarus, A.M. Hubley, and L. Jongbloed, *Associations between social participation and subjective quality of life for adults wih moderate to severe traumatic brain injury.* Disability and Rehabilitation, 2014. **36**(17): p. 1409-18.
41. Conn, V.S., A.R. Hafdahl, S.M. Moore, P.J. Nielsen, et al., *Meta-analysis of interventions to increase physical activity among cardiac subjects.* Int J Cardiol, 2009. **133**(3): p. 307-20.
42. Conn, V.S., A.R. Hafdahl, S.A. Brown, and L.M. Brown, *Meta-analysis of patient education interventions to increase physical activity among chronically ill adults.* Patient Educ Couns, 2008. **70**(2): p. 157-72.
43. Vale, M.J., M.V. Jelinek, J.D. Best, A.M. Dart, 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): p. 2775-83.
44. Leemrijse, C.J., R.J. Peters, C. von Birgelen, L. van Dijk, et al., *The telephone lifestyle intervention 'Hartcoach' has modest impact on coronary risk factors: A randomised multicentre trial.* Eur J Prev Cardiol, 2016. **23**(15): p. 1658-68.
45. Jorstad, H.T., C. von Birgelen, A.M. Alings, A. Liem, et al., *Effect of a nurse-coordinated prevention programme on cardiovascular risk after an acute coronary syndrome: main results of the RESPONSE randomised trial.* Heart, 2013. **99**(19): p. 1421-30.
46. Lear, S.A., J.J. Spinelli, W. Linden, A. Brozic, et al., *The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: a 4-year randomized controlled trial.* Am Heart J, 2006. **152**(2): p. 333-9.
47. Giannuzzi, P., P.L. Temporelli, R. Marchioli, A.P. Maggioni, et al., *Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network.* Arch Intern Med, 2008. **168**(20): p. 2194-204.
48. Janssen, V., V. De Gucht, H. van Exel, and S. Maes, *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence.* J Behav Med, 2014. **37**(2): p. 308-21.

49. Warburton, D.E., C.W. Nicol, and S.S. Bredin, *Health benefits of physical activity: the evidence.* CMAJ, 2006. **174**(6): p. 801-9.
50. van Geffen, M.E., N. Ter Hoeve, M. Sunamura, H.J. Stam, et al., *Fatigue during and after cardiac rehabilitation.* J Rehabil Med, 2015. **47**(6): p. 569-74.
51. Moholdt, T., I.L. Aamot, I. Granoien, L. Gjerde, 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): p. 388-90.
52. Giallauria, F., A. De Lorenzo, F. Pilerci, A. Manakos, et al., *Long-term effects of cardiac rehabilitation on end-exercise heart rate recovery after myocardial infarction.* Eur J Cardiovasc Prev Rehabil, 2006. **13**(4): p. 544-50.
53. Frederix, I., D. Hansen, K. Coninx, P. Vandervoort, et al., *Medium-Term Effectiveness of a Comprehensive Internet-Based and Patient-Specific Telerehabilitation Program With Text Messaging Support for Cardiac Patients: Randomized Controlled Trial.* J Med Internet Res, 2015. **17**(7): e185.
54. Brink, E., G. Grankvist, B.W. Karlson, and L.R. Hallberg, *Health-related quality of life in women and men one year after acute myocardial infarction.* Qual Life Res, 2005. **14**(3): p. 749-57.
55. White, I.R., J. Carpenter, and N.J. Horton, *Including all individuals is not enough: lessons for intention-to-treat analysis.* Clin Trials, 2012. **9**(4): p. 396-407.
56. Solway, S., D. Brooks, Y. Lacasse, and S. Thomas, *A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain.* Chest, 2001. **119**(1): p. 256-70.
57. Beatty, A.L., N.B. Schiller, and M.A. Whooley, *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): p. 1096-102.
58. Lachman, S., M. Minneboo, M. Snaterse, H.T. Jorstad, et al., *Community-based comprehensive lifestyle programs in patients with coronary artery disease: Objectives, design and expected results of Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 trial (RESPONSE 2).* Am Heart J, 2015. **170**(2): p. 216-22.
59. Frederix, I., L. Vanhees, P. Dendale, and K. Goetschalckx, *A review of telerehabilitation for cardiac patients.* J Telemed Telecare, 2015. **21**(1): p. 45-53.
60. Minneboo, M., S. Lachman, M. Snaterse, H.T. Jorstad, et al., *Community-Based Lifestyle Intervention in Patients With Coronary Artery Disease: The RESPONSE-2 Trial.* J Am Coll Cardiol, 2017. **70**(3): p. 318-327.
61. Kraal, J.J., M.E. Van den Akker-Van Marle, A. Abu-Hanna, W. Stut, et al., *Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study.* Eur J Prev Cardiol, 2017. **24**(12): p. 1260-1273.

