Cardiac telerehabilitation: a novel, cost-efficient care delivery strategy in secondary prevention for ischemic heart disease?

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Chapter 01

Introduction and outline of this thesis

Introduction

Background

Cardiovascular disease constitutes one of the predominant causes of morbidity and mortality worldwide [1]. Yearly, 47% of all deaths are caused by this disease category. The World Health Organization (WHO)'s global action plan (2013-2020) for the management of non-communicable diseases indicated cardiovascular risk factor control as a high priority focus area [2]. Ischemic heart disease (IHD) is one of the main cardiovascular disease categories in terms of prevalence and disease severity. Despite the availability of highly effective acute revascularizations and evidence-based pharmacological treatments, the long-term benefits of these treatments are more disappointing than expected [3]. Part of this observation can be explained by the IHD patients' low uptake and adherence to secondary prevention programs [3].

Secondary prevention (i.e. cardiac rehabilitation) is recommended for all IHD patients (Class I, Level B indication for ST-elevation myocardial infarction patients, Class IIa, Level A for non ST-elevation myocardial infarction patients, and Class I, Level A for stable coronary artery disease patients) [4-6]. A recent systematic review indeed showed that multi-disciplinary cardiac rehabilitation still reduces mortality in IHD patients even on top of optimal medical treatment [7]. Unfortunately patients often decide not to attend these programs due to time constraints, lack of transport to the rehabilitation center, interference with vocational activites,…. [8].

Innovations in technology have made it technically possible to treat and supervise the patients from a distance, i.e. e-health based care. e-Health based care can be defined as "the use of emerging information and communication technology to improve or enable health and healthcare delivery" [9]. Telerehabilitation is one example of the application of e-health based care in practice. It can be described as the provision of secondary prevention from a distance. It is composed of remote monitoring (i.e. telemonitoring) of the patients' physiological data, telecoaching, e-learning and social interaction [8]. In its most ideal format, it focuses on all cardiac rehabilitation core components such as physical activity, healthy lifestyle behavior change, cardiovascular risk factor control, psychosocial wellbeing, nutritional and vocational counselling [10].

From a theoretical point of view, cardiac telerehabilitation has the potential to overcome the traditional barriers that prevent IHD patients from participating in conventional center-based programs. In telerehabilitation the patient can engage in secondary prevention wherever and whenever he/she prefers, while being supervised from a distance. In addition, e-health based care empowers patients to take a more active role in their own recovery after the index cardiac event, by encouraging self-monitoring and reacting to clinician driven feedback to the registered and tranferred data. It has been identified by the European Association of Preventive Cardiology (EAPC), together with the Acute Cardiovascular Care Association (ACCA), and the Council on Cardiovascular Nursing and Allied Professions (CCNAP) as one of the promising novel modes of care delivery that can address the challenge of low uptake and adherence described above [11].

Telerehabilitation can be performed in multiple ways and/or focusing on different patient populations. For example, the remote monitoring of physiological data (i.e. telemonitoring) can include the monitoring of physical activities in general (e.g. by accelerometry monitoring), of heart rate, of electrocardiographical

data and/or other parameters. The monitoring itself can be performed during the exercise training sessions or only on a regular basis but not real-time (synchronously or asynchronously respectively). The e-health program can focus only on physical exercise training, and/or other cardiac rehabilitation components can be included. The intensity of the program and the interaction with the patients also can vary widely.

At the start of my PhD trajectory, the scientific evidence related to the clinical efficacy and cost-efficiency of cardiac telerehabilitation in IHD was scarce. Hardly anything was known about the most optimal tele-program content, intensity, mode of delivery. However, given its potential high clinical and health policy impact on healthcare delivery it was an extremely interesting topic to focus on during this PhD.

Aims and objectives of this PhD

The aim of this thesis was to assess the long-term effectiveness and cost-efficiency of additional comprehensive cardiac telerehabilitation in low-to-moderate risk IHD patients. The following sub-objectives were addressed:

i. To assess the effectiveness of additional physical activity telemonitoring (main component of cardiac telerehabilitation) in secondary prevention for IHD patients on improving exercise tolerance levels, daily physical activity levels, and reducing adverse events.

ii. To assess the effectiveness of additional comprehensive cardiac telerehabilitation in secondary prevention for IHD patients on improving exercise tolerance, quality of life, cardiovascular risk factor profile, and reducing adverse events.

iii. To assess the cost-efficiency of additional comprehensive cardiac telerehabilitation in secondary prevention for IHD, when compared to conventional center-based cardiac rehabilitation alone.

Outline of this thesis

The first part of this thesis (chapters 02, 03 and 04) is devoted to the rationale for the conduct of cardiac telerehabilitation in IHD and the previously available scientific evidence in the field.

Chapter 02 describes the different types of patient populations for which secondary prevention programs are indicated. A special focus is put on IHD patients with special co-morbidities. Chapter 03 elaborates more on the challenges that are present in the field of preventive cardiology, introduced earlier in this introductory chapter 01. It contains an overview of the possible future ways on how to move forward and improve secondary preventive care delivery. Chapter 04 contains the results of the review that evaluated the content and role of telerehabilitation in cardiac patients. For each available study it was assessed: i. how many/which cardiac rehabilitation core components were included in the telerehabilitation program, ii. how many/which focus areas of telerehabilitation (i.e. telemonitoring, telecoaching, e-learning) were included, iii. whether or not the telerehabilitation program proved to be effective. Both IHD patients, heart failure patients (with reduced and/or preserved ejection fraction), and patients who had undergone cardiac surgery (valve replacement, valve repair, congenital heart disease) were represented in this review.

The central part of this thesis (chapters 05, 06, and 07) summarizes the results of the Telerehab trials that have been performed as part of this PhD.

Chapter 05 is devoted to the Telerehab II trial. Telerehab II was a prospective, mono-centric, randomized controlled trial. It assessed the effectiveness of an additional 18-week cardiac telerehabilitation program, when compared to a 12-week conventional, center-based, phase II cardiac rehabilitation program alone. 80 low-to-moderate risk IHD patients were included in the trial. The telerehabilitation program consisted mainly of physical activity telemonitoring by accelerometry. Peak aerobic capacity was the primary endpoint. Daily physical activity level and readmission rate constituted the most important secondary endpoints.

Chapters 06 and 07 describe the results of Telerehab III. Telerehab III was a prospective, multi-center, randomized controlled clinical trial. 140 cardiac patients from 3 hospitals (Jessa Hospital, ZOL and St. Franciscus Hospital) entered the study, including both patients with IHD, heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction. The control group patients (N = 70) received classical, center-based cardiac rehabilitation (12-week program). Intervention (i.e. telerehabilitation) group patients (N = 70) received both 12 weeks of center-based cardiac rehabilitation and in addition a 24-week telerehabilitation program. In contrast to Telerehab II, the telerehabilitation progam applied in Telerehab III was more comprehensive. It included both physical activity telemonitoring (as in Telerehab II), but supplemented this with nutritional telecoaching and a "tele-" smoking cessation program. The primary study endpoint was peak aerobic capacity. Secondary endpoints included i. daily physical activity level, ii. cardiovascular risk factor profile, quality of life, and (cardiovascular) readmission rate. A Health Technology Assessment (HTA) compliant cost-utility analysis is also performed looking at cost-efficiency of additional cardiac telerehabilitation from a healthcare provider perspective.

After completion of Telerehab III, its long-term follow-up study was initiated (Telerehab III long-term follow-up study). As part of the Telerehab III long-term follow-up study, all patients of the initial Telerehab III trial were further followed-up for two additional years. During this long-term follow-up period, no center-based cardiac rehabilitation and no telerehabilitation were provided to the study participants. The aim of this follow-up study was to assess whether the observed benefits of cardiac telerehabilitation would persist in the long-term, once the telerehabilitation program was ended. All patients were invited two years after Telerehab III study completion to have a long-term follow-up visit, to re-assess the primary and secondary endpoints as defined in the initial Telerehab III trial.

The last part of this thesis (chapters 08 and 09) positions the Telerehab trials in the more global scientific landscape of cardiac telerehabilitation. It compares Telerehab III with Fit@Home, the other landmark clinical trial in this field. Telerehabilitation program content, and study results are contrasted and summarized. Chapter 09 contains the general discussion and summary of this thesis. It provides the reader with the answers to the questions that were asked at the start of the PhD period. It appraises the observed study results from a broader perspective and identifies the remaining gaps/challenges in e-health based care in cardiology. It philosophizes about what the focus of future research in this field should look like.

The overarching methodology applied during my PhD trajectory is described in this section. To start I conducted a review of the relevant literature related to cardiac telerehabilitation. This allowed me to identify the focus of the remaining part of my PhD. In follow-up of the review I designed, conducted, analysed and published the results of Telerehab II and Telerehab III, two clinical trials that constituted the

main part of the rest of my PhD. For the practical conduct of both clinical studies, I received help from local staff and/or other researchers at the institution.

Wishing you a lot of joy in reading this thesis!

References

[1] European Heart Network, www.ehnheart.org/cvd-statistics.html (2018, accessed 8 January 2018).

[2] World Health Organization, http://www.who.int/nmh/events/ncd_action_plan/en/ (2018, accessed 8 January 2018).

[3] Kotseva K, Wood D, De Bacquer D, 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):636-48. doi: 10.1177/2047487315569401. PMID: 25687109

[4] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2017 [Epub ahead of print]

[5] Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37(3):267-315.

[6] Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34(38):2949-3003.

[7] Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol 2016;23(18):1914-1939.

[8] Frederix I, Vanhees L, Dendale P, et al. A review of telerehabilitation for cardiac patients. J Telemed Telecare 2015;21(1):45-53.

[9] Pagliari C, Sloan D, Gregor P, et al. What is eHealth (4): a scoping exercise to map the field. J Med Internet Res 2005;7(1):e9.

[10] Piepoli MF, Corrà U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 2014;21(6):664-81.

[11] Piepoli MF, Corrà U, Dendale P, et al. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur J Prev Cardiol 2016;23(18):1994-2006.

Chapter 02

Who needs secondary prevention?

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Abstract

Secondary prevention for ischemic heart disease can be defined as a comprehensive set of measures, aiming to reduce the recurrence of cardiovascular disease and to improve long-term prognosis. Despite its proven efficacy, uptake and adherence rates remain poor. This paper summarizes the available European recommendations for secondary prevention in the varying ischemic heart disease populations, including those patients with specific co-morbidities. The scientific evidence supporting these recommendations is provided. The paper relates to the European Association of Preventive Cardiology (EAPC), the Acute Cardiovascular Care Association (ACCA) and the Council on Cardiovascular Nursing and Allied Professions (CCNAP) Secondary Prevention After Acute Myocardial Infarction framework in that it clarifies accurately who needs secondary prevention.

1. What is secondary cardiovascular prevention?

1.1 Definition

The umbrella of preventive cardiology encompasses both, primary and secondary prevention of cardiovascular disease, the latter of which will be the focus of this manuscript. Secondary prevention aims to stop and/or slow down the progress of established cardiovascular disease, to improve functional capacity, to restore quality of life and to reduce the risk of disease recurrence [1]. It is strongly recommended to use a comprehensive approach comprising multiple core components: i. patient assessment, ii. physical activity counselling & exercise training prescription, iii. nutritional counselling, iv. risk factor control, v. psychosocial management, vi. vocational support, vii. therapy adherence and viii. patient education [2]. Traditionally three main phases have been differentiated (the in-hospital phase I, the early out-patient phase II and the long-term maintenance phase III). However, in essence secondary prevention is an uninterrupted, patient-tailored and lifelong care strategy to encourage and enable cardiac patients to resume a normal life. Despite the standardization of cardiac rehabilitation program's objectives and core components, the structure, content, duration, intensity and volume of programs continues to differ widely between and within different European countries. Differences in local and national guidelines, legislations, as well as reimbursement factors are held responsible for this disparity [3].

1.2 Rationale

The most recent European Heart Network's statistics indicate that cardiovascular disease accounts for 47% of all deaths in Europe, thereby currently constituting a disease category of highest public relevance [4]. Each year seven million people suffer from an acute coronary syndrome [5]. Despite the current era of acute revascularization and evidence-based pharmacotherapy (including ACE-inhibitors, anti-platelet therapy, β-blockers and statins), mortality rates one year after a myocardial infarction remain in the range of 10% [6]. About half of the patients that suffer from a major acute coronary event have a history of an acute myocardial infarction [7]. These statistics clearly indicate the need for large-scale deployment, referral to, uptake of and adherence to high-quality secondary prevention programs in order to improve long-term outcomes. Unfortunately, as indicated by the European survey on the management of ischemic heart disease in 24 European countries (EUROASPIRE IV), < 50% of patients access/ are referred to and adhere to these programs due to both patient-, health care provider- and health system-based barriers [8-

9]. As a consequence, the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Council on Cardiovascular Nursing and Allied Professions (CCNAP) called for action. In their "Secondary Prevention After Acute Myocardial Infarction" position statement, they outlined today's challenges and how to address these [10]. The purpose of this paper is to provide the reader with i. the ESC guidelines recommendations regarding secondary prevention for different ischemic heart disease populations, and ii. the relevant clinical evidence supporting these recommendations.

2. Who will benefit from secondary prevention – the ESC guidelines?

2.1 Ischemic heart disease patients

Patients who suffered from a ST-elevation acute myocardial infarction (STEMI) are at high-risk for recurrence and premature death. Therefore the ESC guidelines recommend the initiation of several secondary prevention related lifestyle interventions and pharmacological treatments during the hospital stay for the initial cardiac event [11]. Key lifestyle interventions include smoking cessation (Class I, Level B) and cardiovascular risk factor control. Nutritional counselling, stress management and early resumption of professional activities are encouraged. Participation in an outpatient and/or center-based exercise-based cardiac rehabilitation program is indicated in all patients (Class I, Level B).

Enrolment in a comprehensive secondary prevention program should also be considered for patients who suffered from an acute coronary syndrome type Non-ST-elevation myocardial infarction (NSTEMI) (Class IIa, Level A) to enhance patient compliance, to promote sustained healthy lifestyle behavior change and to allow for nutritional/psychological and vocational counselling [12]. All patients should be recommended to stop smoking (Class I, Level A), to engage in regular physical activities (Class I, Level A) and to adopt a heart-friendly diet (Class I, Level A). Physical activities preferably include aerobic exercise training with a frequency of ≥ 3 times a week and a duration of 30 minutes per session.

Long-term, structured and multidisciplinary cardiac rehabilitation, aiming to reduce symptoms and to improve prognosis, is also recommended for patients with stable coronary artery disease (Class I, Level A) [13]. It encompasses lifestyle modification, pharmacological treatment, cardiovascular risk factor modification and patient education as in patients after an acute coronary syndrome. Stable coronary artery disease patients are encouraged to engage in moderate-to-vigorous intensity aerobic exercise training, ≥ 3 times a week and for 30 minutes per session, as part of the cardiac rehabilitation program.

According to the ESC guidelines, comprehensive secondary prevention should thus be considered and/or recommended for all types of ischemic heart disease (both STEMI, NSTEMI and stable coronary artery disease patients) within this era of acute revascularization and highly effective evidence-based pharmacotherapy. The scientific evidence supporting these recommendations has recently been summarized in two systematic reviews [14, 15]. The Cardiac Rehabilitation Outcome Study (CROS) assessed the prognostic effect of multi-component cardiac rehabilitation in the modern era, i.e. after the introduction of acute percutaneous coronary intervention and the administration of statins in patients who suffered from an acute coronary syndrome, who received a coronary artery bypass graft or who suffered from stable coronary artery disease. It included 25 studies performed after 1995 (n = 1 RCT, n = 7 prospective controlled cohort studies, n = 17 retrospective controlled cohort studies, mean follow-up period: 40 months), evaluating 219,702 patients and reflecting routine clinical practice in nine countries

worldwide. The major finding of CROS was that multi-component cardiac rehabilitation is still associated with a reduced total mortality when compared to usual care for acute coronary syndrome (HR 0.37, 95% CI [0.20 – 0.69]) and coronary artery bypass graft patients (HR 0.62, 95% CI [0.54 – 0.70]) in the era of acute coronary revascularization and modern medical treatment. The latest Cochrane review assessing the effectiveness of all available studies on exercise-based cardiac rehabilitation in ischemic heart disease by pooling the results of 63 RCT's (14,486 patients, mean follow-up time of 12 months) concluded that exercise-based cardiac rehabilitation is effective in reducing cardiovascular mortality by 26% (relative risk: 0.74, 95% CI [0.64-0.86]).

These results confirm the additional benefits of cardiac rehabilitation within the context of contemporary medical treatments and justify a Class I recommendation of current clinical guidelines to attend cardiac rehabilitation for patients with ischemic heart disease.

2.2 Ischemic heart disease patients with special co-morbidities

2.2.1 The elderly and frail patients

Frailty constitutes an important issue in cardiac rehabilitation programs, since elderly patients (> 75 years) represent up to one third of the cardiac rehabilitation population, even though advanced age is frequently reported as an important barrier for participation in secondary prevention programs [16]. Frailty measurements during the initial assessment should therefore be considered for optimization of: i. type and timing of diagnostic procedures, ii. pharmacological and nonpharmacological treatment and iii. exercise prescription. It has been shown, that tailored exercise training in community living or institutionalized frail elderly patients is able to improve physical function and quality of life to some degree [17-18]. Although it is still uncertain whether these positive results can be applied to cardiac rehabilitation patients, frail patients should be offered exercise-based rehabilitation programs in order to improve physical mobility, functional capacity and quality of life, and to prevent falls and disability. Special importance in the elderly should also be attached at nutritional aspects, since a poor nutritional status is one of the main pathophysiological mechanisms for frailty. Recent studies suggest that improving nutritional status may reduce the risk of frailty [19].

2.2.2 Diabetic patients

Impaired glucose tolerance is one of the strongest prognosticators after acute myocardial infarction and diabetes mellitus is associated with an increased risk of coronary artery disease and an impaired prognosis after the acute myocardial infarction. Nevertheless, a substantial proportion of adults meeting the criteria of diabetes are not identified as such. Therefore adequate diagnosis and treatment is of utmost importance. Controversies exist as to the extent to which glycemic control should be undertaken in diabetic patients with an acute coronary syndrome, as the deleterious impact of hypoglycemia on cardiovascular outcomes has been increasingly recognized [20]. According to the 2013 ESC/European Association for the Study of Diabetes Guidelines, glucose-lowering therapies should be considered in acute coronary syndrome patients with significant hyperglycemia [glucose concentration >10 mmol/L (>180–200 mg/dL)] and moderately tight glycemic control (6.6-9.9 mmol/L or 120–180 mg/dL) is independently associated with lower mortality and major complications than that observed after tighter (<6.6 mmol/L or

<120 mg/dL) or more lenient (>9.9 mmol/L or >180 mg/dL) glycemic control [21]. As a general rule, with more advanced cardiovascular disease, older age, longer diabetes duration and more co-morbidities, less stringent glucose control should be applied in the acute phase and at follow-up. Physical activity is not only important in the prevention of the development of type 2 diabetes in people with impaired glucose tolerance but also for the control of glycaemia and related cardiovascular disease complications [22]. Aerobic and resistance training improve insulin action and plasma glucose, lipids, blood pressure and cardiovascular risk [23]. However, regular exercise is necessary for continuing benefit. Combined aerobic and resistance training has a more favorable impact on HbA1c than aerobic or resistance training alone and is able to reduce HbA1c by 0.7%, compared with controls [24]. Structured exercise of >150 min/week is associated with a fall in HbA1c of 0.9% , 150 min/week with a fall of 0.4%. To note however, interventions of physical activity advice are associated with lower HbA1c levels only when combined with dietary advice [25].