Summary

Cardiac Rehabilitation (CR) focusses on the adoption of a healthy lifestyle (including regular physical activity) and the optimization of cardiovascular risk factors and psychosocial status. Standard CR programs last 6-12 weeks. The core of CR exists of an exercise program. In addition, educational sessions and counselling programs on cardiovascular risk factors and a heart-healthy lifestyle are offered. Previous studies have demonstrated that CR successfully improves health (e.g. blood pressure and lipid profile), aerobic capacity, quality of life, and risk of mortality in patients with coronary heart disease (CHD). Notwithstanding these benefits, it has been suggested that standard CR is insufficient for physical activity improvements. Regular physical activity is important since it is associated with substantial health benefits, such as an improved cardiac risk profile and a lower risk of (recurrent) cardiovascular events.

In ***part I*** **(chapters 2-5)** of this thesis we focused on the effects of current standard CR on physical activity and on the secondary outcomes sedentary behaviour, fatigue and participation in society. In ***part II*** **(chapters 6-9)**, we focused on the main objective of this thesis: the effect of extra behavioural lifestyle interventions integrated into standard CR on physical activity. Furthermore, effects of the behavioural interventions on sedentary behaviour, cardiovascular health, aerobic capacity, fatigue, and participation in society were studied.

Chapter 1 of this thesis contains the general introduction which gives background information on CHD (including acute coronary syndromes, ACS), on CR, on the primary outcome physical activity, and on the secondary outcomes. Additionally, the theoretical background of the investigated behavioural lifestyle interventions is described. The chapter concludes with the aims and outline of this thesis.

In ***chapter 2 (part I)***, we systematically reviewed the literature regarding the effects of standard CR on physical activity in patients with ACS. We included 26 randomized controlled trials (RCT's). Results suggest that centre-based CR is insufficient to improve and maintain physical activity. Home-based programs seemed more successful, but the literature is limited. There was no clear evidence that increasing training volume or extending the duration of CR is more effective with regard to physical activity. The majority of the RCT's used self-reported outcome measures for physical activity, which are less valid and reliable. Therefore, in ***chapter 3,*** we studied longitudinal changes in physical activity during standard CR more in-depth using objective accelerometers. We additionally focussed on sedentary behaviour, which is known to be an independent risk factor for health. The standard CR program lasted 6-12 weeks. The core of the program consisted of an exercise program (twice a week). In addition, educational sessions on cardiovascular risk factors and a heart-healthy lifestyle were offered. Upon indication

and motivation, patients could also participate in a stress management program, a dietary program, a smoking cessation program and/or an individualized psychologic program. During this CR program, patients achieved a small improvement in moderate-to-vigorous intensity physical activity (MVPA; +5min/day). More substantial improvements occurred for sedentary behaviour (-22 min/day). Regardless these improvements, by the end of CR, patients still spent relatively little time in MVPA and a long time sedentary. We concluded that standard CR is insufficient and additional resources are needed to further improve physical activity and sedentary behaviour.

In ***chapter 4***, we focused on longitudinal changes in fatigue in patients with CHD. Fatigue decreased during and after standard CR. However, the prevalence of severely fatigued patients remained high one year after CR (8%) as compared to a healthy population (3.5%). Aerobic capacity was weakly associated with fatigue, while depressive symptoms were more strongly associated. Our results indicate that for patients with severe fatigue additional interventions seem necessary. These interventions should probably focus mainly on the mental components of fatigue, instead of the physical components.

In ***chapter 5***, we describe longitudinal changes during standard CR in participation in society (domestic, occupational and recreational activities) in patients with CHD. The frequency of participation did not change during CR. However, the proportion of patients experiencing restrictions in participation decreased from 69% pre-CR to 29% at one-year follow-up. Dissatisfaction with participation decreased from 71% to 53%. Regardless these considerable improvements, the proportion of patients that experienced restrictions and dissatisfaction remained high at follow-up. Since we additionally found that experienced restrictions and dissatisfaction are associated with quality of life, we suggest that a more individualized approach during CR, focusing on activities in which restrictions and dissatisfaction are experienced, is needed.

In ***chapter 6 (part II),*** the design of the OPTICARE study is described. In this RCT, we investigated the added value of two novel behavioural lifestyle interventions on top of standard CR. The first novel CR+F (CR + Face-to-face counselling) intervention consisted of 3 months of standard CR with the addition of three pedometer-based, face-to-face physical activity group counselling sessions. This initial phase was followed by 9 months of aftercare with three face-to-face group counselling sessions focusing on several lifestyle components (e.g. healthy diet, physical activity, and psychosocial functioning). The second novel intervention, the CR+T (CR+Telephonic counselling) intervention consisted of 3 months of standard CR without additions in the initial phase. After the initial phase, patients participated in 9 months of aftercare with five to six telephonic counselling sessions which also focused on several lifestyle components. In the chapters

7-9, we describe the outcomes of the novel interventions as compared to standard CR only (as described for chapter 3 and with no aftercare) in patients with ACS.