2.2.3 The chronic kidney disease patients

The prevalence of chronic kidney disease (eGFR <60 ml/min/1.73m2) in a big cohort of patients in a stationary rehabilitation setting was as high as 38.2% [26]. Depending on the duration and classification of renal failure, a moderate to severe reduction of physical capacity must be expected. This is related to renal anemia, uremic myopathy and polyneuropathy, disturbances in volume status, electrolyte balance and or acid-base metabolism as well as physical inactivity. For a given patient, exercise training should depend on the baseline level of physical capacity and kidney disease severity, however stage I–III renal failure should not affect the ability to perform exercise. In hemodialysis patients, special attention should be turned to avoid injury of the arteriovenous fistula and pain in the shunt-arm. Exercise training should be performed on the day between hemodialysis sessions. In general, patients with coronary artery disease complicated with chronic kidney disease may gain benefit rather than to risk harm from participation in cardiac rehabilitation in terms of eGFR, exercise capacity and plasma BNP concentration [27].

2.2.4 Left ventricular dysfunction/heart failure patients

Physical inactivity is common in patients with symptomatic heart failure and contributes to its progression. Exercise training improves exercise capacity and quality of life, it does not adversely affect left ventricular remodeling, and may reduce mortality and hospitalization rate in patients with mild-to-moderate chronic heart failure. Hence, regular aerobic exercise is recommended to improve functional capacity and symptoms both, in heart failure patients with reduced or preserved ejection fraction (Class I, level A) [28-29]. Enrollment in a multidisciplinary care management program reduces the risk of heart failure hospitalization and mortality and is recommended (Class I, level A).

2.2.5 The female patients

Physicians often misunderstand cardiovascular disease risks in women, and this corresponds with poor referral to cardiac rehabilitation, although women benefit from comprehensive cardiac rehabilitation as much as men [30]. This is also true for older women. At recruitment to cardiac rehabilitation, women typically score lower in health-related quality of life and they are more likely to be diagnosed with

depressive disorders and higher scores of anxiety. The planning and implementation of cardiac rehabilitation in women needs to consider that they are more likely to be older, to have hypertension, diabetes, hypercholesterolemia, obesity and heart failure, as well as lower exercise and functional capacity compared to male patients and may therefore carry a higher cardiac risk. Beyond the impact of the cardiac disease, older women in particular are more likely to experience activity limitations and other exercise-limiting co-morbid conditions such as arthritis, osteoporosis and urinary incontinence. However, cardiac rehabilitation constitutes the standard of care also for women, and this standard should be upheld for all women with cardiovascular disease, regardless of age, race, socioeconomic status or co-morbidities [31].

3. Conclusion

In the current ESC guidelines, comprehensive secondary prevention is recommended and/or considered for patients with various types of ischemic heart disease (both STEMI, NSTEMI and stable coronary artery disease patients). The most recent scientific evidence (i.e. the CROS study and Cochrane review) demonstrates additional benefits of cardiac rehabilitation within the contemporary era of acute revascularization and highly effective evidence-based pharmacotherapy and hence justifies a Class I recommendation. Healthcare professionals should be encouraged to assess relevant co-morbidities in all ischemic heart disease patients in order to improve care delivery. Frailty screening is strongly recommended in the elderly patients to optimize pharmacological treatment and to tailor exercise prescription. Timely identification and proper treatment of concomitant diabetes mellitus is paramount. The presence of chronic kidney disease and/or heart failure should not prevent patients to attend cardiac rehabilitation. Gender-specific exercise-limiting co-morbid conditions should be taken into account when prescribing training programs for female patients.

References

[1] Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Eur Heart J 2016; 37: 2315–2381.

[2] Piepoli MF, Corrà U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 2014; 21(6): 664-81.

[3] Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. Eur J Cardiovasc Prev Rehabil 2010;17:410 – 418.

[4] European Heart Network, www.ehnheart.org/cvd-statistics.html (2016, accessed 14 November 2016).

[5] White HD, Chew DP. Acute myocardial infarction. Lancet 2008; 372(9638): 570-84.

[6] Pedersen F, Butrymovich V, Kelbaek H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol 2014; 64(20): 2101-2108.

[7] Jernberg T, Hasvold P, Henriksson M, 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): 1163-70.

[8] Kotseva K, 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):636-48

[9] Clark A, King-Shier K, Duncan A, et al. Factors influencing referral to cardiac rehabilitation and secondary prevention programs: a systematic review. Eur J Prev Cardiol 2012; 20: 692-700.

[10] Piepoli MF, Corrà U, Dendale P, et al. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur J Prev Cardiol 2016 [Epub ahead of print].

[11] Steg G, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569–2619.

[12] Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016; 37: 267–315.

[13] Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34: 2949–3003.

[14] Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularization and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol 2016; 23(18): 1914-1939.

[15] Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016; 67(1): 1-12.

[16] Giallauria F, Vigorito C, Tramarin R, et al. ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention, Rehabilitation and Prevention. Cardiac rehabilitation in very old patients: data from the Italian Survey on Cardiac Rehabilitation-2008 [ISYDE-2008]. J Gerontol A Biol Sci Med Sci 2010; 65: 1353–1361.

[17] Gine´-Garriga M, Roque´-Fı´guls M, Coll-Planas L, et al. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. Arch Phys Med Rehabil 2014; 95: 753–769.

[18] Weening-Dijksterhuis E, de Greef MH, Scherder EJ, et al. Frail institutionalized older persons: a comprehensive review on physical exercise, physical fitness, activities of daily living, and quality-of-life. Am J Phys Med Rehabil 2011; 90: 156–168.

[19] Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N, et al. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016; 93: 89-99.

[20] De Caterina R, Madonna R, Sourij H, et al. Glycaemic control in acute coronary syndromes: prognostic value and therapeutic options. Eur Heart J 2010; 31: 1557–1564.

[21] Rydén L, Grant PJ, Anker SD, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary. Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD). Diab Vasc Dis Res 2014; 11(3): 133-73.

[22] Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care 2010; 33: 2692–2696.

[23] Vanhees L, Geladas N, Hansen D, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. Eur J Prev Cardiol 2012; 19: 1005–1033.

[24] Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006; 29: 2518–2527.

[25] Sigal RJ, Kenny GP, Boule NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007; 147: 357–369.

[26] Völler H, Gitt A, Jannowitz C, et al. Treatment patterns, risk factor control and functional capacity in patients with cardiovascular and chronic kidney disease in the cardiac rehabilitation setting. Eur J Prev Cardiol 2014; 21(9): 1125-33.

[27] Takaya Y, Kumasaka R, Arakawa T, et al. Impact of cardiac rehabilitation on renal function in patients with and without chronic kidney disease after acute myocardial infarction. Circ J 2014; 78(2): 377-384.

[28] Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev 2014; 4: CD003331.

[29] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J 2016; 37(27): 2129-200.

[30] Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. 2007 update. J Am Coll Cardiol 2007; 49: 1230–1250.

[31] Daniels KM, Arena R, Lavie CJ, et al. Cardiac rehabilitation for women across the lifespan. Am J Med 2012; 125(9): 937.e1-7.

Chapter 03

Challenges in secondary prevention after acute myocardial infarction: A call for action.

Piepoli MF, Corrà U, Dendale P, Frederix I, Prescott E, Schmid JP, Cupples M, Deaton C, Doherty P, Giannuzzi P, Graham I, Hansen TB, Jennings C, Landmesser U, Marques-Vidal P, Vrints C, Walker D, Bueno H, Fitzsimons D, Pelliccia A.

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Abstract

Worldwide, each year more than 7 million people experience myocardial infarction, where 1- year mortality rates are now in the range of 10%, but vary with patient characteristics. The consequences are even more dramatic: among patients who survive, 20% suffer a second cardiovascular event in the first year and approximately 50% of major coronary events occur in those with a previous hospital discharge diagnosis of ischemic heart disease. The people behind these numbers spur this call for action. Prevention after myocardial infarction is crucial to reduce risk and suffering. Evidence based interventions include optimal medical treatment with anti-platelets and statins, achievement of blood pressure, lipid and blood glucose targets, and appropriate lifestyle changes. The European Society of Cardiology and its constituent bodies are determined to embrace this challenge by developing a consensus document where the existing gaps for secondary prevention strategies are reviewed. Effective interventions in relation to the patients, healthcare providers and healthcare systems are proposed and discussed. Finally innovative strategies in hospital as well in outpatient and long-term setting are endorsed.

1. Disease burden

Worldwide, each year more than 7 million people experience acute myocardial infarction (AMI), [1] and although substantial reductions in mortality have been experienced in recent decades, [2] one year mortality rates are still in the range of 10%, [3] varying with patient characteristics. In the Swedish SCAAR registry 1-year mortality rates were approximately 10% among patients aged 70-79 and 24% among patients aged 80-90. [4] The consequences of AMI are more dramatic: among patients who survive a AMI, 20% suffer a second cardiovascular (CV) event in the first year and approximately 50% of major coronary events occur in those with a previous hospital discharge diagnosis of AMI. [5]

While early events are related to ruptured coronary plaques and associated thrombosis, the majority of later events may be the result of coronary and systemic atherosclerosis progression. Thus it is being increasingly appreciated that evidence-based long-term management of ischemic heart disease (IHD) is critical to achieve optimal reduction in mortality and morbidity. [6] Prevention after AMI is a crucial part of this, and is associated with improved prognosis [7,8] with evidence based interventions, such as optimal medical treatment, appropriate lifestyle changes and CV risk factor control. [9] Importantly, the impact of lifestyle change after AMI has a rapid onset: patients who adhere to exercise and diet recommendations have 54% lower risk and smokers who quit smoking, a 43% lower risk of recurrent events six months after AMI. [10]

Despite this compelling evidence, preventive care post AMI remains sub-optimal. Cross-sectional data from the serially conducted EUROASPIRE surveys across Europe in both patients with established IHD and people at high CV risk have demonstrated a high prevalence of unhealthy lifestyles, modifiable risk factors and inadequate use of drug therapies to achieve blood pressure and lipid goals. Most recently, in the 4th survey of coronary patients, after a median time of 1.35 years after their acute event, 48.6% of patients who were smoking at the time of their event persisted in smoking, little or no physical activity was reported in nearly two thirds of interviewees, over a third (37.6%) were obese, 42.7% had blood pressure ≥ 140/90 mmHg (≥140/80 in people with diabetes), 80.5% had low-density lipoprotein cholesterol ≥ 1.8 mmol/l and in those with diabetes, glucose control was relatively poor with less than half reaching the guideline target of HbA1c of <7.0 %. [11]

Similarly, an Italian multi-centre registry study performed in 2010-2012 showed in 11,706 patients from 163 large-volume coronary care units, that at six months drug adherence was 90%, but the recommended targets of blood pressure (<140/90 mmHg) were reached in only 74%, low density lipoprotein (< 1.8 mmol/l) in 76%, Hba1c (< 7% in treated diabetics) in 45% and smoking cessation only in 73% of the participant patients. [12]

2. Secondary Prevention

Secondary prevention programmes, defined as the level of preventive care focusing on early risk stratification, use of referral services, and initiation of treatment to stop the progress of an established disease processes, are highly recommended in all IHD patients, to restore quality of life, maintain or improve functional capacity and prevent recurrence. [13] Cardiac rehabilitation, operationally defined here as a the structured multidisciplinary intervention for CV risk assessment and management, advice on physical activity, psychosocial support and the appropriate prescription and adherence to cardio-protective drugs, is the most investigated modality of secondary prevention interventions, [14] its core components in post-AMI patients well identified (Table 1). [15]

Table 1. Components of secondary prevention in post-AMI patients

Interventions	Components
Risk factor modification /lifestyle Interventions	- Healthy diet - Physical activity - Weight control - Smoking cessation - Stop alcohol abuse
Preventive medications	- Antithrombotic therapies - Beta blockers - ACE inhibitors/ARBs/aldosterone antagonists (if depressed LV function) - Statins
Management of co-morbidities	- Obesity - Dyslipidaemia - Arterial Hypertension - Diabetes - Heart failure - Arrhythmia/arrhythmia risk
Psychosocial factors	- Social isolation - Depression, stress, and anxiety - Sexual activity
Multidisciplinary team follow-up	- Cardiologist - Primary care - Advanced practice nurse/physician assistant - Other relevant medical specialists

	- Other non-medical specialists (e.g. physiotherapist, psychologist, pharmacist, dietician, vocational specialist)
Patient/family education	- Plan of care - Education - Recognition of symptoms, signs and symptoms for urgent vs. emergency evaluations - Risk factor control - Activating EMS - CPR training for family members - Advanced directives
Socioeconomic and healthcare factors	- Access to health insurance coverage - Access to healthcare providers - Disability - Social services - Social networks - Community services - Electronic personal health records

ACE, angiotensin converting enzyme, ARB, angiotensin receptor inhibitors, CPR, cardio-pulmonary resuscitation, EMS, emergency medical system, LV, left ventricle

Although traditionally divided into 3 phases (e.g. inpatient, outpatient, long-term intervention), in reality secondary prevention is a continuous lifelong process, a care pathway that follows the patient journey, made up of key stages that need to occur to enable patients to achieve the return to a normal life. [16] Settings vary in different countries, [17] according to local and national regulations and experiences, involving residential, ambulatory community, or home-based programmes. While the objectives are identical to those for outpatients, residential in-patient programmes are specifically structured to provide more intensive and/or complex interventions, reserved for high-risk patients. [18]

Preventive services in the community offer the opportunity to maintain the benefits in the long term, [19] with potential for overcoming existing barriers to health care such as distance, unfamiliarity and fear/distrust of hospitals, allowing the delivery of a programme that is best placed (i.e. 'tailored') to meet that individual needs. EUROACTION [20] and GOSPEL [21] interventions provided scientific evidence for a beneficial long-term effect of community-based programmes. The EUROACTION study tested a comprehensive, nurse-led, family centred and multidisciplinary model of preventive and rehabilitative care in eight countries in Europe and was subsequently set up as an integrated community centred service in the UK (MyAction) providing care for both vascular patients and those at high cardiovascular risk whilst the GOSPEL study is an Italian long-term multifactorial educational and behavioural intervention (coordinated by a cardiologist) after a standard rehabilitation programme following AMI.

The existing health-economic literature supports comprehensive secondary prevention as a relatively more cost-effective intervention in IHD patients, in comparison to invasive therapies or cardiac surgery. [22] Given the current economic challenges in health care it is noteworthy that in low- and middle-income countries, cardiac prevention has been demonstrated to be both effective and cost-effective. [23]

3. Identification of gaps and potential solutions in implementation

Despite the availability of suitable secondary prevention programmes, only one third to one half of eligible patients are referred [24] or finally take up a preventive programme. [25] A plethora of research indicates that patient-, health care provider- and/or health system-based barriers all hold responsibility for this (Table 2). [26]

3.1. Patient related gaps

3.1.1 Education and empowerment

Patients with IHD understand poorly their disease and perceive themselves as having little control over its course, many lack interest in prevention and/or feel embarrassed about participating in preventive's group sessions. Most of them report not receiving robust information and/or encouragement from physicians and other health professionals regarding how to prevent recurrent events. [27] Other factors, which hinder attendance, include lack of social support, poor psychological wellbeing, inconvenient location with transport difficulties, competing work commitments and financial cost. [16] Inadequacies and time constraints related to education and counselling of patients before they leave hospital lead to deficiencies in implementation of preventive care later on. Patients who have a clear understanding of their after-hospital care instructions are 30% less likely to be readmitted or to visit the emergency department than patients who lack this information. [28] Patients discharged from the hospital with a clear guideline-oriented treatment recommendation, a checklist of measures to ensure risk modification and lifestyle change provided in the discharge letter, educated to care for themselves and to know how or when to seek follow-up care, can better understand the importance of this information and its potential impact. [29] A wide variety of techniques and combinations of techniques have also been evaluated, but only self-monitoring of physical activity and action planning or coping strategies targeting barriers seems to be helpful. [30] (Table 3)

3.1.2 Adherence to healthy lifestyle interventions

A systematic review and meta-analysis of adherence to cardio-protective medicines in more than 350,000 patients found low adherence in both individuals at high CV risk (66%) and in patients with CVD (50%) a median of two years after initiation of a prescription. [31] This results in worse outcomes and higher healthcare costs. [32,33] The reasons for non-adherence are complex and influenced by factors including demography, socioeconomic factors, health systems factors, intensity of follow up, time since last provider visit, adverse effects of therapy, complex medication regimens and health literacy (Table 2). For these reasons, the health care provider should assess not only adherence to medication, but also identify reasons, and promote adherence according to established principles (Table 4). In this aspect, the active role of the pharmacists should be encouraged: in UK, the new Pharmacist led Medicines Optimisation Clinics is a model of implementation of the contribution of the pharmacists to support patients post MI.

A Cochrane review [34] of interventions to improve medication adherence advised drawing on the support of allied professionals such as nurses and pharmacists to deliver complex interventions, which may include telephone follow-up, interim appointments, and monitoring of repeat prescriptions. Drawing on the support of non-professional people within the social context of the patient, such as spouses, other family members, carers or other key figures, and lay groups in the community, may prove to be a cost-effective way to improve adherence. However the review acknowledged that such interventions may be difficult to replicate in everyday clinical care due to cost and availability of personnel.