Chapter 7 focuses on the additional benefits with regard to physical activity (primary outcome). Compared to standard CR, adding three pedometer-based physical activity counselling sessions (initial phase CR+F) improved daily step count with an additional 500 steps/day. Furthermore, time spent in prolonged MVPA periods (>10min, which is suggested for health benefits) increased. There were no changes in total MVPA time or sedentary behaviour. At completion of the CR+F aftercare program, improvements in step count partly diminished. However, the additional improvements in prolonged MVPA were maintained. No additional benefits were found for the CR+T intervention with regard to physical activity or sedentary behaviour. Based on the results, we recommend that face-to-face physical activity group counselling sessions including objective feedback (CR+F) be added to standard CR, although aftercare optimization is needed. Our results give several directions for optimization, which are further discussed in chapter 7.

The aim of ***chapter 8*** was to investigate the additional effect on SCORE, a risk function that estimates the 10 years risk of cardiovascular death based on total cholesterol, systolic blood pressure, and smoking status. None of the novel interventions did lead to additional benefits with respect to SCORE or any of its individual components. Patients largely reached target levels for modifiable risk factors already following standard CR. These outcomes suggest that with regard to cardiovascular risk factors, no additional resources are needed.

In ***chapter 9***, we describe secondary outcomes. The CR+F intervention was successful in sustaining aerobic capacity gains up to 12 months and reaching long-term improvements in fatigue. 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.

Chapter 10 contains the general discussion. In this chapter, the main findings of this thesis are described and interpreted, and methodological considerations are discussed. Furthermore, we address the clinical implications of our outcomes and give future directions for optimization of cardiac rehabilitation and for further research into this area.

Samenvatting

Hartrevalidatie (HR) richt zich op het ontwikkelen van een gezonde leefstijl (inclusief het doen van regelmatige lichamelijk activiteit) en op het verbeteren van cardiovasculaire risicofactoren en de psychosociale status. Standaard HR duurt 6 tot 12 weken. De kern van HR bestaat uit een trainingsprogramma en daarnaast kunnen patiënten diverse voorlichtingen en behandelprogramma's over cardiovasculaire risicofactoren en een gezonde leefstijl volgen. Wetenschappelijk onderzoek heeft aangetoond dat deelname aan HR leidt tot een verbetering in de cardiovasculaire gezondheid (bijv. bloeddruk en lipidenprofiel), lichamelijke fitheid, kwaliteit van leven, en mortaliteit bij patiënten met een coronaire hartziekte (CHZ). Ondanks deze gunstige effecten wordt vaak gesuggereerd dat de huidige HR-programma's onvoldoende zijn voor het ontwikkelen van een lichamelijk actieve leefstijl. Mogelijk zijn aanvullende leefstijlinterventies nodig. Regelmatige lichamelijke activiteit is belangrijk voor de gezondheid en is bijvoorbeeld gerelateerd aan een verbetering van cardiovasculaire risicofactoren en een reductie in het aantal (her)opnamen ten gevolge van nieuwe hartproblemen.

In ***deel I (hoofdstuk 2-5)*** van dit proefschrift worden de effecten van standaard HR op lichamelijk activiteit en op de secundaire uitkomstmaten sedentair gedrag, vermoeidheid en maatschappelijke participatie beschreven. In ***deel II (hoofdstuk 6-9)*** richten we ons op de primaire doelstelling van dit proefschrift: het bepalen van de toegevoegde waarde van twee verschillende leefstijlinterventies, als aanvulling op standaard HR, op lichamelijke activiteit. Daarnaast beschrijven we de effecten van deze leefstijlinterventies op sedentair gedrag, cardiovasculaire risicofactoren, fitheid, vermoeidheid en maatschappelijke participatie.

In het inleidende ***hoofdstuk 1*** wordt achtergrondinformatie gegeven over CHZ (inclusief acute coronaire syndromen, ACS), over HR, over de primaire uitkomstmaat lichamelijke activiteit en over de secundaire uitkomstmaten. Daarnaast wordt de theoretische achtergrond van de onderzochte leefstijlinterventies beschreven. Het hoofdstuk sluit af met een overzicht van de doelstellingen van dit proefschrift.

In ***hoofdstuk 2 (deel 1)*** worden de uitkomsten van een systematische review besproken, waarin we de resultaten van eerder wetenschappelijke onderzoek samenvatten die de effecten van standaard HR op lichamelijk activiteit in hartpatiënten met ACS hebben onderzocht. Er werden 26 gerandomiseerde studies (RCT's) geïncludeerd. Resultaten tonen aan dat standaard HR onvoldoende is voor het verbeteren van lichamelijke activiteit. Er werden aanwijzingen gevonden dat revalideren in de thuissituatie betere resultaten oplevert dan revalideren in een centrum. De literatuur op dit gebied is overigens beperkt. Er werd geen bewijs gevonden dat het verlengen van de duur van revalidatieprogramma's of het verhogen van trainingsvolume leidt tot betere effecten. De meerderheid van de

geïncludeerde RCT's baseerden hun conclusies op zelf-gerapporteerde lichamelijke activiteit, waarvan bekend is dat dit een uitkomstmaat is met beperkte validiteit en betrouwbaarheid. Om deze reden hebben we in ***hoofdstuk 3*** objectieve accelerometers gebruikt om lichamelijk activiteit meer gedetailleerd te kunnen meten tijdens standaard HR bij hartpatiënten met ACS. Aanvullend hebben we ook gekeken naar veranderingen in sedentair gedrag, waarvan bekend is dat dit een onafhankelijke risicofactor is voor de gezondheid. Het standaard HR-programma duurde 6 tot 12 weken. De kern bestond uit een trainingsprogramma (2 maal per week). Daarnaast konden patiënten diverse voorlichtingen over cardiovasculaire risicofactoren en een gezonde leefstijl volgen, en meedoen aan groepsbehandelprogramma's waarin begeleiding werd geboden bij stoppen met roken, gezond afvallen, en omgaan met stress. Indien noodzakelijk kon de patiënt individuele begeleiding krijgen van een diëtist, maatschappelijk werker, psycholoog, of psychiater. Tijdens deelname aan dit HR programma steeg het aantal minuten dat werd besteed aan matig tot intensieve lichamelijke activiteit gemiddeld met 5 minuten per dag en verminderde sedentair gedrag gemiddeld met 22 minuten per dag. Ondanks deze verbeteringen, besteedden patiënten na afloop van HR nog steeds relatief weinig tijd aan lichamelijke activiteit en waren zij relatief veel tijd sedentair. De resultaten suggereren dat standaard HR onvoldoende is en aanvullende interventies nodig zijn om lichamelijke activiteit en sedentair gedrag verder te verbeteren.

In ***hoofdstuk 4*** hebben we ons geconcentreerd op veranderingen in vermoeidheid bij hartpatiënten met CHZ. Resultaten laten zien dat vermoeidheidsklachten significant dalen tijdens en na deelname aan standaard HR. Echter, de prevalentie van patiënten met ernstige vermoeidheidsklachten was een jaar na HR nog steeds relatief hoog (8%) in vergelijking met een gezonde populatie (3.5%). Verbeteringen in vermoeidheidsklachten waren slechts zwak geassocieerd met verbeteringen in lichamelijke fitheid. De associatie was sterker met verbeteringen in depressieve symptomen. Onze resultaten impliceren dat patiënten met ernstige vermoeidheidsklachten aanvullende interventies nodig hebben. Deze interventies zullen zich waarschijnlijk vooral moeten concentreren op de mentale componenten van vermoeidheid, in plaats van op de lichamelijke componenten.

In ***hoofdstuk 5*** beschrijven we veranderingen tijdens standaard HR in maatschappelijke participatie (huishoudelijke-, werk gerelateerde-, en vrijetijdsactiviteiten) bij hartpatiënten met CHZ. Frequentie van participatie veranderde niet. Echter, het percentage patiënten dat beperkingen ervaart in de maatschappelijke participatie daalde van 89% voor HR tot 29% een jaar na HR. Het aantal patiënten dat ontevreden was met de eigen participatie daalde van 71% naar 53%. Ondanks deze aanzienlijke verbeteringen, was het percentage patiënten dat beperkingen ervaarde of ontevreden was nog steeds

hoog één jaar na HR. Aanvullende analyses lieten zien dat deze ervaren beperkingen en ontevredenheid gerelateerd zijn aan de kwaliteit van leven. Deze bevindingen benadrukken het belang van meer geïndividualiseerde aandacht tijdens HR voor activiteiten waarin beperkingen en ontevredenheid worden ervaren.

In ***hoofdstuk 6 (deel 2)*** wordt de aanleiding en opzet van het OPTICARE onderzoek beschreven. In deze gerandomiseerde trial (RCT) hebben we de toegevoegde waarde van twee leefstijlinterventies bovenop standaard HR onderzocht. De CR+F (CR+Face-to-face counselling) interventie bestond uit 3 maanden standaard HR met de toevoeging van een beweegstimuleringsprogramma bestaande uit 3 groepssessies waarin gewerkt werd met stappentellers. Na afloop van deze eerste drie maanden (initiële fase) werden patiënten uitgenodigd voor een nazorgprogramma van 9 maanden bestaande uit drie groepssessies die zich richtten op blijvende leefstijlveranderingen op het gebied van gezonde voeding, lichamelijke activiteit, maar ook op het gebied van psychosociaal herstel. De tweede nieuwe leefstijlinterventie (CR+T; CR+Telefonische counselling) bestond alleen uit standaard HR in de eerste 3 maanden. Na afloop van de initiële fase, werden patiënten uitgenodigd voor 9 maanden nazorg bestaande uit vijf tot zes individuele telefonische counselling sessies, die zich net als het CR+F nazorgprogramma richtten op blijvende leefstijlaanpassingen en pychosociaal herstel. In de hoofdstukken 7-9 vergelijken we de uitkomsten van de twee nieuwe interventies met standaard HR (zonder toevoegingen) bij hartpatiënten met ACS.