3.1.3 Adherence to preventive pharmacological therapy

Adherence to medication is low in individuals at high risk and in patients with CVD, resulting in worse outcomes and higher healthcare costs. [11] Non-adherence is multifactorial and is influenced by demographic and socioeconomic factors, time since last provider visit, adverse effects of therapy, and complex medication regimens (Table 2). For these reasons, the health care provider should assess not only adherence to medication, but also identify reasons, and promote adherence according to established principles [35,36] (Table 3, 4). Furthermore the development in many patients of real or presumed 'drug intolerance" should be considered, and how quick the physicians label patient as such, may severely disadvantage post MI patients. The post-MI patients may also present several co-morbidities, which need multiple treatments, sometimes in conflict with each other. Role of the physician is also trying to simplify the treatment regimen to the lowest acceptable level, with repetitive monitoring and feedback. The use of the polypill and combination therapy to increase adherence to drug therapy may be considered. Finally, medicines optimisation" may also mean de-prescribing: physicians should also evaluate when to stop and de-prescribe medicines: e.g. there is NICE recommendation for stopping long term beta-blocker in post MI in patients who do not have HF or other specific indication. [37]

Table 2 Factors leading to therapeutic inertia in CV prevention, attributed to the patient-, clinician-, and health care system-level

Patient	Clinician/ Healthcare provider	Healthcare system
Medication side effects	Failure to initiate treatment	Lack of clinical guideline
Too many medications	Failure to titrate to goal	Lack of care coordination
Cost of medications	Failure to set clear goals	No visit planning
Denial of disease	Underestimation of patient need	Lack of decision support
Denial of disease severity	Failure to identify and manage comorbid conditions	Poor communication between physician and others involved in a patient's healthcare provision
Forgetfulness	Insufficient time	No disease registry
Perception of low susceptibility	Insufficient focus of emphasis on goal attainment	No active outreach
Absence of disease symptoms	Reactive rather than proactive	Perverse incentives

Poor communication with physician	Poor communication skills	Pressure to short length of hospital stay
Mistrust of physician	Shortage of time	Health care systems focused on acute care (hospital-based Health systems)
Depression, mental disease, substance abuse	Poor awareness on value of preventive measure	Lack of preventive structure

Table 3. Components of an optimal, standardized, patient-centred discharge process

Creating a clear follow-up plan, coordinating appointments for clinician follow-up, post-discharge testing, and transportation arrangements
Giving the patient a written discharge plan at the time of discharge, explaining the reason for hospitalization and information about medications.
Assessing the patient's understanding of his/her diagnosis, of the clinical tests and evaluations performed in the hospital, of the discharge plan, including medications, lifestyle changes, (in case, by asking the patient to explain the discharge plan in his or her own words in order to identify and resolve barriers to understanding)
Educating the patient about recognition of cardiac symptoms, problem solving strategies, and review appointments plans
Providing hospital contact details, and telephone contacts after discharge to address concerns
Sending the discharge summary to the physicians and other services responsible for the patient's care after discharge together with contact details of relatives and health care providers where appropriate

Table 4. Adherence factors

'Agree' rather than 'dictate' a drug regimen and tailor it to personal lifestyle and needs.
Provide advice regarding benefits and possible adverse effects of medications, and duration and timing of doses
Consider patients' habits and preferences, encourage self-monitoring, use of cues and technologies to act as reminders
Reduce dosage demands to the lowest feasible level and simplify the dosing regimen when possible.
Ask patients in a non-judgemental way how the medication works

Back up verbal instructions with clear written instructions.
Implement repetitive monitoring and feedback and regular review of medicines to minimise polypharmacy
Introduce trained nurses or physician assistants if needed and feasible
Promoting the active role of the pharmacist in assessing drug adherence and in encouraging patients to discuss their medicines and any concerns they may have about them
Involve the partner, other family member or carer in the patient's treatment
In case of persistent no adherence, offer multisession or combined behavioural intervention

3.2. Healthcare provider gaps

3.2.1 Health care provider's knowledge and motivation

In the description of the core curriculum for the cardiologist, the ESC defines in detail the knowledge needed in regard to secondary prevention, including evaluation and management of CV risk, as well as the provision of appropriate prevention to CVD patients. [38] However, it is questionable whether such requirements are part of the curriculum of most cardiologists or specialist allied health professionals trained in Europe. This gap in knowledge and motivation apply also to GP and non-cardiology healthcare professionals and need to be closed, by specific educational training.

Furthermore, for decades, much attention and many resources have been directed at encouraging physicians and providers to shift care as much as possible away from costly inpatient hospital stays toward less expensive outpatient treatment. [39] Among the most important metrics for gauging the success of this endeavour is the shortening of the hospital length of stay, early discharge even directly from intensive care units, although real savings has not been proven. [40] This leaves a limited amount of time for information and education. In addition it does not allow for optimization of risk stratification and secondary prevention therapy, particularly medication dose titration prior to hospital discharge.

3.2.2 Risk stratification

Risk stratification is the pre-requisite for improving care management. Because the risk of events decreases with time, early assessment (e.g. infarct size and resting LV function) is crucial before discharge. [41] Current guidelines recommend evaluation of metabolic risk markers during the index admission, such as fitness level, body mass index, low-density lipoprotein (LDL) cholesterol, fasting glucose level. [13]

3.2.3 Post discharge plan

Strategies effective to increase uptake include not only patient education and empowerment (see 3.1.1) but also, at post hospital discharge, the development of gender-tailored sessions, structured follow-up

via either telephone call or visit by a healthcare professional or both, a specific programme for older patients, and planned early appointments to programmes. [42-44]

3.2.4 Awareness and communication among health professionals in acute care and in primary care

The transfer of the specialist's knowledge to the community team remains a major challenge, as only about half of the general practitioners use guidelines in everyday practice and knowledge of treatment goals is often insufficient. [45] Delayed communication or inaccuracies in information transfer among health care professionals has substantial implications for continuity of care, patient safety, patient and clinician satisfaction, and resource use. [46]

Educational meetings, audit and feedback, with local opinion leaders and access to computer decision support devices can lead to improved continuity of care. [47] Regular review and provision of patient education in primary care leads to improved adherence to lifestyle advice (more physical activity, better diet), reduced symptoms, improved quality of life and reduced mortality. [48] In the UK, the clinical indicators of GPs' performance in chronic disease monitoring include checklists relating to medication and risk factor control, and engagement in this process is incentivized by financial reward. [49]

3.3. Healthcare systems gaps

Patients consistently cite physicians and other healthcare providers as the main sources of encouragement for subsequent participation in preventive programmes. [30] Unfortunately, several factors negatively influence current referral rates.

3.3.1 Availability of structured secondary prevention programme

The lack of prevention centres constitutes an obstacle to the implementation of rehabilitation programmes in many European areas but particularly in less advantaged regions. [50]

3.3.2 Referral to structured secondary prevention intervention

Lack of *referral* is an important impediment to participation in preventive programmes. The presence of inter-hospital variability in referral rates suggests that several healthcare system factors might have a strong influence, including insurance coverage, hospital characteristics (dimension, geographic location) and other unidentified factors. [50] Limited financial incentives for the physician to implement preventive measure and the pressures of competing workload priorities may negatively influence current referral rates. [51]

Various strategies can address the lack of referral and improve enrolment. [52] (Figure 1). Systematic processes such as automatic referral and liaison systems to connect cardiac patients with the preventive programme have been developed and can increase referral rates by >50%.[53] Evidence is emerging to suggest that mechanisms to support automatic patient referral via electronic health records or discharge protocols are effective in increasing referral. Strength of physician endorsement for referring cardiac patients is a pivotal step to improve participation and its associated improved outcomes after AMI. [53]

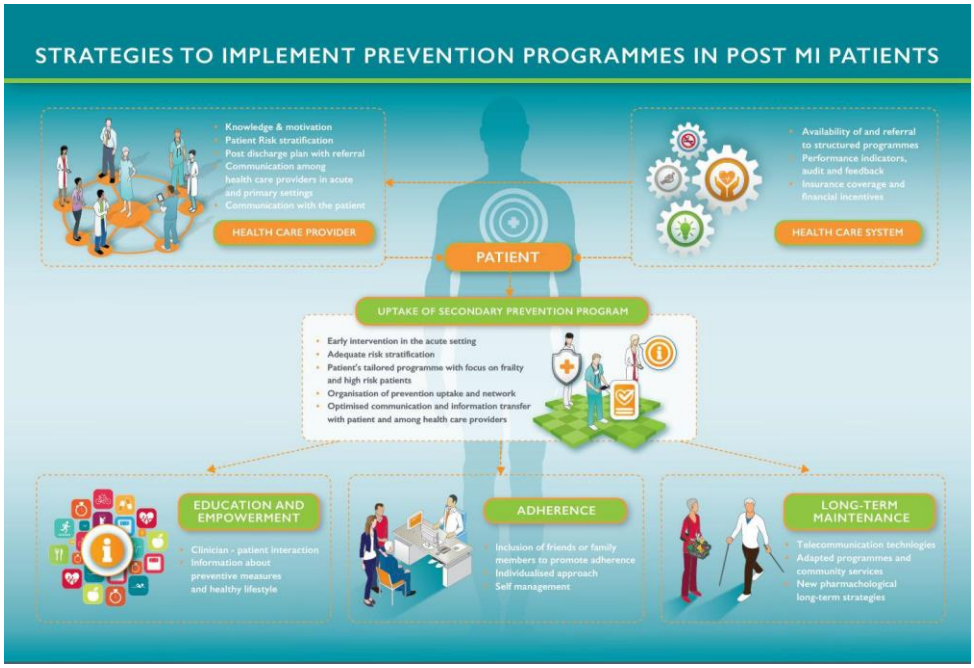

Figure 1. Strategies to address the lack of referral and improve enrolment in cardiovascular secondary prevention programme

3.3.3 Performance indicators

The lack of benefit from some interventions (e.g. RAMIT trial) [54] highlights the need for quality and minimum standard in the delivery of preventive programmes. Audit and control of the programmes should include information about the core components and their implementation, results with clinical outcomes and patient satisfaction. Benchmarking against local, regional and national standards provides measures of performance and quality for commissioners and services providers. [15] Accountability measures, including referral performance/quality indicators (e.g.: % of cardiac patients referred to programmes) and financial incentives for centres performing well on the quality indicators should increase physicians' willingness to refer and improve the delivery of prevention. Furthermore the appropriate prescription of evidenced based medications (e.g. lipid lowering drugs, antiplatelet) the titration of the vasodilators, such as angiotensin converting enzyme inhibitors or angiotensin receptor, blockers beta-blockers are well recognised performance indicators. [15] Table 5 enumerates some examples of interventions on patient, provider and system level.

Table 5. Examples of CV preventive intervention on patient, provider and system level (adapted from Nieuwlaat R. et al.[47])

Example of intervention	Description	Effect
Patient-level interventions		
Patient decision aids	Tools that help people become involved in decision-making by providing information about	- 60% increase in accuracy of patient's risk perception,

	the options and outcomes of a treatment, and clarifying personal values	- 30% reduction in post-menopausal hormone use, -20% reduction in discretionary surgery
Self-management	Patients monitoring themselves, and making medication dosing decisions, with health-care provider back-up	-49% reduction in thrombotic events in self-management of vitamin K antagonist: -56% reduction in heart failure hospitalizations in self-management of heart failure
Provider-level interventions		
Continuing education meetings	Conferences, lectures, workshops, seminars, symposia, and courses for health professionals	-6–10% increase in uptake of recommended care
Audit and feedback	Any summary of clinical performance over a specified period of time, given in a written, electronic or verbal format	-5–16% increase in the uptake of recommended diagnostic and therapeutic strategies
Educational outreach visits	Visits by a trained person to health professionals. 'Face-to-face' visits, also referred to as academic detailing	-5.6–21% increase in uptake of recommended care
Local opinion leaders	Health-care professionals considered by colleagues as 'educationally influential'	-12% increase in uptake of recommended care
Computer-assisted clinical decision support	Automated clinical decision advice, based on individual patient data	Modest effects on process of care for a range of management issues
Organizational/system-level interventions		
Clinical pathways	Structured multidisciplinary care plans used by health services to detail essential steps in the care of patients with a specific clinical problem	-42% reduction of in-hospital complications for patients undergoing an intervention, primarily surgery -12% improvement of documentation in medical records
Financial incentives	Financial reward for professionals for affecting behaviour, including for a specified time period of work, for each service, episode or visit, for a patient or specific	Potential improvement in practice, but effects on patient outcomes are unknown

	population, for providing a pre-specified level or providing a change in activity or quality of care	
Legislation-based smoking bans	Legislative smoking bans and restrictions affecting populations	Reduction in admissions for acute coronary syndromes, related to improvements in first-hand and second-hand smoking exposure

4. The Way Ahead - Embracing current challenges

4.1 In-hospital or acute intervention

This represents the earliest intervention, beginning immediately after the acute event during the hospital stay, and it should be given as high a priority as initial acute care. Acknowledging the formally shared responsibilities of all professionals involved in the cardiac patients care (i.e. nurses, general practitioners, intensivists, acute invasive cardiologists and cardiovascular surgeons) provides the first avenue. However, convincing all acute care clinicians remains challenging and is related to both the individual professional and the healthcare organization. [55] Poor knowledge regarding the benefits of early initiation of secondary prevention could be a possible explanation. This underscores the need to increase awareness and to provide information regarding the available evidence. As a collaborative initiative, the EACPR, ACCA and CCNAP elaborated videos on the benefits and challenges of secondary prevention after AMI [http://escardio.org/The-ESC/Communities/European-Association-for-Cardiovascular-Prevention-&-Rehabilitation-%28EACPR%29/European-Association-for-Cardiovascular-Prevention-Rehabilitation].

4.2 Early outpatient prevention programmes. Core delivery rehabilitation

As mentioned above, patient uptake and adherence proves to be particularly challenging and innovative strategies are urgently needed to address this problem. There are clearly some programmes that do better than others, at engaging patients in prevention, which creates a further opportunity to learn from others in regional or clinical networks.

4.2.1 Telecommunication technologies

Recent developments in telecommunication have enabled the advent of new preventive delivery strategies, supplementing conventional centre-based services to expand its capabilities and to address the broad and extensive range of barriers preventing cardiac patients from participating. As such, cardiac telemedicine was introduced, i.e. a comprehensive mHealth mode of care delivery, as a personalized prevention tool for cardiac patients to manage their own recovery and to prevent recurrent events remotely. [56] The optimal programme consists of several modules devoted to monitoring, coaching, e-learning, social interaction, and two-way communication with the caregiver. [57]

4.2.2 Adapted preventive programmes and community services

Adapted preventive cardiology programmes, such as nurse-coordinated and family-based care, can be valuable alternatives to traditional inpatient and/or outpatient programmes. [20] Professionals in primary care are essential for this task as they often have detailed knowledge of an individual's social, medical and/or cultural background. This applies especially for the disadvantaged groups (poor, less educated, and older people), who are most likely to drop out.

4.2.3 New models of Individualised interventions

Efforts are waged to individualise programmes based on patient stratification to maximize clinical benefit and optimize safety. This can be achieved by prescribing patient-specific and tailored programmes, based on differing combinations of CV risk factors, underlying cardiac disease processes and/or exercise modifiers. Currently, the EXPERT (EXercise Prescription in Everyday practice & Rehabilitative Training) flowchart project, combining the collaborative work and knowledge of >35 experts (out of 11 European countries) in rehabilitation of chronic internal diseases is being elaborated. It aims to aid future physicians in defining such individualized training programmes, based on the existing guidelines and position papers for different patient populations. [58]

4.2.4 Focus on the identification of frailty syndrome post-AMI and high-risk patients

Patients with frailty syndrome, ie. older than 65 years, characterized by vulnerability to stress-related factors and a decrease in physiological reserves, [59] suffer more often from AMI (15.4% vs. 7.4%), with increased mortality and hospitalization risk after the index cardiac event. [60] Future efforts need to focus on improved frailty identification, and to adapt/intensify prevention programme, by adjusting medical therapies, modifying dosages and rehabilitative protocols. Several prognostic scores were developed to specifically identify the post-AMI patients, being at highest risk for future adverse events (the Global Registry of Acute Coronary Events (GRACE) score and ACHTUNG-Rule). [61]

4.3 Long term prevention

4.3.1. Long term adherence to healthy lifestyles and medications

It constitutes a joint lifelong effort of patient, primary care physician, nurse, therapist and cardiologist. In this era of an ever increasing CVD epidemic, most current cardiac centres do not have the capacity to deliver long-term supervised and centre-based prevention to all eligible patients. One model might be to transfer resources from short-duration residential services to longer-duration outpatient services of lesser intensity, designed for lower-risk patients, but of larger number. A successful example already implemented in routine clinical practice for low-risk patients is the EUROACTION model: all aspects of a healthy lifestyle, comprehensive risk factor management and appropriate use of cardio-protective drugs are addressed, without the use of specialised hospital or community facilities. [20] In other countries, such as Italy, sport-medicine specialists, operating in selected community-based, Sport Medicine Centres, in collaboration with specially trained physiotherapists have developed dedicated programmes for exercise based rehabilitation, follow-up and care in low risk patients. Home-based programmes can be equally effective as centre-based [62] and tele-interventions to be efficacious in both medium- and long-term, encouraging large-scale deployment of innovative models of care delivery. [63] Finally fixed dose combination tablet (also called polypill) showed to improve adherence compared to separate medications.

[64] However potential adverse effects of a single drug component cannot be specifically corrected and therefore may also affect the treatment adherence to the other components.

4.3.2. Pharmacologic strategies to strengthen long-term secondary prevention

Recent progresses in drug strategies have widened the possibility in CVD prevention. Three issues in particular are here considered: i. enhanced lipid-lowering therapy in addition to statins, according to the evidences of the efficacy of monoclonal antibodies targeted to proprotein convertase subtilisin/kexin type 9 (PCSK9) [65] and of the ezetimibe added therapy, [66] ii. enhanced antithrombotic therapy where new options have been demonstrated to be particularly effective in further reducing coronary events, such as prolonged up to 30 months (in contrast to recommended 12 months) after acute coronary events) dual antiplatelet therapy (DAPT), [67] and in particular the combination of aspirin and ticagrelor, [68] and the addition of new anticoagulants, such as rivaroxaban, to DAPT, [69] iii. enhanced blood pressure control to improve outcome, as shown by new strategies involving spironolactone add-on therapy in resistant hypertension, [70] amiloride plus hydrochlorothiazide in patients requiring a diuretic [71] and finally by a research protocol where a lower blood pressure target of 120 mmHg in patients at high cardiovascular risk was associated with higher survival. [72]

These advances open new possibilities in long-term secondary prevention after AMI. However, the cost is high, from both a clinical perspective (potential serious side-effects) and from an economic perspective, to make it unlikely that these pharmacologic strategies will be widely-indicated for reducing residual risk in the near future. For this reason, identification of the highest-risk patients is pertinent, that is, those who are most likely to benefit from very intense preventive therapy.

4.4 Moving forward and improving care delivery

4.4.1 The role of the government

National legislation regarding preventive programs is absent in 54 % of the participating countries to the European Cardiac Rehabilitation Inventory Survey (ECRIS). [17] Legislation provides an imperative to make available and to optimize services and needs to be extended to all countries if citizens of Europe are to be treated equitably. The national societies of cardiology are therefore encouraged to lobby their respective governments to promote this. The role of the ESC in relation to advocacy at a European level, is crucial for setting standards and for promoting good practices amongst its members.

4.4.2 The role of health insurance industry

As noted by ECRIS, in 46% of European countries, patients covered the total cost for the long term intervention, while in 18% countries, patients received a small financial support from patient clubs, private health insurance companies. Given the highly proven clinical benefits of long-term persistence of healthy lifestyle in secondary prevention, efforts to convince the health insurance industry to support long-term prevention programmes are justified. Higher reimbursement to systems that provide high-value evidence-based care and incentives for individuals with persistent adherence to healthy lifestyle changes should be encouraged.

4.4.3 The role of professional organizations

Numerous professional National and European-wide organizations such as the ESC, EACPR, ACCA and CCNAP are committed to the different facets of secondary prevention after a AMI. They have an important cross-fertilizing role in sharing expertise and in supporting colleagues to develop better services. By collaborative efforts in establishing professional guidelines, cutting-edge scientific research and implementing initiatives that encourage good clinical practice, they play a pivotal role in assuring the flourishing of secondary prevention. As an example, the EACPR, the ESC and the HFA of the ESC support the Preventive Cardiology, Sports Cardiology & Exercise based Rehabilitation – From Set-up to New Frontiers course (Bern, 2015). This course enabled secondary prevention experts to accelerate their knowledge sharing with colleagues in the field.

4.5 Need for further research

Future research should focus on cost-effectiveness evaluations of novel care delivery strategies, to inform policy makers how limited health care resources should be allocated. Each nation and European partners should look to audit their own services against clinical minimum standards in delivery and outcomes. The development of action plans by the different individual stakeholders to move forward and improve care delivery is urgently needed.

References

[1] White HD, Chew DP; Chew (August 2008). "Acute myocardial infarction". Lancet 372 (9638): 570–84. doi:10.1016/S0140-6736(08)61237-4. PMID 18707987.