In ***hoofdstuk 7*** beschrijven we de toegevoegde waarde van de nieuwe interventies met betrekking tot lichamelijke activiteit (primaire vraagstelling). De toevoeging van het beweegstimuleringprogramma (groepssessies) aan standaard HR (initiële fase CR+F) leidde tot een extra verbetering van 500 stappen per dag. Tevens leidden deze extra counselling sessies tot een verdere verbetering van de verdeling van lichamelijke activiteit over de dag: lichamelijke activiteit werd vaker uitgevoerd in blokken van minimaal 10 minuten. Het CR+F beweegstimuleringsprogramma resulteerde niet in extra verbeteringen in totale tijd in matig-tot-intensieve lichamelijke activiteit en sedentair gedrag. Aan het einde van het CR+F nazorgprogramma waren de extra verbeteringen in stappen per dag afgenomen. De aanvullende verbetering in verdeling van lichamelijk activiteit over de dag bleef behouden. De CR+T interventie was niet succesvol met betrekking tot de genoemde uitkomstmaten. Gebaseerd op de uitkomsten adviseren wij om het beweegstimuleringprogramma (groepssessies als onderdeel van CR+F) toe te voegen aan standaard HR, alhoewel optimalisatie van het nazorgprogramma noodzakelijk is. Onze resultaten geven diverse richtingen voor verbeteringen, welke verder worden besproken in hoofdstuk 7.

In ***hoofdstuk 8*** beschrijven we het aanvullende effect van de nieuwe interventies op SCORE, een formule die het 10-jarig risico op sterfte door hart- en vaatziekten inschat op basis van totaal cholesterol, systolische bloeddruk en rookstatus. Beide nieuwe interventies leidden niet tot extra verberingen in de SCORE-uitkomst of in de afzonderlijke componenten van de SCORE. Onze resultaten laten zien dat patiënten de streefwaarden voor cardiovasculaire risicofactoren grotendeels al behaalden na afloop van standaard HR. Hieruit concluderen we dat er geen extra interventies nodig zijn voor verdere verbetering van cardiovasculaire risicofactoren zoals bloeddruk en cholesterol.

In ***hoofdstuk 9*** beschrijven we secundaire uitkomsten. De CR+F interventie was succesvol in het op peil houden van de lichamelijke fitheid tot 12 maanden en het langdurig verbeteren van vermoeidheid. Er werden geen extra verbeteringen gevonden in de maatschappelijke participatie. De CR+T interventie verbeterde geen van de secundaire uitkomsten ten opzichte van standaard HR. De gunstige effecten gevonden voor lichamelijke fitheid en vermoeidheid verhogen de klinische relevantie van de CR+F interventie.

Hoofdstuk 10 bevat de algemene discussie waarin de belangrijkste bevindingen van dit proefschrift worden beschreven en geïnterpreteerd. Tevens worden de sterke en zwakke punten van de gebruikte methodologie besproken. Daarnaast bespreken we in dit hoofdstuk de klinische implicaties van onze uitkomsten en geven aanbevelingen voor optimalisatie van hartrevalidatie en ideeën voor verder onderzoek op dit gebied.

Dankwoord

Dit proefschrift was natuurlijk nooit tot stand gekomen zonder de hulp van vele mensen om mij heen. Jullie hebben een aantal stappen voor mij gezet of samen met mij gezet. Ik ga niet iedereen bij naam noemen, maar ik ben jullie wel allemaal even dankbaar!

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Mijn copromotoren en promotor

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De rest van het OPTICARE team

Wat vormen wij een gezellig team! Mijn mede-promovendus Madoka: we zijn ondertussen heel veel vergaderingen, bijgestelde plotjes met inclusieaantallen en avonden met kleffe broodjes of zelfgemaakte creaties verder. Het einde leek soms ver, maar we hebben het gewoon voor elkaar gekregen! Het was fijn een aantal hobbels in het onderzoek samen te kunnen overwinnen. We vullen elkaar goed aan. Myrna, jij was onze reddende engel. Bedankt voor de structuur die je bracht in het onderzoek (en vaak ook in mijn hoofd), maar ook voor je hulp met het verzamelen van data, meedenken over het onderzoek, het schrijven van artikelen en nog veel meer. Onze studieverpleegkundigen Els, Verena en Saskia wil ik bedanken voor het bijhouden van al die mappen vol SAE's en data, ontelbare telefoontjes over bloeduitslagen, het informeren van patiënten en het uitvoeren van metingen. Ik ben blij dat jullie altijd vrolijk de moed erin hebben gehouden! Ook heel veel dank natuurlijk voor Eric Boersma en Marcel Geleijnse. Jullie kritische blik en bijsturing was zeer waardevol. Ken, bedankt voor je hulp bij de kosteneffectiviteit berekeningen. Als laatste wil ik graag de CEC (Mattie Lenzen en Arend Schinkel) bedanken voor hun tijd.

Leden van de kleine en grote commissie

Naast mijn promotoren en copromotoren wil ik ook graag de overige leden van de kleine commissie (prof. Eric Boersma, prof. Jan van Busschbach en prof. Wilma Scholte op Reimer) en grote commissie (prof. Lisbeth Utens en Dr. Rienk Dekker) hartelijk bedanken voor hun tijd en enthousiasme.

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Mijn collega's bij Capri

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Het Hartcoach team

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Mijn collega's in het Erasmus MC

Al mijn collega's in het Erasmus en specifiek op de 16e. Heel fijn om mensen om je heen te hebben die af en toe kunnen meedenken of je weer op het goede spoor kunnen zetten als je er zelf even niet uit komt. Alle gezelligheid (wielrentochtjes, taartjes, feestjes,

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Studenten van het Erasmus MC

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Mijn co-auteurs

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De ontwerper(s) van mijn omslag

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Mijn vrienden en familie

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Bernardo, sem esta tese nunca nos teríamos conhecido. Muito obrigada pela tua infinita paciência e por todas as outras coisas. Tu fazes-me muito feliz! Preparemo-nos para a próxima festa ☺.

About the author

CURRICULUM VITEA

Nienke ter Hoeve was born in Berkel en Rodenrijs on the 9th of May 1986. After finishing high school (VWO) in Lisse in 2004, she started her study Human Movement Sciences at the VU University in Amsterdam. She obtained her Bachelor's degree in 2007 and her Master in 2009, with a specialization in rehabilitation medicine. During her master she won the Gerrit Jan van Ingen Schenau promising young scientist award, which gave her the opportunity to perform her research internship abroad at the prestigious Miami Project to Cure Paralysis.

In 2009 Nienke started to work as junior researcher at Capri Cardiac Rehabilitation, collaborating with the Department of Rehabilitation Medicine of the Erasmus University Medical Centre in Rotterdam. First, she started as research coordinator and built an infrastructure to perform research. Furthermore, she developed a routine outcome monitor to measure the progress of participants in the cardiac rehabilitation program. In 2011, she designed the OPTICARE RCT, together with colleagues in the same collaboration, and was able to combine her work as research coordinator at Capri Cardiac Rehabilitation with her PhD training.

In 2016, Nienke co-authored a successful grant application (ZonMw) on a project focusing on cardiac rehabilitation for patients with obesity. This project is currently performed in a collaboration between Capri Cardiac Rehabilitation and the Department of Rehabilitation Medicine and the Department of Cardiology of the Erasmus University Medical Centre. Nienke will continue her scientific career as a post-doc on this project, as well as by continuing studies on the association between physical behaviour and health in cardiac patients.

LIST OF PUBLICATIONS

Publications in international journals

ter Hoeve N, Sunamura M, Stam HJ, van Domburg RT, van den Berg-Emons HJG. Extended cardiac rehabilitation improves aerobic capacity and fatigue: a randomized controlled trial. *Submitted*

Sunamura M, Ter Hoeve N, van den Berg-Emons RJ, Boersma E, van Domburg RT, Geleijnse ML. Cardiac rehabilitation in patients with acute coronary syndrome with primary percutaneous coronary intervention is associated with improved 10-year survival. Eur Heart J Qual Care Clin Outcomes, 2018. *In press*

ter Hoeve N, Sunamura M, Stam HJ, Boersma H, Geleijnse ML, van Domburg RT, van den Berg-Emons HJG. Effects of two behavioral cardiac rehabilitation interventions on physical activity: A randomized controlled trial. Int J Cardiol, 2018. 255: p. 221-8.

Sunamura M[*], ter Hoeve N[*], van den Berg-Emons HJG, Geleijnse ML, Haverkamp M, Stam HJ, Boersma H, van Domburg RT. Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes. Heart, 2018. 104(5): p. 430-7. [*]**shared first authorship**

Pieters K, Spronk A, Sunamura M, Dulfer K, ter Hoeve N, Utens E, van Domburg RT. Short- and Longer-Term Association Between Body Mass Index and Health Status in Cardiac Rehabilitation Patients. J Cardiopulm Rehabil Prev, 2018. 38(2): p. 85-91.

Sunamura M, ter Hoeve N, Geleijnse ML, Steenaard RV, van den Berg-Emons HJG, Boersma H, van Domburg RT. 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): p. 618-28.

ter Hoeve N, Sunamura M, van Geffen ME, Fanchamps MH, Horemans HL, Bussmann JB, Stam HJ, van Domburg RT, van den Berg-Emons HJG. Changes in Physical Activity and Sedentary Behavior During Cardiac Rehabilitation. Arch Phys Med Rehabil, 2017. 98(12): p. 2378-84.