[2] Smolina K, Wright FL, Rayner M, et al. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ. 2012 Jan 25;344:d8059. doi:10.1136/bmj.d8059.

[3] Pedersen F, Butrymovich V, Kelbaek H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol 2014; 64(20):2101-2108

[4] Velders MA, James SK, Libungan B, et al. Prognosis of elderly patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention in 2001 to 2011: A report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry. Am Heart J 2014; 167(5):666-673

[5] Jernberg T, Hasvold P, Henriksson M, 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 May 14;36(19):1163-70. doi: 10.1093/eurheartj/ehu505. Epub 2015 Jan 13.

[6] Kontis V, Mathers CD, Bonita R, et al. Regional contributions of six preventable risk factors to achieving the 25 × 25 non-communicable disease mortality reduction target: a modelling study. Lancet Glob Health. 2015 Oct 20. pii: S2214-109X(15)00179-5. doi: 10.1016/S2214-109X(15)00179-5.

[7] Wilson K, Gibson N, Willan A, et al. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000; 160(7):939-944.

[8] Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013 Apr 4;368(14):1279-90. doi: 10.1056/NEJMoa1200303. Epub 2013 Feb 25

[9] Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

[10] Chow CK, Jolly S, Rao-Melacini P, et al. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation. 2010 Feb 16;121(6):750-8

[11] Kotseva K, Wood D, De Bacquer D, et al; on behalf of the EUROASPIRE Investigators. 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. 2015 Feb 16. pii: 204748731556940

[12] Urbinati S, Olivari Z, Gonzini L, et al; for the BLITZ-4 Investigators. Secondary prevention after acute myocardial infarction: Drug adherence, treatment goals, and predictors of health lifestyle habits. The BLITZ-4 Registry. Eur J Prev Cardiol. 2014 Dec 1. pii: 2047487314561876.

[13] Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33(13): 1635–701.

[14] Piepoli MF, Corrà U, Benzer W, et al; Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation 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 Feb;17(1):1-17.

[15] Piepoli MF, Corra` U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery. A Policy Statement from the Cardiac Rehabilitation Section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol. 2012;21(6):664-81.

[16] Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. BMJ. 2015 Sep 29;35.

[17] Bjarnason-Wehrens B, McGee H, Zwisler AD, et al; Cardiac Rehabilitation Section European Association of Cardiovascular Prevention and Rehabilitation. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. Eur J Cardiovasc Prev Rehabil. 2010 Aug;17(4):410-8. doi: 10.1097/HJR.0b013e328334f42d.

[18] Voller H, Reibis R, Schwaab B, et al . The ESC Textbook of Preventive Cardiology, Part 4. Setting and delivery of preventive cardiology. Hospital-based rehabilitation units. Ed Oxford University Press 2015. 285-293.

[19] Connolly S, Cupples M. The ESC Textbook of Preventive Cardiology, Part 4. Setting and delivery of preventive cardiology. Community-based prevention centres. Ed Oxford University Press 2015. 312-319.

[20] Wood DA, Kotseva K, Connolly S, et al; on behalf of the EUROACTION Study Group. EUROACTION: a European Society of Cardiology demonstration project in preventive cardiology. A paired cluster randomised controlled trial of a multi-disciplinary family based preventive cardiology programme for coronary patients and asymptomatic high risk individuals. Lancet 2008; 371: 1999–2012.

[21] Giannuzzi P, Temporelli PL, Marchioli R, 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: 2194–204.

[22] Fidan D1, Unal B, Critchley J, et al. Economic analysis of treatments reducing coronary heart disease mortality in England and Wales, 2000-2010. QJM. 2007 May;100(5):277-89.

[23]Oldridge NB, Pakosh MT, Thomas RJ. Cardiac rehabilitation in low- and middle-income countries: a review on cost and cost-effectiveness. Int Health. 2015 Jul 24.

[24] Brown T, Hernandez A, Bittner V, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients. J Am College Cardiol 2009; 54: 515-521.

[25] Karmali KN, Davies P, Taylor F, et al.; Cochrane Database Syst Rev. 2014 Jun 25;6:CD007131. doi: 10.1002/14651858.CD007131.pub3. Promoting patient uptake and adherence in cardiac rehabilitation).

[26] Clark A, King-Shier K, Duncan A, et al. Factors influencing referral to cardiac rehabilitation and secondary prevention programs: a systematic review. Eur J Prev Cardiol 2012; 20: 692-700.

[27] McCorry NK, Corrigan M, Tully MA, et al. Perceptions of Exercise among People who have not Attended Cardiac Rehabilitation following Myocardial Infarction. J of Health Psychology 2009;14:924-32

[28] Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. Ann Intern Med. 2009;150:178-187

[29] Piepoli MF, Corrà U, Abreu A, et al. Cardiac Rehabilitation Section of the European Association for Cardiovascular Prevention & Rehabilitation of the ESC. Challenges in secondary prevention of cardiovascular diseases: a review of the current practice. Int J Cardiol. 2015 Feb 1;180:114-9. doi: 10.1016/j.ijcard.2014.11.107.

[30] Cole JA, Smith SM, Hart N, et al. Do practitioners and friends support patients with coronary heart disease in lifestyle change? a qualitative study. BMC Fam Pract 2013;14:126

[31] Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. The American journal of medicine. 2012;125(9):882-7

[32] Corrao G, Conti V, Merlino L, et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther 2010;32(2):300–310

[33] Aubert RE, Yao J, Xia F, et al. Is there a relationship between early statin compliance and a reduction in healthcare utilization? Am J Manag Care 2010;16(6):459–466

[34] Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;11:CD000011

[35] NICE. National Institute for Health and Care Excellence. Medicine optimisation: the safe and effective use of medicines to enable the best possible outcomes. 4 March 2015. www.nice.org.uk/guidance/ng5

[36] Adherence to long-term therapies, Evidence for action. World Health Organisation. Geneva, 2003. www. http://who.int/chp/knowledge/publications/adherence_full_report.pdf

[37] NICE. National Institute for Health and Care Excellence. Myocardial infarction: cardiac rehabilitation and prevention of further MI. Clinical guideline. 13 November 2013. www.nice.org.uk/guidance/cg172

[38] Thierry C. Gillebert; Nicholas Brooks, Ricardo Fontes-Carvalho, et al: ESC Core Curriculum for the General Cardiologist (College of Medical Quality. 2009;24:344-346

[45] Wachter RM, Goldman L. The hospitalist movement 5 years later. JAMA. 2002;287:487-494

[46] Coleman EA, Min SJ, Chomiak A, et al. Posthospital care transitions: patterns, complications, and risk identification. Health Serv Res. 2004;39:1449-1465

[47] Nieuwlaat R. et al., Why are we failing to implement effective therapies in cardiovascular disease? European Heart Journal (2013) 34, 1262–1269.

[48] Cupples ME, McKnight A. A five year follow-up study of patients at high cardiovascular risk who took part in a randomised controlled trial of health promotion. BMJ 1999; 319: 687-8.)

[49] http://www.hscic.gov.uk/qof.

[50] Piepoli MF, Binno S, Coet al Seferovic P, Conraads V, Jaarsma T, Schmid JP, Filippatos G, Ponikowski PP; Committee on Exercise Physiology & Training of the Heart Failure Association of the ESC. ExtraHF survey: the first European survey on implementation of exercise training in heart failure patients. Eur J Heart Fail. 2015;17(6):631-8

2013); European Heart Journal (2013) 34, 2381–2411

[39] https://data.oecd.org/healthcare/length-of-hospital-stay.htm

[40] Taheri PA1, Butz DA, Greenfield LJ. Length of stay has minimal impact on the cost of hospital admission. J Am Coll Surg. 2000 Aug;191(2):123-30.

[41] Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, et al. Esc guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation. European heart journal. 2012;33:2569-2619

[42] Mercado MG, Smith DK, McConnon ML. Myocardial infarction: Management of the subacute period. American family physician. 2013;88:581-588

[43] Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalization: A randomized trial. Annals of internal medicine. 2009;150:178-187

[44] Clancy CM. Reengineering hospital discharge: A protocol to improve patient safety, reduce costs, and boost patient satisfaction. American journal of medical quality : the official journal of the American

[51] Hobbs FD, Jukema JW, Da Silva PM, et al. Barriers to cardiovascular disease risk scoring and primary prevention in Europe. QJM 2010;103:727–739

[52] Thomas R, Denna T. The role of cardiac rehabilitation following acute coronary syndromes. Curr Cardiol Rep 2014; 16: 534.

[53] Grace S, Russell K, Reid R, et al. Effect of cardiac rehabilitation referral strategies on utilization rates: a prospective, controlled study. Arch Intern Med 2011; 171: 235-241.

[54] West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. Heart. 2012 Apr;98(8):637-44.

[55] Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458–1465.

[56] Frederix I, Vanhees L, Dendale P, et al. A review of telerehabilitation for cardiac patients. J Telemed Telecare. 2015 Jan;21(1):45-53

[57] Frederix I, Hansen D, 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:e185.

[58] http://www.escardio.org/The-ESC/Communities/European-Association-for-Cardiovascular-Prevention-&-Rehabilitation-(EACPR)/News/The-EACPR-EXPERT-Flowchart-Project

[59] Myers V, Drory Y, Gerber Y. Clinical relevance of frailty trajectory post myocardial infarction. Eur J Prev Cardiol 2014; 21: 758-766.

[60] Uchmanowicz I, Lisiak M, Wontor R, et al. Frailty Syndrome in cardiovascular disease: Clinical significance and research tools. *Eur J Cardiovasc Nurs* 2015; 14: 303-309.

[61] Barra S, Providencia R, Paiva L, et al. ACHTUNG-Rule: a new and improved model for prognostic assessment in myocardial infarction. Eur Heart J Acute Cardiovasc Care 2012; 1: 320-336.

[62] Taylor R, Dalal H, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation (Review). Cochrane Database Syst Rev 2015; 18;8.

[63] Frederix I, Hansen D, et al. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization rate, medical costs and quality of life: A cost-effectiveness analysis. Eur J Prev Cardiol 2015; [Epub ahead of print].

[64] Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. J Am Coll Cardiol. 2014 Nov 18-25;64(20):2071-82..

[65] Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. BMC Cardiovasc Disord. 2014;14:121.

[66] Cannon CP, Blazing MA, Giugliano RP, et al, for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97. DOI: 10.1056/NEJMoa1410489

[67] Mauri L, Kereiakes DJ, Yeh RW, et al.; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371:2155–66.

[68] Bonaca MP, Bhatt DL, Cohen M, et al.; PEGASUS TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791–800.

[69] Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19.

[70] Williams B, MacDonald TM, Morant S, et al., for The British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015; 386: 2059–68.

[71] Brown MJ, Williams B, MacDonald TM, et al. Comparison of single and combination diuretics on glucose tolerance (PATHWAY-3): protocol for a randomized double-blind trial in patients with essential hypertension. BMJ Open 2015;5:e008086. doi:10.1136/bmjopen-2015-008086

[72] A randomized trial of intensive versus standard blood-pressure control. The SPRINT Research Group. N Engl J Med 2015;373:2103-16. DOI: 10.1056/NEJMoa1511939

Chapter 04

A review of telerehabilitation for cardiac patients.

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Summary

We conducted a literature review of telerehabilitation interventions on cardiac patients. We searched for studies evaluating some form of telerehabilitation in cardiac patients. A total of 116 publications were screened initially, of which 37 publications were eligible for further review. We assessed study strength, based on the level of evidence and the quality of the intervention. The majority of the articles (70%) had the highest level of evidence. Most interventions were of good (46%) or fair (51%) quality. Most studies evaluated the efficacy of the telerehabilitation interventions (84%), while 38% reported on feasibility and acceptance. Most studies did not include safety and/or cost-benefit analyses. Most telerehabilitation interventions (90%) employed only one or two core components of cardiac rehabilitation (CR). Of the CR core components, physical activity was most frequently evaluated. Telerehabilitation appears to be a feasible and effective additional and/or alternative form of rehabilitation, compared to conventional in-hospital CR. Evaluations of telerehabilitation programmes taking into account patient safety and health economics are now required.

Introduction

Cardiovascular disease (CVD) is the world's leading killer, which accounted for 30% of all deaths in 2010.[1] Secondary prevention of CVD by means of cardiac rehabilitation (CR) is recommended.[2] An holistic management strategy, including exercise training, is recommended in heart failure patients to improve functional capacity and symptoms.[3] CR comprises different core components such as physical activity, behavioural change, risk factor modification, nutritional counselling and psychosocial wellbeing.[4,5] The medical benefits of daily physical activity have been proven.[6] Unfortunately, despite the clinical effectiveness of hospital-based CR, the long-term clinical effectiveness of this intervention is often poor, due to the lack of attendance at rehabilitation sessions and non-adherence to recommendations.[7]

In Belgium, one-third of the patients do not follow any rehabilitation session after percutaneous coronary intervention or surgical procedure and more than half of the outpatients (55%) do not attend any rehabilitation session after hospital discharge.[8] A variety of factors contribute to these poor uptake rates. Patients regularly choose not to attend the rehabilitation sessions in the hospital due to a lack of transport, ill-health, time and scheduling commitments associated with returning to work or reimbursement problems. Hansen *et al*. concluded that only 27% of patients with coronary artery disease adhered to the recommended physical activity level of CR at 18 months follow-up. Conrads *et al*. concluded that heart failure patients, even when they were enrolled in a supervised exercise training or multidisciplinary CR programme, showed low adherence.[9] However non-compliance with lifestyle and risk factor recommendations in CR is associated with adverse outcomes. It is thus important to implement new strategies and interventions with the primary goal to motivate patients with heart disease to sustain a healthy lifestyle after completion of hospital-based CR.

Telerehabilitation may be an effective strategy to increase both attendance rates to CR sessions and long-term adherence to recommendations. In telerehabilitation, the patients are not restricted to the hospital environment for CR, and can implement the rehabilitation programme in their daily routine at home. Telerehabilitation can support or even partially replace conventional in-clinic rehabilitation. Although the first publications on simple forms of telerehabilitation date from the 1990s, general interest has only occurred recently, illustrated by the rapid increase in papers describing some form of telerehabilitation. However, these studies are very heterogeneous with respect to patient population, telerehabilitation intervention used, primary and secondary outcome measures. We have therefore conducted a literature review of telerehabilitation interventions on cardiac patients.

Methods

We searched the following databases: PubMed/Medline, Embase, Cochrane Library, EuroPubMed. Articles were selected when they reported some form of telerehabilitation in cardiac patients. To search for these articles different combinations of Medical Subject Headings (MeSH) terms relating to some component of telerehabilitation were used. MeSH terms such as telemedicine, telecoaching, telecare, telerehabilitation, telecardiology, telemonitoring, remote monitoring, cardiac rehabilitation, transtelephonic monitoring, internet-based rehabilitation, cardiac patient, heart disease, internet-based rehabilitation, telephone-based rehabilitation, motion sensor were used in the different databases. We also performed manual searching of relevant conference proceedings.

Initial selection of eligible manuscripts was based on the information in their abstracts. During the second step, relevant articles were obtained for thorough review. To be included in the review, publications needed to have a publication date of 1999 or later, they needed to be written in English and they had to evaluate some form of telerehabilitation in cardiac patients. Articles that described alternative forms of CR that did not include some form of telerehabilitation, that were only available in abstract form or that were duplicates of articles already selected for inclusion in the literature study, were excluded.

Two reviewers independently screened the abstracts. Studies selected by either or both reviewers were subject to full text assessment against the inclusion and exclusion criteria. In cases of disagreement, a third reviewer independently examined the full-text-reports.

Study strength

The study strength of the reviewed articles was based on a combination of the level of evidence and the quality of the intervention used in the study. The level of evidence was classified as:

1A when the article described a meta-analysis of multiple well-designed controlled studies,

1 for well-designed randomized controlled trials,

2 for well-designed non-randomized controlled trials (quasi-experiments),

3 for observational studies with controls (retrospective studies, interrupted time-series studies, case-control studies, cohort studies with controls),

4 for observational studies without controls (cohort studies without controls and case series).

The quality of the used intervention was classified as:

good, for clinically relevant well-described interventions making the intervention reproducible by external readers.

fair, for those interventions that did not qualify as good or poor

poor, for interventions with substantial limitations regarding relevance, rehabilitation method used and/or reproducibility.

The level of evidence of each study was classified as 1, 2, 3 or 4 (X), after collapsing the first two levels into a single category. The quality of the intervention was classified as good, fair, poor (Y). This resulted in X×Y (i.e. 12) study strength classifications.

Study patients

Three groups of cardiac patients were defined. The first group was coronary artery disease patients, who had suffered from an acute coronary syndrome for which a percutaneous coronary intervention or coronary artery bypass graft was performed. The second group was heart failure patients, with reduced or preserved ejection fraction. The third group were patients who had undergone surgery for valve replacement, for valve repair or for congenital heart disease.

Intervention

The concept of telerehabilitation is that the patient rehabilitates remotely from the hospital. Several different monitoring devices (e.g. accelerometers, pedometers) can be used. Information from the patient/sensor needs to be transmitted to the caregiver. We divided the

telerehabilitation interventions into four categories, based on the medium for data transfer from the patient to the caregiver and vice versa.

For the telephone-based interventions, transtelephonically guided CR was used. The Internet was the medium for data transfer in the Internet-based interventions. For the videoconferencing interventions, communication between patient and caregiver was delivered by videoconferencing. Finally combined telerehabilitation interventions used more than one of the aforementioned media for data transfer.

Outcome assessment

All eligible publications were assessed regarding four broad categories of outcome measures for the telerehabilitation intervention(s). The first outcome measure was feasibility and acceptance, based on the patient's satisfaction with the technology used and their compliance with the telerehabilitation intervention. The second outcome measure was the efficacy of the intervention, based on the different core components of CR. The third outcome measure was safety, based on on intervention-related adverse events and mortality. The fourth outcome measure was cost, the costs associated with conventional and telerehabilitation were included, and also the costs due to re-hospitalisations for both cardiovascular and non-cardiovascular adverse events.

In each article, we searched for significant results favouring or not favouring telerehabilitation. A positive study favoured telerehabilitation, a neutral study found no significant difference in the results between the groups anda negative study concluded in favour of the conventional intervention (i.e. the control group).

Two forest plots were created. The first assessed the effect of the interventions on adverse events and re-hospitalisations. Adverse events were defined as cardiovascular events prompting the patients to visit their general practitioner, the emergency department or their cardiologist and possibly leading to re-hospitalisation. Mortality due to cardiovascular events was defined as a serious adverse event and hence included in this calculation.

The second forest plot assessed the effect of the interventions on adherence to physical activity guidelines. In accordance with the guidelines for cardiovascular disease prevention,[10] a protocol of aerobic exercise training of moderate to vigorous intensity of 3-5 sessions/week, 30 min per session was recommended as secondary prevention for patients with a previous acute myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention or chronic heart failure. Physical activity data were extracted from the papers to calculate the number of patients adhering/not adhering to this recommendation. Based on these numbers, the Odds Ratios were calculated.

Cardiac rehabilitation core components

CR comprises different core components such as physical activity, behavioural change, risk factor modification, nutritional counselling and psychosocial wellbeing (Heart Related Quality of Life). CR includes a combination of these core components. However, physical activity is the most important core component of CR.[8] We assessed whether the studies reviewed evaluated only one, or a combination of several core components of CR in the telerehabilitation programme.

Focus areas

The main focus areas of a comprehensive telerehabilitation programme were defined as telemonitoring, e-learning, telecoaching and social networking. For each reviewed publication we evaluated whether the telerehabilitation intervention iincluded one or more of these main focus areas. Telemonitoring was defined as sensor data collection and analysis to obtain a precise and complete image of the patient. Telecoaching included techniques to motivate the patient. In studies including social networking, the patient had access to different social networks including one for peers and one that contained caregivers and cardiologists. E-learning meant that the evaluated tele-intervention taught patients using medically and scientifically sound questionnaires/challenges and interactive didactic material, with the aim of enabling the patients to gain a better understanding of the aetiology, pathophysiology and clinical presentation of their condition and ways of preventing recurrences and deteriorations.

Results

The initial screening produced a total of 116 publications (Figure 1). One article was only available in German, one publication was a duplicate, one publication was not available in full-text and 76 publications evaluated some form of CR but did not include telerehabilitation. Most of the 37 publications for final review assessed telephone-based telerehabilitation interventions (65%).

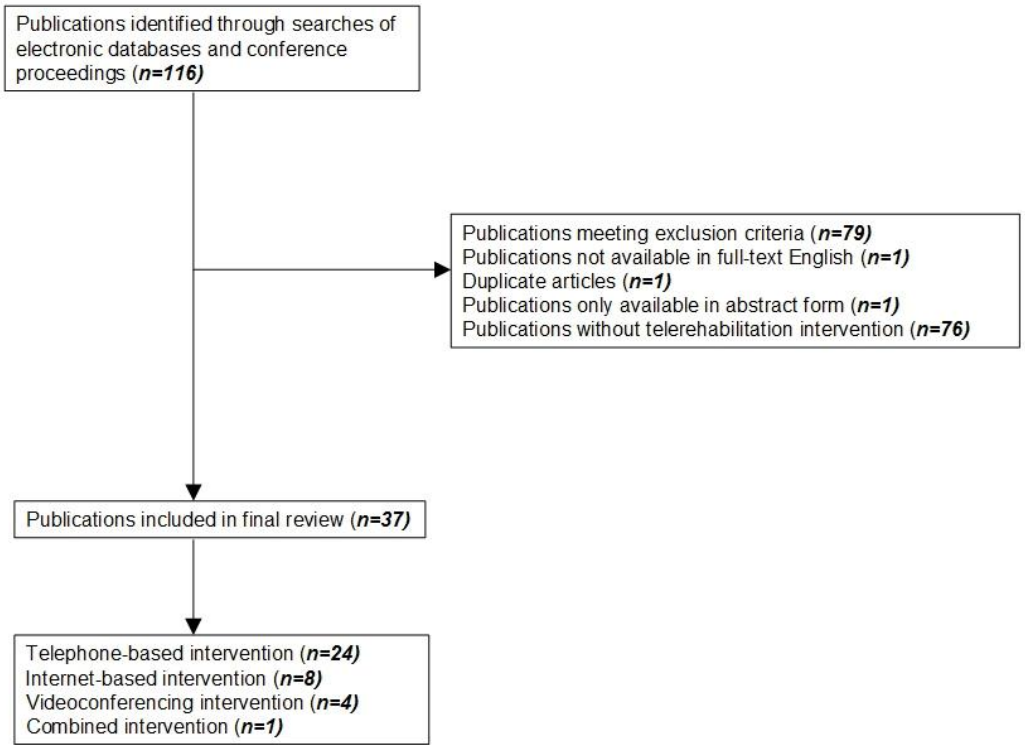

Figure 1. Study flowchart

Study strength

The majority of the articles (70%) had the highest level of evidence, although seven of them (19%) had the lowest level of evidence (Table 1). The quality of the intervention was good or fair (97%) in all studies, except one. There were more studies at the highest level of evidence which had a fair intervention quality than in the other subgroups.

Table 1. Strength of the studies reviewed (n=37).

		Level of evidence				
		1	2	3	4	Total
Quality of intervention	Good	7	2	1	7	17
	Fair	18	1	0	0	19
	Poor	1	0	0	0	1
	Total	26	3	1	7	

Outcomes

Most studies evaluated the efficacy of the telerehabilitation interventions (84%), while 38% reported on feasibility and acceptance. Most studies did not include safety and/or cost-benefit analyses (Table 2). In all four outcome categories, most articles concluded in favour of telerehabilitation compared to conventional rehabilitation. Only one article concluded that telephone coaching for acute coronary syndrome patients post-hospitalization could not accomplish long-term life-style behaviour change.[27]

Table 2. Outcome measures. A positive study favoured telerehabilitation, a neutral study found no significant difference between the groups and a negative study concluded in favour of the conventional intervention (i.e. the control group)

	Feasibility and acceptance	Efficacy	Safety	Cost-effectiveness
Negative study	0	1	0	0
Neutral study	0	8	0	0
Positive study	14	22	3	4
Outcome not described	23	6	34	33

Pooling the available studies in forest plots (Figures 2 and 3) showed that tele-interventions were favoured regarding the risk for adverse events and re-hospitalisations for cardiovascular reasons, and adherence to physical activity guidelines.

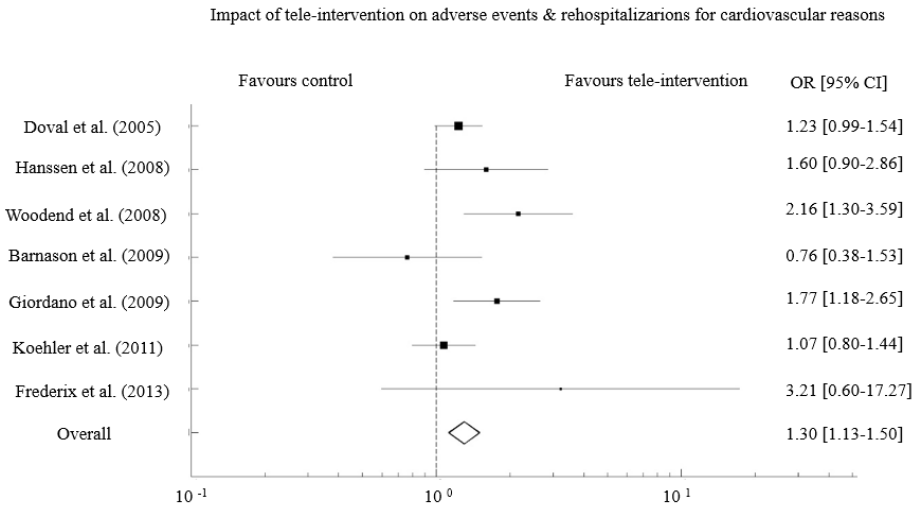

Figure 2. Forest plot depicting the effect of the interventions on adverse events and re-hospitalisations for cardiovascular reasons. An OR > 1 favours the tele-intervention. It means that fewer adverse events and cardiovascular hospitalisations were associated with the tele-intervention. OR: Odds Ratio, CI: Confidence Interval

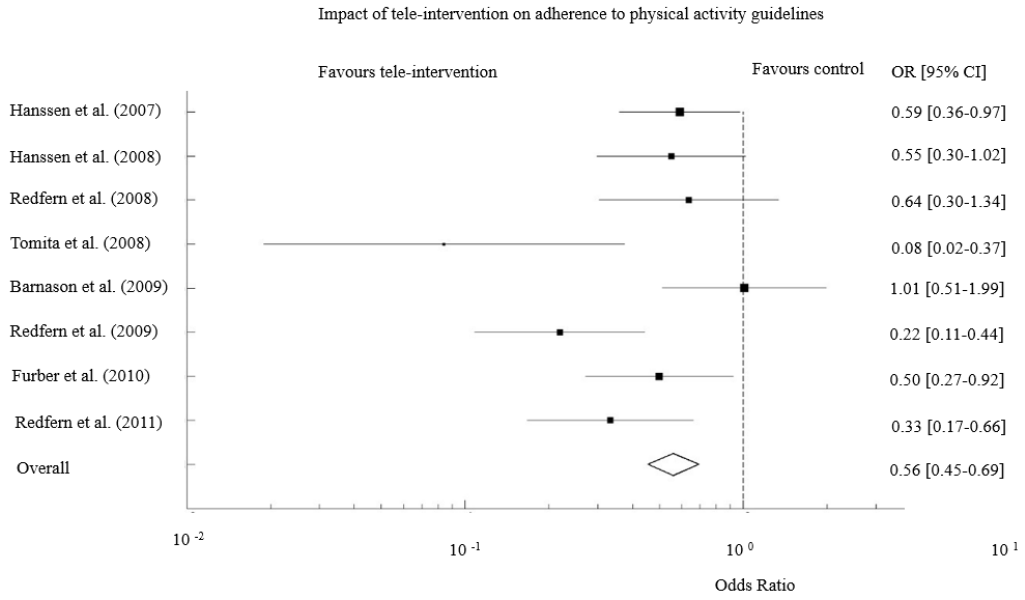

Figure 3. Forest plot depicting the effect of the interventions on adherence to physical activity guidelines. An OR < 1 favours the tele-intervention. It means that there was an improved adherence to physical acitivity guidelines, associated with the tele-intervention. OR: Odds Ratio, CI: Confidence Interval

Cardiac rehabilitation core components

Most telerehabilitation interventions (90%) employed only one or two core components of CR (Figure 4). None of the published trials included all core components in the telerehabilitation intervention. Of the CR core components, physical activity was most frequently evaluated.

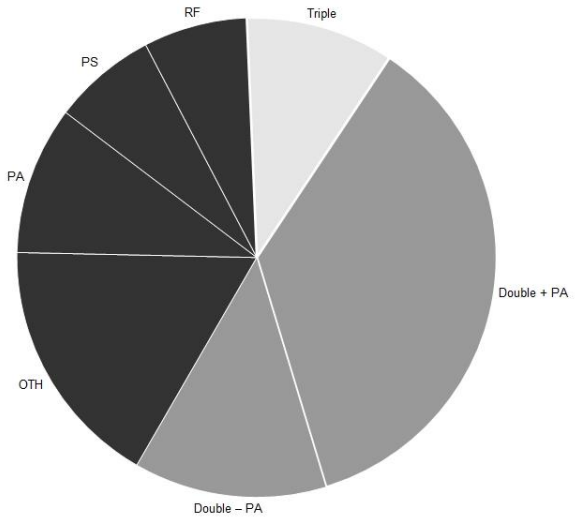

Figure 4. Studies that evaluated one, two or three core components of CR. The darkest grey represents the studies reporting on a single core component (PA: physical activity, RF: risk factor modification, PS: psychosocial wellbeing, OTH: other). The intermediate grey represents the studies reporting on two core components (Double+PA: studies reporting on two core components, with PA including one of them, Double-PA: studies reporting on two core components, without PA). The lightest grey represents studies reporting on three core components

Focus areas

Most studies focused on telemonitoring or telecoaching. Only 16% of publications had a combined focus and only 5% focused on more than two focus areas (Figure 5).

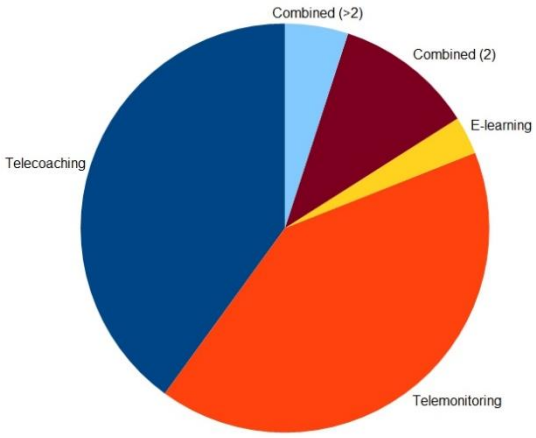

Figure 5. Focus areas in comprehensive rehabilitation programmes. Combined (2) means that two focus areas were included. Combined (>2) means that more than two focus areas were included in the rehabilitation programme.

Discussion

In the majority of the articles reviewed, the comparison of telerehabilitation with conventional hospital rehabilitation yielded positive results for telerehabilitation. However, most studies only reported feasibility, acceptance and/or efficacy. Studies of safety and cost-effectiveness were lacking. Since some ICT familiarity, patient education and interest were required for cardiac patients to be included in the Internet-based and videoconferencing telerehabilitation programmes, patient selection bias could have influenced results on feasibility and acceptance. Only 10% of the telerehabilitation trials assessed included a multi core component approach. Therefore the possible value of this method of remote rehabilitation may have been underestimated. Telemonitoring and telecoaching were the preferred focus areas of telerehabilitation, and the use of combined approaches was limited.

An analysis of study strength showed that more studies with lower level of evidence had a good intervention quality, compared to studies with the highest level of evidence. This somewhat contradictory finding was due to the higher level of evidence articles reporting relatively more on study results.

As with the introduction of a new drug, safety assessment of telerehabilitation is essential. In telerehabilitation, the patients rehabilitate at a distance from the hospital, in contrast to conventional rehabilitation where the patients rehabilitate near to their cardiologist. Thus the

safety of the intervention must be demonstrated. However, little has been published on this matter. Piotrowicz *et al*.[32] assessed the safety of a home-based CR programme in heart failure patients. Patients in the intervention group exercised at home, and sent ECG-recordings transtelephonically to their cardiologist at predefined moments (coordinated with the training sessions) or whenever they felt worrying symptoms. Piotrowicz *et al*. concluded that heart failure patients undergoing home-based telemonitored CR did not develop any arrhythmia which required a change of the procedure, providing evidence that the intervention was safe. Although this study included high-risk patients (such as those waiting for elective orthotopic heart transplantation or with an implantable cardioverter-defibrillator and a history of cardiac arrest), further research is required.

Kortke *et al*.[30] were one of the first groups to report cost-effectiveness in a non-randomized controlled trial assessing a transtelephonic guide for ambulatory rehabilitation in cardiac surgery patients. They concluded that their intervention could reduce total rehabilitation costs. We have reported that the addition of an Internet-based telerehabilitation programme to conventional CR can reduce the costs associated with re-hospitalisation for cardiovascular diseases, compared to conventional rehabilitation alone.[48] The calculated mean cost for patients in the intervention group was lower than for patients in the control group, although not significant (P=0.14). However thorough cost-effectiveness analyses comparing telerehabilitation with conventional CR are lacking. Because of the ageing population and the expected increase in elderly people suffering cardiac disease and needing chronic care and rehabilitation, and sometimes re-hospitalisation, insurance companies are very interested in the costs and potential savings of integrated telerehabilitation.

Although data are lacking on the possible added benefit of a multidisciplinary CR approach over physical activity alone,[8] CR should include a combination of the different core components. Most telerehabilitation interventions selected only physical activity and risk factor management. Further research on telerehabilitation that integrates all core components in one intervention thus seems highly desirable.

As well as monitoring and coaching, comprehensive programmes can encourage cardiac patients in their rehabilitation process using social networking and e-learning.[49] Peer pressure/support from social networks can motivate cardiac patients in their rehabilitation programme.[50] E-learning tools can provide patients with the best medical and scientific information, thereby improving the patient's knowledge about their condition and possibly leading to greater compliance with therapy.[51] Comprehensive telerehabilitation programmes including all these focus areas are sparse, but are likely to be necessary to achieve a significant effect on the patients' health condition.

Limitations

Some of the limitations of the present study were caused by the heterogeneity and lack of details provided in the articles analysed. Most studies were very heterogeneous regarding the study population, the intervention, study follow-up period and outcome measures, thereby making comparisons between studies difficult. Most telerehabilitation trials included only one specific cardiac patient subgroup (e.g. only heart failure patients, only coronary artery disease patients) limiting the generalizability of the results. Some trials were not transparent regarding the phase of rehabilitation. Since there are substantial differences between phase 2 (the subacute phase), phase 3 (the intensive outpatient CR phase) and phase 4 (the independent ongoing conditioning phase) of rehabilitation, this impeded the interpretation of study results. Finally, it was not always clearly stated whether the telerehabilitation intervention was a substitute for conventional CR, or an addition.

Conclusion

Based on the present review, telerehabilitation appears to be a feasible and effective additional and/or alternative form of rehabilitation, compared to conventional in-hospital CR. Multi-disciplinary evaluations of telerehabilitation programmes taking into account patient safety and health economics however are lacking. Most published articles studied telerehabilitation interventions focussing on only one or two CR core components, in only a single cardiac patient subgroup. Implementing physical activity, behavioural change, risk factor modification, nutritional counselling and psychosocial wellbeing in a telerehabilitation programme, and focusing on a broad cardiac patient population thus seems highly desirable. Telerehabilitation programmes might be further optimized by combining e-learning, social networking, telemonitoring and telecoaching.