Pieters K, Utens EM, ter Hoeve N, van Geffen M, Dulfer K, Sunamura M,van Domburg RT. Age does matter: Younger pPCI patients profit more from cardiac rehabilitation than older patients. Int J Cardiol, 2017. 230: p. 659-62.

Rooijers J, Sunamura M, Utens EM, Dulfer K, ter Hoeve N, van Geffen M,Draaijer J, Steenaard R, van Domburg RT. Marital quality and loneliness as predictors for subjective health status in cardiac rehabilitation patients following percutaneous coronary intervention. Eur J Prev Cardiol, 2016. 23(12): p. 1245-51.

ter Hoeve N, van Geffen ME, Post MW, Stam HJ, Sunamura M, van Domburg RT, van den Berg-Emons HJG. Participation in society in patients with coronary artery disease before and after cardiac rehabilitation. Arch Phys Med Rehabil, 2015. 96(6): p. 1110-6.

ter Hoeve N, Huisstede BM, Stam HJ, van Domburg RT, Sunamura M, van den Berg-Emons HJG. Does cardiac rehabilitation after an acute cardiac syndrome lead to changes in physical activity habits? Systematic review. Phys Ther, 2015. 95(2): p. 167-79.

van Geffen ME, ter Hoeve N, Sunamura M, Stam HJ, van Domburg RT, van den Berg-Emons HJG. Fatigue during and after cardiac rehabilitation. J Rehabil Med, 2015. 47(6): p. 569-74.

Sunamura M, ter Hoeve N, van den Berg-Emons HJG, Haverkamp M, Redekop K, Geleijnse ML, Stam HJ, Boersma H, van Domburg RT. 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): p. 324-30.

Houdijk H, ter Hoeve N, Nooijen C, Rijntjes D, Tolsma M, Lamoth C. Energy expenditure of stroke patients during postural control tasks. Gait Posture, 2010. 32(3): p. 321-6.

Nooijen CF[*], ter Hoeve N[*], Field-Fote EC. Gait quality is improved by locomotor training in individuals with SCI regardless of training approach. J Neuroeng Rehabil, 2009. 6: p. 36. [*]**shared first authorship**

Publications in Dutch journals

ter Hoeve N, Janssen V, Kraaijenhagen RA, van den Berg-Emons HJG. Hartrevalidatie in beweging. Ned Tijdschr Revalidatiegeneeskd, 2015. 6: p. 288-290.

ter Hoeve N, Post MWM., van Domburg RT, van der Zee CH, van den Berg-Emons HJG. USER-Participatie omrekenprocedure**.** Ned Tijdschr Revaidatiegeeskd, 2014. 1: p. 40-41.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Nienke ter Hoeve	**PhD Period**: 2011-2018
Erasmus MC Department: Rehabilitation Medicine	**Promotor**: Prof. Dr. H.J. Stam
Research School: NIHES	**Supervisors**: Dr. H.J.G. van den Berg-Emons & Dr. R.T. van Domburg

1. PhD training	**year**	**hours (ECTS)**
General Academic Skills		
- CPO mini Course	2011	8 (0,3)
- Biomedical English Writing and Communication	2012	112 (4)
- BROK course	2012	30 (1)
- Research Integrity	2014	8 (0,3)
- BROK course update	2016	8 (0,3)
Research skills		
- Biostatistics for clinicians (NIHES EWP22)	2012	20 (0,7)
- Hands on performing exercise intervention trials in cardiovascular prevention and rehabilitation (EACPR workshop)	2015	14 (0,5)
- Stepping stones for funding and grant writing	2015	4 (0,2)
- Regression analysis (NIHES ESP09)	2015	53 (1,9)
In-depth courses		
- Motivational interviewing	2011	28 (1)
- ECG interpretation	2015	8 (0,3)
Seminars and workshops		
- PhD day human movement sciences	2011	8 (0,3)
- Tussen lab en leven LUMC (Hart & Vaatgroep)	2012	6 (0,2)
- Tussen lab en leven Erasmus MC (Hart & Vaatgroep)	2012	6 (0,2)
- Congres landelijk actieprogramma zelfmanagement	2012	8 (0,3)
- PhD day Erasmus MC	2012	6 (0,2)
- NVVC congress hartrevalidatie	2012	6 (0,2)
- Puls evenement Hartstichting	2013	8 (0,3)
- PhD day Erasmus MC	2015	6 (0,2)
- VVBN symposium	2015	8 (0,3)
- Puls evenement Hartstichting	2015	8 (0,3)
- NVVC congress hartrevalidatie	2015	6 (0,2)
- VVBN symposium	2017	8 (0,3)
Presentations		
- Oral presentation: *Wetenschappelijk onderzoek bij Capri Hartrevalidatie.* Capri relatie evenement, Rotterdam	2011	10 (0,4)
- Workshop: O*ntmoeting met een onderzoeker*. Tussen lab & leven Hart en Vaatgroep, Rotterdam	2012	10 (0,4)