References

[1] Economist Intelligence Unit. The heart of the matter: rethinking prevention of cardiovascular disease. Available from http://www.economistinsights.com/healthcare/analysis/heart-matter (last checked 10 August 2014)

[2]Massimo FP, Ugo C, Werner B, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery. *Eur J Prev Cardiol* 2012; 1: 1-18

[3] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. *Eur Heart J* 2012; 33: 1787-847

[4] Ting P, Saner H, Dafoe W. The lexicon of 'Cardiac Rehabilitation': is it time for an evolutionary new term? *Eur J Cardiovasc Prev Rehabil* 2010; 17: 251-3

[5] Griffo R, Ambrosetti M, Furgi G, et al. Standards and outcome measures in cardiovascular rehabilitation. Position paper GICR/IACPR. *Monaldi Arch Chest Dis* 2012; 78: 166-92 [Italian]

[6] Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013; 128: 873-934

[7] Janssen V, De Gucht V, van Exel H, et al. Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients. *Eur J Prev Cardiol* 2013; 20: 431-41

[8] Van Vlaenderen I, Worrall J, Raza S, et al. Cardiale revalidatie: klinische doeltreffendheid en gebruik in België. Available from https://kce.fgov.be/nl/publication/report/cardiale-revalidatie-klinische-doeltreffendheid-en-gebruik-in-belgi%C3%AB#.VCXTymd_vr4 (last checked 27 September 2014)

[9] Conraads VM, Deaton C, Piotrowicz E, et al. Adherence of heart failure patients to exercise: barriers and possible solutions: a position statement of the Study Group on Exercise Training in Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2012; 14: 451-8

[10] Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; 33: 1635-701

[11] Arthur HM, Smith KM, Kodis J, et al. A controlled trial of hospital versus home-based exercise in cardiac patients. *Med Sci Sports Exerc* 2002; 34: 1544-50

[12] Mittag O, China C, Hoberg E, et al. Outcomes of cardiac rehabilitation with versus without a follow-up intervention rendered by telephone (Luebeck follow-up trial): overall and gender-specific effects. *Int J Rehabil Res* 2006; 29: 295-302

[13] Barnason S, Zimmerman L, Nieveen J, et al. Influence of a symptom management telehealth intervention on older adults' early recovery outcomes after coronary artery bypass surgery. *Heart Lung* 2009; 38: 364-76

[14] Gallagher R, McKinley S, Dracup K. Effects of a telephone counseling intervention on psychosocial adjustment in women following a cardiac event. *Heart Lung* 2003; 32: 79-87

[15] Hanssen TA, Nordrehaug JE, Eide GE, et al. Improving outcomes after myocardial infarction: a randomized controlled trial evaluating effects of a telephone follow-up intervention. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 429-37

[16] Hanssen TA, Nordrehaug JE, Eide GE, et al. Does a telephone follow-up intervention for patients discharged with acute myocardial infarction have long-term effects on health-related quality of life? A randomised controlled trial. *J Clin Nurs* 2009; 18: 1334-45

[17] Redfern J, Briffa T, Ellis E, et al. Patient-centered modular secondary prevention following acute coronary syndrome: a randomized controlled trial. *J Cardiopulm Rehabil Prev* 2008; 28: 107-15

[18] Redfern J, Briffa T, Ellis E, et al. Choice of secondary prevention improves risk factors after acute coronary syndrome: 1-year follow-up of the CHOICE (Choice of Health Options In prevention of Cardiovascular Events) randomised controlled trial. *Heart* 2009; 95: 468-75

[19] Vale MJ, Jelinek MV, Best JD, et al. Coaching patients with coronary heart disease to achieve the target cholesterol: a method to bridge the gap between evidence-based medicine and the "real world" -- randomized controlled trial. *J Clin Epidemiol* 2002; 55: 245-52

[20] Jelinek M, Vale MJ, Liew D, et al. The COACH program produces sustained improvements in cardiovascular risk factors and adherence to recommended medications-two years follow-up. *Heart Lung Circ* 2009; 18: 388-92

[21] Neubeck L, Freedman SB, Briffa T, et al. Four-year follow-up of the Choice of Health Options In prevention of Cardiovascular Events randomized controlled trial. *Eur J Cardiovasc Prev Rehabil* 2011; 18: 278-86

[22] Fernandez RS, Davidson P, Griffiths R, et al. A pilot randomised controlled trial comparing a health-related lifestyle self-management intervention with standard cardiac rehabilitation following an acute cardiac event: Implications for a larger clinical trial. *Aust Crit Care* 2009; 22: 17-27

[23] Holmes-Rovner M, Stommel M, Corser WD, et al. Does outpatient telephone coaching add to hospital quality improvement following hospitalization for acute coronary syndrome? *J Gen Intern Med* 2008; 23: 1464-70

[24] GESICA Investigators. Randomised trial of telephone intervention in chronic heart failure: DIAL trial. *BMJ* 2005; 331: 425

[25] Southard BH, Southard DR, Nuckolls J. Clinical trial of an Internet-based case management system for secondary prevention of heart disease. *J Cardiopulm Rehabil* 2003; 23: 341-8

[26] Tomita MR, Tsai BM, Fisher NM, et al. Improving adherence to exercise in patients with heart failure through internet-based self-management. *J Am Geriatr Soc* 2008; 56: 1981-3

[27] Zutz A, Ignaszewski A, Bates J, et al. Utilization of the internet to deliver cardiac rehabilitation at a distance: a pilot study. *Telemed J E Health* 2007; 13: 323-30

[28] Dalleck LC, Schmidt LK, Lueker R. Cardiac rehabilitation outcomes in a conventional versus telemedicine-based programme. *J Telemed Telecare* 2011; 17: 217-21

[29] Whitten P, Mickus M. Home telecare for COPD/CHF patients: outcomes and perceptions. *J Telemed Telecare* 2007; 13: 69-73

[30] Woodend AK, Sherrard H, Fraser M, et al. Telehome monitoring in patients with cardiac disease who are at high risk of readmission. *Heart Lung* 2008; 37: 36-45

[31] de Lusignan S, Wells S, Johnson P, et al. Compliance and effectiveness of 1 year's home telemonitoring. The report of a pilot study of patients with chronic heart failure. *Eur J Heart Fail* 2001; 3: 723-30

[32] Clark RA, Tideman P, Tirimacco R, et al. A pilot study of the feasibility of an Internet-based electronic Outpatient Cardiac Rehabilitation (eOCR) program in rural primary care. *Heart Lung Circ* 2013; 22: 352-9

[33] Clark RA, Conway A, Poulsen V, et al. Alternative models of cardiac rehabilitation: a systematic review. *Eur J Prev Cardio*l 2013 [Epub ahead of print]

[34] Ades PA, Pashkow FJ, Fletcher G, et al. A controlled trial of cardiac rehabilitation in the home setting using electrocardiographic and voice transtelephonic monitoring. *Am Heart J* 2000; 139: 543-8

[35] Körtke H, Stromeyer H, Zittermann A, et al. New East-Westfalian postoperative therapy concept: a telemedicine guide for the study of ambulatory rehabilitation of patients after cardiac surgery. *Telemed J E Health* 2006; 12: 475-83

[36] Scalvini S, Zanelli E, Comini L, et al. Home-based exercise rehabilitation with telemedicine following cardiac surgery. *J Telemed Telecare* 2009; 15: 297-301

[37] Piotrowicz E, Jasionowska A, Banaszak-Bednarczyk M, et al. ECG telemonitoring during home-based cardiac rehabilitation in heart failure patients. *J Telemed Telecare* 2012; 18: 193-7

[38] Piotrowicz E, Baranowski R, Bilinska M, et al. A new model of home-based telemonitored cardiac rehabilitation in patients with heart failure: effectiveness, quality of life, and adherence. *Eur J Heart Fail* 2010; 12: 164-71

[39] Kouidi E, Farmakiotis A, Kouidis N, et al. Transtelephonic electrocardiographic monitoring of an outpatient cardiac rehabilitation programme. *Clin Rehabil* 2006; 20: 1100-4

[40] Furber S, Butler L, Phongsavan P, et al. Randomised controlled trial of a pedometer-based telephone intervention to increase physical activity among cardiac patients not attending cardiac rehabilitation. *Patient Educ Couns* 2010; 80: 212-8

[41] Roth A, Malov N, Steinberg DM, et al. Telemedicine for post-myocardial infarction patients: an observational study. *Telemed J E Health* 2009; 15: 24-30

[42] Koehler F, Winkler S, Schieber M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 2011; 123: 1873-80

[43] Giordano A, Scalvini S, Zanelli E, et al. Multicenter randomised trial on home-based telemanagement to prevent hospital readmission of patients with chronic heart failure. *Int J Cardiol* 2009; 131: 192-9

[44] Karagiannis GE, Stamatopoulos VG, Roussos G, et al. Health and lifestyle management via interactive TV in patients with severe chronic cardiovascular diseases. *J Telemed Telecare* 2006; 12 (Suppl. 1): 17-9

[45] Lieback A, Proff J, Wessel K, et al. Remote monitoring of heart failure patients using implantable cardiac pacing devices and external sensors: results of the Insight-HF study. *Clin Res Cardiol* 2012; 101: 101-7

[46] Varma N, Epstein AE, Irimpen A, et al. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Safely Reduces Routine Office Device Follow-up (TRUST) trial. *Circulation* 2010; 122: 325-32

[47] Raatikainen MJ, Uusimaa P, van Ginneken MM, et al. Remote monitoring of implantable cardioverter defibrillator patients: a safe, time-saving, and cost-effective means for follow-up. *Europace* 2008; 10: 1145-51

[48] Frederix I, Driessche NV, Hansen D, et al. Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients. *Eur J Prev Cardiol* 2013 [Epub ahead of print]

[49] MobiGuide. Guiding patients anytime everywhere. See http://www.mobiguide-project.eu/ (last checked 10 August 2014)

[50] Maitland J. Getting better together? Opportunities and limitations for technology-facilitated social support in cardiac rehabilitation. *Stud Health Technol Inform* 2011; 164: 251-5

[51] Vera-Munoz C, Arredondo MT, Ottaviano M, et al. HeartCycle: user interaction and patient education. *Conf Proc IEEE Eng Med Biol Soc* 2013; 2013: 6988-91

Chapter 05

Telerehab II:

Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients.

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Abstract

Background. The purpose of this study was to evaluate the effect of a physical activity telemonitoring program on daily physical activity level, oxygen uptake capacity (VO2peak), and cardiovascular risk profile in coronary artery disease (CAD) patients who completed phase II cardiac rehabilitation (CR).

Methods. Eighty CAD patients who completed phase II CR were randomly assigned to an additional physical activity telemonitoring intervention or standard CR. The patients in the intervention group (n=40) wore a motion sensor continuously for 18 weeks. Each week these patients received a step count goal, with the aim to gradually increase the patients' physical activity level. In the control group (n = 40), the patients wore an unreadable motion sensor for seven days for measurement purposes only (at start of follow-up, and after 6 and 18 weeks). At start of follow-up and after 18 weeks blood lipid profile, glycemic control, waist circumference and body mass index was assessed. VO2peak was assessed at start of follow-up, and after 6 and 18 weeks. Re-hospitalisation rate was followed during this timeframe.

Results. In the intervention group, the VO2peak increased significantly during follow-up (P=0.001), whereas in the control group it did not (P=0.273). A significant correlation was found between daily aerobic step count and improvement in VO2peak (P=0.030, r=0.47). Kaplan-Meier curve analysis showed a trend towards fewer re-hospitalisations for patients in the physical activity telemonitoring group (P=0.09).

Conclusions. The study showed that, to maintain exercise tolerance and lower rehospitalisation rate after hospital-based CR in CAD patients, a physical activity telemonitoring program might be an effective intervention.

Introduction

Secondary prevention of cardiovascular disease by means of cardiac rehabilitation (CR) is highly recommended (Class IB) by the European Society of Cardiology, the American Heart Association and the American College of Cardiology. [1] CR is comprised of different core components, of which exercise intervention is primordial to reduce morbidity and mortality after an acute coronary event. [2] Moreover, meta-analyses indicate that CR significantly lowers cardiac mortality, all-cause mortality and improves cardiovascular risk factors, including blood pressure, body weight and lipid profile. [3]

Unfortunately, despite the clinical effectiveness of hospital-based CR, long-term clinical effectiveness of this intervention is often poor. [4] It has been shown that the cardiovascular disease risk profile of coronary artery disease (CAD) patients progressively worsens after the in-clinic CR phase, due to non-adherence to the recommended volume of physical activity. [5] To further optimise the long-term clinical effectiveness of CR, and hereby reduce cardiovascular disease burden, it is thus important to implement strategies/interventions with the primary aim to sustain a healthy lifestyle in subjects with CAD after completion of hospital-based CR. It has already been shown that a reinforced, multifactorial educational and behavioural intervention with

multiple one-to-one support sessions (between the patient and a medical supervisor) is effective in decreasing the patient's cardiovascular risk profile up to three years after phase II CR. [6] However this strategy of follow-up requires significant input from the medical staff.

Thanks to technological innovations during the last decade, telerehabilitation can be an effective alternative to overcome the above-mentioned limitations. In telerehabilitation, the patient is monitored from a distance and receives regular feedback. The monitoring can be done using several different devices (motion sensor, blood pressure monitor, ECG-recordings, heart rate monitoring, etc.). The registered data are then transmitted to the medical staff by mobile phone or the internet.

Most of the previous papers' reporting experiences of telerehabilitation in the care of CAD patients have mainly focused on feasibility and acceptance issues. Only a few studies explored the (medium-term) clinical benefits of this intervention, indicating that CR is effective in secondary prevention of cardiovascular disease. For example, it has been shown that telemedicine provides an opportunity to monitor ECG-recordings and/or heart rate data. [7]

The purpose of this study was to evaluate the medium-term clinical effectiveness of a physical activity telemonitoring program (patients wearing a motion sensor with automated feedback by e-mail or SMS) on top of and after conventional phase II CR. It was hypothesised that the physical activity telemonitoring program would further improve the cardiac patient's physical fitness, quality of life, and cardiovascular risk factors.

Methods and materials

Patient population

All patients were recruited during their phase II CR between January 2011 and December 2012 in the Rehabilitation Centre of Jessa hospital, Hasselt, Belgium.

We included patients that suffered from an acute coronary syndrome for which a percutaneous coronary intervention or coronary artery bypass graft was performed. All patients had access to a computer with internet connection. On average 42 days elapsed from presentation with an acute coronary syndrome at the hospital, to the inclusion in the Telerehab II study.

Patients that (i) were more than 80 years old, (ii) had an implantable cardioverter defibrillator or pacemaker, (iii) suffered from severe arrhythmias, (iv) had persistent exertional ischaemia after revascularization therapy, were not invited to participate in this study. Patients with (v) severe heart failure (NYHA class III and IV), (vi) neurological or orthopaedic disability limiting their capability to exercise, were also excluded.

The study sample was based on an a priori study sample calculation. To attain a statistical power of 0.95 with a two-tailed alpha error probability <0.05, power calculations indicated that 80 patients needed to participate in this study, taking into account a change in oxygen uptake capacity (VO2peak) of 15% as result of intervention and a dropout rate of 20% during follow-up. Subjects were informed about the nature and risks of the experimental procedures before their written

informed consent was obtained. This study was approved by the local medical ethical committee of Jessa Hospital, Hasselt, Belgium (reference number: 10.68/cardio10.15).

Study protocol

The study was a prospective randomized controlled trial, including an 18-week intervention. All patients were included after week 6 of their conventional phase II CR. During phase II of conventional CR, all patients (those in the intervention and control group) were educated about the core components of CR including healthy nutrition, risk factor management (lipids, hypertension, weight, diabetes, and smoking), psychosocial management and physical activity counseling. During the first six weeks of the intervention, patients in the intervention group continued exercising in the hospital's rehabilitation centre using an out-patient service, in combination with an exercise training program with telemonitoring support. Patients in the control group continued exercising in the hospital's rehabilitation centre using an out-patient service, without participating in the exercise training program with telemonitoring support. Starting from the seventh week in the study period, patients in the intervention group finished their phase II CR in the hospital's rehabilitation centre but continued their exercise training program with telemonitoring support, patients in the control group finished their phase II CR in the hospital's rehabilitation centre. Randomization of patients took place at the sixth week of the patients' conventional phase II CR program in the hospital's rehabilitation centre, corresponding with the day of inclusion in the Telerehab II study. Randomization was done using blinded envelopes.

All patients underwent a maximal cardiopulmonary exercise test (CPET) and a clinical examination (with determination of waist circumference, blood pressure, body mass index) after randomization, and also during the sixth and 18th week of the Telerehab II study period. A fasting blood sampling was taken from all patients during the first and 18th week of the Telerehab II study period.

Cardiopulmonary exercise test

All subjects performed CPET's on a bicycle ergometer (Ergo 1500, Ergofit, Pirmasens, Germany). [8] The cycling target frequency was set at 70 cycles/min and the test ended when the patient failed to maintain a pedal frequency of at least 60 cycles/min. Exercise tests were prematurely ended when myocardial ischaemia and/or severe ventricular arrhythmias occurred. When the patient's respiratory gas exchange ratio (RER) exceeded 1.1, it was assumed that maximal exercise effort was achieved. [9] Pulmonary gas exchange analysis was performed with a calibrated cardiopulmonary ergospirometry device (Schiller CS200, Schiller AG, Switzerland). Heart rate was recorded continuously by a 12-lead electrocardiogram and averaged every 10 seconds. Oxygen consumption was measured continuously using breath-by-breath analysis. VO2peak was defined as the highest oxygen uptake level achieved during the final 30 seconds of the CPET.

Blood sample analysis

Subjects reported at the laboratory at 08.00-10.00 AM after an overnight fast. The blood levels of glycosylated hemoglobin (HbA1c) were measured with the Menarini type HA, 8160 device, fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were measured with the Beckman Coulter AU2700 or AU5811 device, and the HDLcholesterol/total cholesterol ratio was calculated.

Body mass index and waist circumference

Body mass was measured using a calibrated analogue weight scale (Tanita model TBF-300). Waist circumference was quantified at the level of noticeable waist narrowing located approximately half way between costal border and iliac crest.

Intervention

All subjects in the intervention group received a motion sensor (a triaxial accelerometer, which was manufactured by the Yorbody company) [10] at the start of follow-up. They wore the motion sensor all day long (also while exercising in the hospital's rehabilitation centre) during the whole study period of 18 weeks. They were only allowed to take the motion sensor off while asleep or bathing. All modalities of exercise training were allowed (walking, running, bicycle riding, etc.). The motion sensors registered activity data during all these exercise sessions. The patients were instructed to weekly upload their physical activity data on their personal computer by means of an USB-connection to their online patient account. Each patient received weekly personalised automated feedback on their physical activity by e-mail or SMS. The program was designed to encourage the patient to increase his/her daily amount of steps with 10% each week from baseline. Thereby the patients were encouraged to gradually increase their physical activity level to reach the recommended daily step count for the secondary prevention of cardiovascular disease of 6,500-8,500 steps/day. [11]

All patients in the control group wore a modified motion sensor for seven consecutive days during the first, sixth and 18th week of the Telerehab II study period. These motion sensors were modified to hide all information from the patient. They wore the modified motion sensor all day long (also while exercising in the hospital's rehabilitation centre) and were only allowed to take it off while asleep or bathing. All modalities of exercise training were allowed (walking, running, bicycle riding, etc.). The motion sensors registered activity data during all these exercise sessions. These patients did not upload their physical activity themselves, but they brought back their sensors to the hospital's rehabilitation centre each time after these seven consecutive days where the medical staff uploaded the physical activity data. Patients from the control group did not receive feedback about their physical activity and had no access to the recorded physical activity.

The motion sensor was able to register the daily number of aerobic steps, regular steps and total steps. Aerobic daily steps were defined as steps at ≥60 steps/minute during at least 10 minutes, without stopping for more than two minutes. The regular daily steps were defined as steps at <60

steps/minute. The number of total daily steps was calculated from the sum of the aerobic and regular steps.

Statistical analysis

SPSS software (v. 18.0) was used for the analysis. All data are expressed as means ± SD. The Shapiro-Wilk test confirmed that data were not normally distributed. For all data, non-parametric tests were used. The Mann-Whitney U-test was used to compare continuous parameters between groups and the Chi-Square test was used to compare the categorical data between groups. For the within group analysis, the Wilcoxon Signed Ranks test was used. Relations between parameters were analyzed by Spearman correlations. A Kaplan-Meier curve evaluated the re-hospitalisation rate between groups. Re-hospitalisations were examined over 125 days since the start of follow-up. All types of re-hospitalisations (for pathologies involving the cardiovascular system or not) were taken into account. Data from dropout patients were omitted. The frequency and reasons for drop-out were similar in both the intervention and the control group. Missing values for patients not considered to be dropout patients were imputated. A two-tailed probability level of $P<0.05$ was considered to be significant.

Results

Subjects

1247 patients were assessed for eligibility, of whom 80 patients were randomized in the study.

In the control group, six patients dropped out (15%) (fig. 1). In the intervention group eight patients dropped out (20%). The main causes for dropout were the development of a new pathology (thyroid gland disease, pneumonia, inguinal herniation…) and the loss of interest in the physical activity telemonitoring program. In the control group, 3 patients (50%) dropped out because of development of a new pathology and 3 patients (50%) because of the loss of interest in the physical activity telemonitoring program. In the intervention group the respective number of patients (percentages) were 5 patients (62.5 %) and 2 patients (25 %). 1 patient (12.5 %) dropped out because of ICT problems.

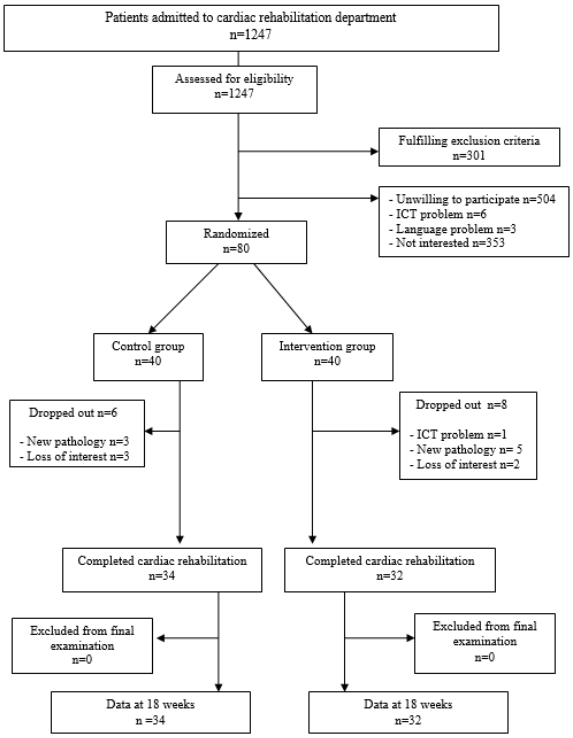

Figure 1. Patient flow in the study. ICT, information and communication technology.

Table 1 depicts the baseline characteristics of the randomized subjects. At baseline, significant differences for age and BMI between groups were found. However, these parameters did not correlate with changes of the outcome measures (P>0.10).

Table 1. Baseline characteristics of patients

	Control group	Intervention group	P-value
Demographic characteristics			
Male (%)	85	81	ns
Age (years), mean ± SD	63 ± 10	58 ± 9	0.033*
Length (meters), mean ± SD	1.73 ± 0.11	1.74 ± 0.07	ns
Weight (kg), mean ± SD	80.8 ± 2.6	88.7 ± 2.9	ns
BMI (kg/m2), mean ± SD	26.8 ± 3.6	29.1 ± 4.9	0.049*
Blood parameters			
Glucose (mg/dl), mean ± SD	109 ±18	103 ± 2	ns
HbA1c (%), mean ± SD	5.7 ± 0.6	5.6 ± 0.4	ns
Total cholesterol (mg/dl), mean ± SD	139.00 ± 31.61	129.29 ± 32.13	ns

LDL-cholesterol (mg/dl), mean ± SD	68.83 ± 22.31	65.89 ± 21.89	ns
HDL-cholesterol (mg/dl), mean ± SD	46.60 ± 16.54	42.14 ± 8.21	ns
Triglycerides (mg/dl), mean ± SD	122.00 ± 67.89	123.71 ± 63.44	ns
Exercise tolerance			
RERmax, mean ± SD	1.11 ± 0.10	1.14 ± 0.10	ns
HRmax (beats/minute), mean ± SD	122 ± 25	129 ± 19	ns
VO2 peak (ml/min), mean ± SD	1746 ± 109	2048 ± 124	ns
Cardiovascular risk factors			
Hypercholesterolemia (%)	85	94	ns
Hypertension (%)	38	63	ns
Smoking (%)	15	9	ns
Diabetes mellitus (%)	24	25	ns
Family predisposition (%)	50	71	ns
Medication			
Aspirin (%)	94	100	ns
Statin (%)	91	94	ns
b-blocker (%)	85	81	ns
ACE inhibitor or ARB (%)	56	66	ns
Indication			
CABG (%)	29	23	ns
PCI (%)	71	77	ns

HbA1C: glycosylated haemoglobin, LDL-cholesterol: low-density lipoprotein cholesterol, HDL-cholesterol: high-density lipoprotein cholesterol, RER: respiratory gas exchange ratio, HR: heart rate, VO_2: oxygen consumption, ACE inhibitor: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention. Data are presented as mean values ± SD., *P < 0.05.

Changes in blood parameters and exercise tolerance

In the intervention group blood HbA1c and HDL-cholesterol exhibited a significant change during follow-up (P<0.001). Also, in the intervention group, VO2peak increased significantly during follow-up (P=0.001), whereas in the control group it did not (P=0.273). Between group analysis yielded significant results (P=0.013) for VO2peak (Table 2).

Table 2. Changes in blood parameters and exercise tolerance during follow-up

	Start of follow-up		End of follow-up		Within group analysis		Between group analysis (P-value)
	Control subjects	Intervention subjects	Control subjects	Intervention subjects	Control group (P-value)	Intervention group (P-value)	
Biochemical characteristics							
Glucose (mg/dl)	108 ±16	102 ± 10	106 ± 14	104 ± 8	0.764	0.606	0.438
HbA1c (%)	5.8 ± 0.6	5.5 ± 0.3	5.8 ± 0.6	5.7 ± 0.4	0.208	<0.001***	0.063
Total cholesterol (mg/dl)	147.05 ± 32.71	136.25 ± 31.94	145.05 ± 28.24	141.90 ± 22.95	0.368	0.232	0.105
LDL-cholesterol (mg/dl)	75.70 ± 25.96	69.20 ± 20.47	73.20 ± 23.55	74.13 ± 17.83	0.514	0.099	0.065
HDL-cholesterol (mg/dl)	46.08 ± 15.77	42.15 ± 9.06	49.35 ± 12.07	46.85 ± 8.09	0.025*	<0.001***	0.270
Triglycerides (mg/dl)	123.25 ± 65.75	133.28 ± 66.86	118.23 ± 59.92	105.35 ± 36.93	0.393	0.015*	0.090
Ergospirometrical characteristics							
RERmax	1.11 ± 0.10	1.14 ± 0.09	1.16 ± 0.11	1.18 ± 0.07	0.004**	0.074	0.447
HRrest (beats/min)	72 ± 14	75 ± 13	74 ± 16	73 ± 11	0.773	0.608	0.563
HRmax (beats/min)	122 ± 24	130 ± 18	128 ± 19	140 ± 15	0.020*	0.001**	0.311
DBPrest (mmHg)	83 ± 15	84 ± 20	97 ± 24	89 ± 15	0.013*	0.244	0.465
DBPmax (mmHg)	113 ±	106 ±	109 ±	104 ±	0.943	0.819	0.910

	34	36	39	30			
SBPrest (mmHg)	129 ± 19	125 ± 20	128 ± 22	135 ± 24	0.926	0.257	0.357
SBPmax (mmHg)	174 ± 31	167 ± 28	168 ± 31	175 ± 41	0.699	0.404	0.182
RPPrest (mmHg*beats/min)	9288 ± 2219	9212 ± 1799	9516 ± 2918	9933 ± 1988	0.681	0.215	0.447
RPPmax (mmHg*beats/min)	21521 ± 7015	21625 ± 5431	21291 ± 4454	24852 ± 7001	0.538	0.023*	0.101
VO_2 peak (ml/min)	1748 ± 588	2110 ± 607	1791 ± 503	2360 ± 475	0.273	0.001**	0.013 *
VO_2 peak (ml/min/kg)	22 ± 6	24 ± 7	23 ± 6	28 ± 6	0.150	0.001**	0.006 **

HbA1C: glycosylated haemoglobin, LDL-cholesterol: low-density lipoprotein cholesterol, HDL-cholesterol: high-density lipoprotein cholesterol, RER: respiratory exchange ratio, HR: heart rate, DBP: diastolic blood pressure, SBP: systolic blood pressure, RPP: rate pressure product, VO2: oxygen consumption, Data are presented as mean values ± SD, *P < 0.05, **P < 0.01, ***P < 0.001.

Re-hospitalisation rate

After 125 days of follow-up, 4 patients (12,5 %) in the intervention group had been re-hospitalised, 2 of which had been re-hospitalised for cardiovascular reasons (angina). In the control group, 9 patients (26,5 %) had been re-hospitalised during the follow-up period. 6 of them were re-hospitalised for cardiovascular reasons: 1 patient because of adverse effects of cardiac medical therapy, 1 patient because of restenosis of cardiac stent, 1 patient because of a syncope and 3 patients because of angina. The Kaplan-Meier curve (fig. 2) showed a trend toward fewer re-hospitalisations in the intervention group, compared to the control group (P=0.09).

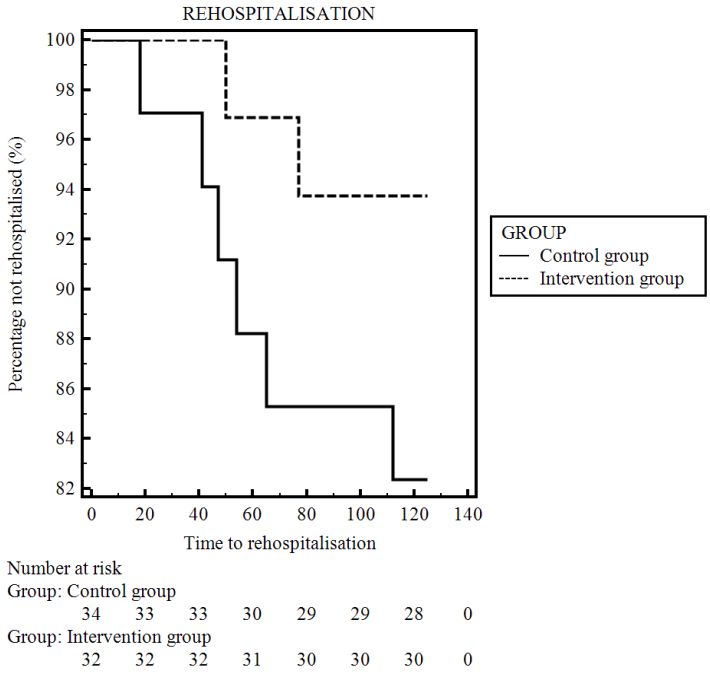

Figure 2. Kaplan-Meier curve depicting re-hospitalisation rate during follow-up.

Correlations

A significant correlation was found between the aerobic daily step count and the increase in VO2peak during follow-up (P=0.030, r=0.47), whereas no correlation was found between regular daily step count or total daily step count and increase in VO2peak during follow-up. A significant correlation was found between the magnitude of increase in blood HDL-cholesterol content and total daily step count (P=0.021, r=0.489) as well as regular daily step count (P=0.030, r=0.163). No correlation was found between the magnitude of increase in blood HDL-cholesterol content and aerobic step count (P=0.110, r= 0.350).

Discussion

The main finding in this study was that in CAD patients the implementation of a physical activity telemonitoring program during the last six weeks of hospital-based CR and twelve weeks after the hospital-based CR was more effective to increase the patient's physical fitness (peak oxygen uptake, VO2peak), when compared to conventional CR. The registered daily aerobic step count correlated significantly with the increase in physical fitness. Also, the subjects included in the telemonitoring intervention experienced a trend towards a lower re-hospitalisation rate.

The concept of telerehabilitation has been introduced only recently in CR settings. In telerehabilitation, the patient is monitored remotely and receives feedback based on recorded data. Numerous devices have been described in the literature that can be used for tele-monitoring such as a blood pressure monitor, motion sensor, and/or weight scale. In the present study, a 3D

accelerometer with remote reporting capabilities (motion sensor), combined with automated personalised feedback by means of e-mail or SMS, was used. A motion sensor was used because the study concentrated on physical activity levels and physical fitness. The 3D accelerometer principle was favoured over other pedometer principles, since collected data were more accurate [10] with this device. In this study the patients' physical activities were guided completely automatically by a system that weekly calculated the patients' new step goals based on the 10% incremental method, thereby reducing the needed input from medical professionals.

Most of the previous papers' reporting experiences of telerehabilitation programs, have mainly focused on feasibility and acceptance issues. [12-13] Only a few studies explored the effectiveness of this innovative intervention. [14] One study considered a home-based telemonitored CR using an ECG-recording device with automated data transfer to a monitoring centre. It showed that home-based telemonitored CR led to a significantly greater improvement in NYHA class, compared to the standard CR (P=0.0070) [15] in heart failure patients. Another trial [16] showed that a pedometer-based telerehabilitation intervention could increase the CAD patient's physical activity level after 6 months and 12 months of follow-up. Another pilot study including 15 CAD patients assessed the effectiveness of a virtual CR program, that used the internet to deliver CR at a distance. The virtual CR program consisted of online chat sessions with a nurse, dietician, and exercise specialist. After 12 weeks of follow-up, the virtual CR program group significantly increased their weekly physical activity and exercise specific self-efficacy (P<0.05). [17]

The most important finding of this study was that in the intervention group, the VO2peak increased significantly during follow-up (P=0.001), whereas in the control group it did not (P=0.273). The amount of the increase in VO2peak correlated with the number of daily aerobic steps. However, no significant correlations were found between total number of daily steps, or number of regular steps and amount of increase in VO2peak. Therefore it was concluded that physical activity at a certain intensity level is mandatory to improve physical fitness. These findings are important because VO2peak has been shown to be a powerful predictor of both non-fatal and fatal cardiac events among subjects with or without common cardiovascular risk factors. [18] Moreover, our findings indicate that in the promotion of physical activity after CR the volume of exercise might be important (x steps/week, or x min/week) but also the applied exercise intensity. It might be speculated that CAD patients should select exercise intensities in daily life which corresponds with those achieved during brisk walking.

In the Telerehab II study, the amount of increase in HDL-cholesterol correlated with total daily step count (P=0.021, r=0.489). Results from earlier research indicated a dose-response relationship between volume of physical activity and increase in blood HDL-cholesterol content. [19] From previous studies, and based on our data, it seemed that a sufficient amount of daily physical activity was mandatory to augment blood HDL-cholesterol content in CAD patients.

This trial found a trend toward fewer re-hospitalisations among subjects in the intervention group (P=0.09). Therefore, it might be speculated that a physical activity telemonitoring program has the potential to be a cost-effective alternative to conventional CR. This finding is consistent with an earlier published trial, making a cost-effectiveness analysis of internet-based CR among cardiovascular disease patients. This analysis found a trend toward fewer cardiovascular events

among the patients in the intervention group (P=0.053), resulting in a gross cost savings of $ 1418 per patient. [20]

Patient safety is an important issue, especially for those who rehabilitate at a distant site using telemonitoring. However, the benefits of physical activity surpass exercise-related risks and research indicates that home-based exercise programmes are safe and effective in appropriately selected patients. [21] Piotrowicz et al. [21] reported that none of the subjects perceived worrying signs or symptoms during telemonitored exercise sessions, nor was it necessary to stop rehabilitation urgently for any patient. In our study, the survival analysis by means of the Kaplan-Meier curve, showed a trend toward fewer re-hospitalisations in the intervention group, compared to the control group. Also, the time to rehospitalisation appeared to be longer in the intervention group. This further suggested that the performed tele-intervention was a safe alternative, compared with conventional CR.

Although the findings of the implemented physical activity telemonitoring program are promising, the ideal program using a cardiac patient training companion still needs to be developed. The cardiac patient training companion is a theoretical concept, defined as the ideal telemonitoring device specifically designed for the cardiac patient. It is able to record and store the patient's data accurately and to transfer these data automatically to a platform that is available for computerised care systems and to the patient's caregivers.

Limitations

We acknowledge that only 80 patients have been included in the Telerehab II study. CAD patients were included and heart failure patients were excluded from the study. This reduces the generalizability of the results towards the general heart patient population. Also, the limited number of participating patients resulted in not finding a significant difference in time to re-hospitalisation between the intervention and control group. Larger trials will be necessary in the future to confirm the hypothesis that the physical activity telemonitoring program reduces the number of re-hospitalisations. Also the duration of the intervention in this study was only 18 weeks. The intervention was comprised of an exercise training program with telemonitoring support. However, cardiac telerehabilitation includes other important core components (nutritional counseling, risk factor management, psychosocial management) on top of physical activity training. Therefore, in the Telerehab II study physical acivity telemonitoring rather than telerehabilitation was assessed.

Conclusion

The study demonstrated that in CAD patients, the addition of a physical activity telemonitoring program to conventional CR, could improve the patient's physical fitness (VO2peak) with greater magnitude, compared with standard CR, during an 18-week follow-up. The amount of improvement in VO2peak correlated with number of daily aerobic steps. Furthermore, the survival analysis showed a trend toward fewer re-hospitalisations among subjects in the intervention group.

References

[1] Massimo FP, Ugo C, Werner B, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery. Eur J Prev Cardiol 2012; 1: 1-18.

[2] Ting P, Saner H, Dafoe W. The lexicon of 'cardiac rehabilitation": is it time for an evolutionary new term? Eur J Prev Cardiol 2010; 17: 251-253.

[3] Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011; 162: 571-584.

[4] Janssen V, De Gucht V, Van Exel H, et al. Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients. Eur J Prev Cardiol 2013; 20: 431-441.

[5] Hansen D, Dendale P, Raskin A, et al. Long-term effect of rehabilittion in coronary artery disease patients : randomized clinical trial of the impact of exercise volume. Clin Rehabil 2010; 24: 319-327.

[6] Giannuzzi P, Temporelli PL, Marchioli R, 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: 2194-2204.

[7] Piotrowicz E, Jasionowska A, Banaszak-Bednarczyk M, et al. ECG telemonitoring during home-based cardiac rehabilitation in heart failure patients. J Telemed Telecare 2012; 18: 193-197.

[8] Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 2001; 104:1694–740.

[9] Hansen D, Dendale P, Berger J, et al. The importance of an exercise testing protocol for detecting changes of peak oxygen uptake in cardiac rehabilitation. Arch Phys Med Rehabil 2007; 88:1716–9.

[10] Frederix I, Dendale P, Berger J, et al. Comparison of two motion sensors for use in cardiac telerehabilitation. J Telemed Telecare 2011; 17: 231-234.

[11] Makoto A, Brubaker PH, Dobrosielski D, et al. Target Step Count for the Secondary Prevention of Cardiovascular Disease. Circ J 2008; 72: 299-303.

[12] Walters DL, Sarela A, Fairful A, et al. A mobile phone-based care model for outpatient cardiac rehabilitation: the care assessment platform (CAP). BMC Cardiovasc Disord 2010; 10: 1-8.

[13] Varnfield M, Karnanithi MK, Sarela A, et al. Uptake of a technology-assisted home-care cardiac rehabilitation program. Med J Aust 2011; 194: 15-19.

[14] Guiraud T, Granger R, Gremeaux V, 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: 2141-2147.

[15] Piotrowicz E, Baranowski R, Bilinska M, et al. A new model of home-based telemonitored cardiac rehabilitation in patients with heart failure: effectiveness, quality of life, and adherence. Eur J of Heart Fail 2010; 12: 164-171.

[16] Reid RD, Morrin LI, Beaton LJ, et al. Randomised trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. Eur J Prev Cardiol 2012; 19: 1357-1364.

[17] Zutz A, Ignazewki A, Bates J, et al. Utilisation of the internet to deliver cardiac rehabilitation at a distance: a pilot study. Telemed J E Health 2007; 13: 323-330.

[18] Laukkanen JA, Kurl S, Salonen R, et al. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. Eur Heart J 2004; 25: 1428-1437.

[19] Kokkinos PF, Holland JC, Narayan P, et al. Miles run per week and high-density lipoprotein cholesterol levels in healthy, middle-aged men. A dose-response relationship. Arch Intern Med 1995; 155: 415-420.

[20] Southard BH, Southard DR, Nuckolls J. Clinial Trial of an internet-based Case Management System for Secondary Prevention of Heart Disease. J Cardiopulm Rehabil 2003; 23: 341-348.

[21] Giannuzzi P, Saner H, Vanhees L, et al. Secondary prevention through cardiac rehabilitation. Position paper of the working group on cardiac rehabilitation and exercise physiology on the European Society of Cardiology. Eur Heart J 2003; 24: 1273-1278.