-	Workshop: *Actieve leefstijlmodule: een waardevolle aanvulling?* NVVC congres hartrevalidatie, Amersfoort	2012	10 (0,4)
-	Oral presentation: *OPTICARE: onderzoek naar de effecten van cardiorevalidatie op het dagelijks bewegen*. Regional meeting for rehabilitation physicians, Rotterdam	2013	10 (0,4)
-	Oral poster presentation: *Current cardiac rehabilitation programmes are not sufficient for ACS patients to reach long-lasting changes in physical activity habits.* ESC congress, Amsterdam	2013	10 (0,4)
-	Oral presentation: *Current cardiac rehabilitation programmes are not sufficient for ACS patients to reach long-lasting changes in physical activity habits*. VRA congress, Noordwijkerhout	2013	28 (1)
-	Poster presentations: *Social participation during and after cardiac rehabilitation: frequency, perceived restrictions and satisfaction.* EuroPrevent, Amsterdam	2014	8 (0,3)
-	Poster presentation: *Improvements in physical fitness and depression are related to improvements in social participation during and after cardiac rehabilitation.* EuroPrevent, Amsterdam.	2014	8 (0,3)
-	Oral presentation: *Does cardiac rehabilitation lead to changes in physical activity habits? A systematic review.* ICBM, Groningen.	2014	28 (1)
-	Poster presentation: *Persisting restrictions and dissatisfaction with participation in society after cardiac rehabilitation.* ESC, Barcelona	2014	8 (0,3)
-	Oral presentation: *Kenniscentrum Capri Hartrevalidatie: wetenschappelijk onderzoek*. Symposium Capri 40 jaar, Rotterdam	2015	28 (1)
-	Oral presentation: *Effects of cardiac rehabilitation extended with a behavioural group intervention on physical activity and physical fitness.* AHA congress, New Orleans	2016	28 (1)
-	Poster presentation: *Is cardiac rehabilitation extended with a telephonic behavioural intervention beneficial with regard to physical activity and physical fitness in ACS patients?* EuroPrevent, Malaga	2017	8 (0,3)
-	Oral poster presentation: *Improvements in physical activity and physical fitness after extending cardiac rehabilitation with a behavioural group intervention*. EuroPrevent, Malaga	2017	10 (0,4)
-	Oral presentation: *Resultaten OPTICARE studie.* Regional meeting for rehabilitation physicians, Rotterdam	2017	10 (0,4)
-	Oral presentation: *Does cardiac rehabilitation extended with a behavioral group intervention lead to changes in physical activity and sedentary behavior? The OPTICARE randomized controlled trial. DCRM congress, Maastricht*	2017	10 (0,4)
-	Oral presentations: *Several topics*. Research meetings dept. of Rehabilitation Medicine Erasmus MC, Rotterdam	2011-2017	28 (1)

International conferences			
-	EuroPrevent (Dublin)	2012	28 (1)
-	ESC congress (Amsterdam)	2013	28 (1)
-	Europrevent (Amsterdam)	2014	28 (1)
-	ICBM (Groningen)	2014	28 (1)
-	ESC congress (Barcelona)	2014	28 (1)
-	EuroPrevent (Lisbon)	2015	28 (1)
-	ESC congress (Rome)	2016	28 (1)
-	AHA scientific sessions (New Orleans)	2016	28 (1)
-	EuroPrevent (Malaga)	2017	28 (1)
Other			
-	Organizing member PhD day human movement sciences 2011	2011	10 (0,4)
-	Organizing research meetings department Rehabilitation Medicine	2012-2014	28 (1)
-	Participating in weekly research meetings department Rehabilitation Medicine	2011-2017	200 (7)
-	Organizing research meetings Capri Cardiac Rehabilitation	2011-2017	28 (1)
-	Participating in research meetings Capri Cardiac Rehabilitation	2011-2017	28 (1)
-	Co-Author grant application ZonMW doelmatigheid (awarded)	2016	28 (1)
-	Organizing member PhD day human movement sciences 2017	2017	10 (0,4)
2.	**Awards**		
-	Best moderated poster price, EuroPrevent, Malaga	2017	-
-	Best presentation price, DCRM congress, Maastricht	2017	-
3.	**Teaching**		
Lecturing			
-	Minor Rehabilitation Medicine for medical students	2011-2017	72 (2,4)
Supervising			
-	Supervising master thesis human movement sciences	2012-2013	40 (1,4)
-	Supervising medical students scientific internship	2012-2016	28 (1)
-	Supervising medical students with review assignment	2012	10 (0,4)
-	Supervising medical students with review assignment	2014	10 (0,4)
-	Supervising medical students with review assignment	2015	10 (0,4)
-	Co-supervising PhD student	2016-2017	40 (1,4)
Total			**1387 (49,8)**