Chapter 06

Telerehab III:

(Cost-) Effectiveness of a Comprehensive Internet-Based and Patient-Specific Telerehabilitation Program.

This chapter summarizes study results reported in:

Frederix I, et al. Medium-term Efefctiveness 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.

Frederix I, et al. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization rate, medical costs, quality of life: A cost-effectiveness analysis. Eur J Prev Cardiol 2016;23(7):674-82.

Abstract

Background. Cardiac telerehabilitation has been introduced as an adjunct or alternative to conventional center-based cardiac rehabilitation to increase its long-term effectiveness. Before large-scale implementation and reimbursement in current health care systems is possible, however, well-designed studies on the effectiveness of this new additional treatment strategy are needed.

Objective. The aim of this trial was to assess the medium-term (cost-) effectiveness of an internet-based, comprehensive and patient-tailored telerehabilitation program with short message service support for cardiac patients.

Methods. The present multi-center randomized controlled trial comprised 140 cardiac rehabilitation patients, randomized (1:1) to a 24-week telerehabilitation program in combination with conventional cardiac rehabilitation (intervention group) or to conventional cardiac rehabilitation alone (control group). In the telerehabilitation program, initiated 6 weeks after the start of ambulatory rehabilitation, patients were stimulated to increase physical activity level. Based on registered activity data, they received semi-automatic telecoaching via e-mail and SMS, encouraging them to gradually achieve predefined exercise training goals. Patient-specific dietary and/or smoking cessation advice was also provided as part of the telecoaching. The primary endpoint was peak aerobic capacity (VO2peak). Secondary endpoints included accelerometer recorded daily step counts, self-assessed physical activities by IPAQ and quality of life (QoL), assessed by the HeartQol questionnaire at baseline, 6 weeks and 24 weeks study period. A cost-utility analysis was performed, for which the incremental cost-effectiveness ratio (ICER) was calculated.

Results. Mean VO2peak increased significantly in intervention group patients (n = 69) from baseline [22.46 ± 0.78 ml/kg/min] to 24 weeks [24.46 ± 1.00 ml/kg/min] ($P < .001$), contrary to control group patients (n = 70) where it did not change significantly (from 22.72 ± 0.74 ml/kg/min to 22.15 ± 0.77 ml/kg/min, $P = .09$). Between-group analysis of aerobic capacity confirmed a significant difference between the intervention group and control group in favor of the intervention group ($P < .001$). At 24 weeks, self-reported physical activity (MET-min/week) improved more in the intervention group, when compared to the control group ($P = .01$), as did the global QoL score ($P = .01$). An ICER of – 21,707 €/QALY was calculated.

Conclusions. The present study showed that an additional 6-month patient-specific, comprehensive telerehabilitation program can lead to a bigger improvement in both physical fitness (VO2peak) and associated health-related quality of life, compared to center-based cardiac rehabilitation alone. It is also more cost-efficient than classical cardiac rehabilitation alone. These results are supportive in view of possible future implementation in standard cardiac care.

Introduction

During the last years, cardiac telerehabilitation was introduced as an adjunct or alternative to conventional cardiac rehabilitation in order to increase uptake rates, to enable more prolonged care and to improve long-term success. Two recent systematic reviews concluded telerehabilitation to be non-inferior and/or superior, when compared to standard cardiac rehabilitation [5,6]. However, the European Heart Network emphasizes the need for more studies to be carried out on eHealth interventions to ensure its (cost-)effectiveness before large-scale implementation in current health care systems [7].

The aim of this multi-center, prospective randomized, controlled trial was to assess medium-term effectiveness of a patient-specific, comprehensive cardiac telerehabilitation program in addition to standard ambulatory cardiac rehabilitation. Contrary to most prior clinical trials on cardiac telerehabilitation, it included both telemonitoring and telecoaching strategies and focused on multiple cardiac rehabilitation core components (physical activity, nutritional counselling and smoking cessation) [5]. It was hypothesized that the addition of cardiac telerehabilitation to standard cardiac rehabilitation leads to significant greater increments in physical activity level and physical fitness. As part of this study, cost-utility analysis based on intervention costs, cardiovascular disease related health care costs and health-related quality of life was performed.

Methods

Patient recruitment

Telerehab III (ISRCTN29243064) was a multi-center, prospective, randomized, controlled clinical trial, run at Jessa Hospital (Hasselt) (n = 103), Ziekenhuis-Oost Limburg (Genk) (n = 27) and St. Franciscus Hospital (Heusden-Zolder) (n = 10) in Belgium between February 2013 and 2015. Patients were recruited/enrolled over a timeframe of 19 months (from February 2013 to August 2014). A detailed description of the study protocol has been published previously [8].

Patients were eligible for participation in Telerehab III when they entered cardiac rehabilitation for (i) CAD and treated conservatively, with a percutaneous coronary intervention or with coronary artery bypass grafting, (ii) CHF with reduced EF (NYHA I, II and III) or (iii) CHF with preserved EF (NYHA I, II and III) (as defined in the ESC guidelines). Patients were required to have a computer at home with internet access (they had to be computer and internet literate). The main exclusion criteria were (i) CHF NYHA class IV, (ii) symptomatic and/or exercise induced cardiac arrhythmia within the previous six months, (iii) physical disability related to musculoskeletal or neurological problems and (iv) severe cognitive impairment. All patients provided offline informed consent, after the nature and possible consequences of the study were explained, prior to study enrollment. Patients were recruited offline at the hospitals' rehabilitation centers by face-to-face information sessions. They were randomly assigned (1:1) to internet-based telerehabilitation in addition to center-based rehabilitation (intervention group) or center-based rehabilitation alone (control group). A central computerized randomization system, using block randomization, ascertained equal distribution of patients in the different recruiting hospitals for both treatment arms.

The study was conducted in accordance with the principles stated in the Declaration of Helsinki (reviewed version of 2008), local and national regulations. The study protocol was approved by Jessa Ethics Committee (reference number: B243201216043). The trial is reported in accordance with CONSORT-EHEALTH.

Study intervention

Center-based cardiac rehabilitation program

Both groups participated in a 12-week conventional center-based cardiac rehabilitation program, including 45 pluridisciplinary rehabilitation sessions with at least two exercise training sessions per week [10]. Patients were instructed to exercise for 45-60 min per session at a target heart rate and/or workload corresponding to an intensity between their first ventilatory threshold (VT1, as detected by V-slope method) and respiratory compensation point (RCP, as detected by carbon dioxide equivalent (VE/VCO2) slope method). Endurance training consisted of walking/running, and/or cycling and arm cranking. They also had at least one consultation with the dietician and the psychologist of the rehabilitation center. The dietician provided the patients with general guidelines on healthy diet, the psychologist aimed to improve the patient's self-efficacy to change prior unhealthy lifestyle behavior to a more healthy lifestyle behavior. He also assessed the patients' potential mood disorders (depression, anxiety,…..) related to their cardiac event.

Telerehabilitation program

Intervention group patients received a 24-week internet-based, comprehensive telerehabilitation program in addition to the conventional center-based cardiac rehabilitation. The telerehabilitation program started at week six of the 12-week center-based cardiac rehabilitation, allowing the intervention group patients to become familiarized with the telerehabilitation's motion sensor (Yorbody accelerometer, Belgium) and associated password-protected webservice during the 6-week overlap period. The program focused on multiple cardiac rehabilitation core components and used both physical activity telemonitoring and dietary/smoking cessation/physical activity telecoaching strategies. For the telemonitoring part, intervention group patients were prescribed with patient-specific exercise training protocols, based on achieved peak aerobic capacity (VO2peak) during initial maximal cardiopulmonary exercise testing and calculated body mass index (BMI) [8]. Intervention group patients were instructed to continuously wear the accelerometer and to regularly transmit their registered activity data to the telerehabilitation center's local server. They were instructed to transmit their physical activity data at least once weekly, but preferably daily. Data were transmitted to the telerehabilitation center's local server in just a few minutes after starting the transmission. These data enabled a semi-automatic telecoaching system to provide the patients with feedback via e-mail and SMS (once weekly), encouraging them to gradually achieve predefined exercise training goals. In addition patients received e-mails and/or SMS's (once weekly) with tailored dietary and smoking cessation recommendations. The dietary telecoaching program included a module for diabetes mellitus, for arterial hypertension, for obesity

and a healthy module. Cardiovascular risk factor profiling at entry of study determined which module(s) were prescribed for each patient. The smoking cessation telecoaching program included information on major risks associated with smoking, the health benefits of smoking cessation and nicotine replacement therapy. It provided smokers with encouraging messages towards smoking cessation.

The content of the feedback messages differed from the content of the center-based cardiac rehabilitation program in that it changed over time based on how well the patient changed his prior lifestyle behavior. For example, the exercise training feedback was intended to encourage patients to achieve predefined patient-specific training goals. If a patient succeeded in getting closer towards these predefined goals, the feedback would encourage the patient to improve his/her training even more. In contrary, if the patient's exercise training deteriorated during study period, the feedback aimed to get the patient back on track. One independent person was responsible for technical assistance in case of sensor/system failure (part-time). One care provider supervised sent e-mails and/or SMS's, he/she was responsible for consistency and correctness of the content of sent messages. He/she also intervened in case of serious abnormal registrations (part-time). Access to registered data by the care provider was password-protected. The care provider that supervised sent e-mails and/or SMS's, was a staff member that coached cardiac patients already for more than five years during their conventional center-based cardiac rehabilitation program. During his training period, he had also received a specific course on how to detect and what to do in case of alarming signs/symptoms. During whole study period, one cardiologist supervised the care provider. She was available to answer questions and to assist the care provider if necessary.

Outcome measures

All outcome assessors were blinded to group allocation. The primary outcome measure was peak aerobic capacity (VO2peak), measured during maximal cardiopulmonary exercise testing [11] with breath-by-breath gas exchange analysis at baseline, after 6 and 24 weeks of study period (Jaeger MS-CPX). The cardiopulmonary exercise test was maximal in case of an achieved heart rate >85% of the maximal predicted heart rate, a Respiratory gas Exchange Ratio (RER) >1.1, and/or a ventilatory reserve (VR: VE peak/MVV) >80% [11]. The first ventilatory threshold (VT1) and the oxygen uptake efficiency slope (OUES) were used as surrogate markers for VO2peak in case of submaximal cardiopulmonary exercise test. VT1 was defined by the V-slope method, OUES was calculated using the method of Baba et al. [12]. Two independent investigators, blinded to treatment allocation interpreted cardiopulmonary exercise test reports.

The first secondary outcome measure was daily physical activity [13], both registered by triaxial accelerometry (Yorbody sensor) and self-assessed by the patient. The accelerometer provided daily recordings of aerobic (defined as sustained activity at ≥60 steps/min for ≥10 minutes), regular (activity at <60 steps/min) and total (sum of aerobic and regular) steps. Self-reported physical activity was based on the offline IPAQ questionnaire, completed at baseline, after 6 and 24 weeks. MET-minutes were computed by multiplying predefined MET-scores by the minutes of a specific activity performed, to weigh each type of activity by its energy requirement (for the domain leisure

time activity and for all domains together). Following MET-scores were used: 3.3 METs for walking, 4.0 METs for moderate and 8.0 METs for vigorous physical activity, respectively.

HbA1c, glycemic control and lipid profile were assessed by blood sampling at study start and after 24 weeks study period.

The 14-item offline HeartQol questionnaire was used to assess health-related quality of life (HRQL) at study start, after 6 and 24 weeks [14]. Mean (± SD) scores were calculated for both the physical (10-item) and emotional (4-item) subscale. The proportion of patients at the floor ("floor effect", defined as the lowest possible score on the questionnaire) and at the ceiling ("ceiling effect", defined as the best possible score) was determined to assess sensitivity to positive and negative changes in HRQL.

Qualitative feedback on the cardiac telerehabilitation system was obtained from intervention group patients by special offline feedback forms. Intervention group patients were requested to fill in these forms after study completion.

Cardiovascular rehospitalisations

Rehospitalisations were defined as both emergency visits (< 24 hours), hospital admissions (> 24 hours) and day procedures. All rehospitalisations (both cardiovascular and non-cardiovascular) were retrieved from the patients' electronic medical files in the recruiting hospitals by the study investigators. They were cross-checked with those on file in the patients' medical insurance records to ascertain accurateness. A Clinical Endpoint Committee (CEC), composed of three independent cardiologists blinded to treatment allocation, classified all rehospitalisations to (non-) cardiovascular and provided physician reported diagnoses. The time to first cardiovascular rehospitalisation was calculated as were the number of days lost due to cardiovascular rehospitalisations and the proportion of actual to theoretical maximal days alive and out of hospital.

Cost-effectiveness

The cost-effectiveness evaluation was conducted from a society and patient perspective, taking into account both intervention and health care resource costs. As the majority of patients was retired, productivity losses due to illness-related absence from the workplace were not estimated.

Intervention costs were those associated with delivering the center-based CR and telerehabilitation program. The National Sickness and Invalidity Insurance Institution (INAMI/RIZIV)'s (dd. 01/2015) nomenclature-based tariffs were employed to quantify the center-based CR costs (code nr. 771212). Expenditure records were used to determine the equipment and consumable resources for telerehabilitation. Health care costs were the aggregated costs of emergency visits, hospital admissions and day procedures for cardiovascular reasons (together cardiovascular rehospitalisations) as also specialist visits and associated diagnostics. The cardiovascular rehospitalisations' related costs were derived from invoices retrieved from the recruiting hospitals'

financial departments. INAMI/RIZIV's nomenclature-based tariffs defined specialist visits and diagnostics denominations.

Quality adjusted life years (QALY's) were used as generic measure of effectiveness. Estimates of QALY's were derived from the EQ-5D questionnaire, which was completed by participants at baseline, at 6 weeks and 24 weeks of follow-up period. The EQ-5D scores were converted to utility scores. The utility estimates were converted to adjusted mean QALY's by calculating the 'area under the curve' (AUC) utility estimates for all time intervals for each patient, weighed by the length of follow-up at that time interval. The change from baseline utility (adjusted differential incremental QALY's) was then calculated, using the multiple regression model to control for baseline utility differences.

The incremental cost-effectiveness ratio (ICER) was calculated [ICER= (Cost intervention group – Cost control group)/(Effectiveness intervention group – Effectiveness control group)] to compare costs and outcomes (effectiveness) across both treatment groups. The incremental cost was determined by the difference in total average cost per patient between the intervention group and control group. The incremental effectiveness was estimated by the adjusted differential incremental QALY's.

Statistical analysis

Data analysis was performed using SPSS v. 22 according to the intention-to-treat principle, by assigned treatment group. Nonparametric alternatives were used for parametric statistics in case assumptions for the latter were violated. The Shapiro-Wilk test was used to assess normality. Paired t-tests (parametric) or Wilcoxon signed-rank tests (non-parametric) were used for within-group analysis, independent t-tests (parametric) or Mann-Whitney U tests (non-parametric) for between-group analysis. Repeated measures ANOVA (parametric) or Friedman's ANOVA (non-parametric) compared multiple dependent means. Chi-square tests were used in case of categorical variables, Fisher's exact tests were used when expected frequencies were small. Pearson's (r) or Spearman's (rs) correlation coefficients were calculated to express relationships between variables (bivariate correlations). The significance level for tests was 2-sided α of 0.05. Effect sizes for the HeartQol questionnaire were reported using the standardized response mean methodology [standardized response mean = (A –B)/D], where A and B are the mean scores at time 2 and time 1, respectively. D represents the score change standard deviation [14]. Sensitivity analysis of accelerometric activity measurements was performed to cope with incomplete activity registrations. Inclusion thresholds of 1,000, 2,000, 3,000, 4,000 and 5,000 total daily steps or ≥ 7, ≥ 8 and ≥ 9 daily measurement hours were arbitrarily chosen, because these represented reliable registrations. All available data were used, no data imputation was performed for missing values. A priori sample size calculation yielded 140 necessary patients to detect a 20% effect size of the primary outcome measure (VO2 peak) [9] between groups (intervention group vs control group), with a statistical power of 95% at a 2-sided type I error level of 0.05 and a dropout rate of 30%. Cumulative survival curves for the time-to-first rehospitalisation analyses were made according to the Kaplan-Meier method, the log-rank statistic evaluated the difference between the curves. The Cox

regression model was used to estimate the hazard ratio (HR), treatment was the only covariate. Censoring was applied in case of dropout and when the study terminated before the first event of interest occurred.

Results

A total of 140 patients agreed to participate in the study. The numbers and reasons for dropout during study period were similar for both treatment groups. Dropout patients were included in the final analysis, with the exception of one intervention patient (diagnosed with non-cardiac related pathology i.e. lung cancer) that was excluded from final analysis. Intervention patients transmitted their activity data 1.0 ± 0.3 times per week. When averaged over the whole study period (24 weeks), 76% of the intervention group patients (52 out of 69 patients) did > 2000 total daily steps or measured ≥ 8 hours per day. Both treatment groups had similar baseline demographics, clinical characteristics and medication use (Table 1).

Table 1. Baseline demographics, clinical characteristics and medication use.

		Intervention Group (n=69)	Control Group (n=70)	*P*
Age (years)		61±9	61±8	.95
Gender				.38
	Female	14% (10)	21% (15)	
	Male	86% (59)	79% (55)	
Type of cardiac pathology				.53
	CAD	94% (65)	93% (65)	
	HFrEF	3% (2)	6% (4)	
	HFpEF	3% (2)	1% (1)	
NYHA class				.10
	NYHA I	78% (54)	87% (61)	
	NYHA II	18% (12)	6% (4)	
	NYHA III	4% (3)	7% (5)	
EF				.32
	EF>50%	75% (52)	71% (50)	
	EF 35-50%	0% (0)	4% (3)	
	EF<35%	25% (17)	24% (17)	
Atrial fibrillation		7.2% (5)	9% (6)	.99
Diabetes mellitus		24.6% (17)	27% (19)	.85
Hyperlipidemia		76.8% (53)	79% (55)	.84
Arterial hypertension		60.0% (40)	63% (44)	.61

Family history		49.3% (34)	51% (36)	.87
Smoking				.99
	Current smoker	26% (18)	26% (18)	
	Prior smoker	32% (22)	33% (23)	
	Non-smoker	42% (29)	41% (29)	
BMI		28±5	28±4	.54
Peripheral artery disease		12% (8)	16% (11)	.62
On Beta blocker		77% (53)	81% (57)	.61
On ACE-inhibitor		64% (44)	69% (48)	.72
On Statin		96% (66)	91% (64)	.16
On anti-platelet therapy				.88
	DAPT	54% (37)	57% (40)	
Anti-platelet monotherapy		42% (29)	39% (27)	
No anti-platelet therapy		4% (3)	4% (3)	
On diuretics		17% (12)	20% (14)	.76
On oral anti-diabetics		15% (10)	14% (10)	.94
On insulin		10% (7)	7% (5)	.51
On anticoagulative therapy		6% (4)	7% (5)	.76
On anti-arrhythmics		6% (4)	4% (3)	.67

Aerobic capacity

Table 2 shows the cardiopulmonary exercise test outcome measures assessed at baseline, after 6 and 24 weeks of study period. Mean VO2 peak improved significantly in intervention group patients from baseline [22.46 ± 0.78 ml/min*kg] to 24 weeks [24.46 ± 1.00 ml/min*kg] (P < .001). In the control group mean VO2 peak did not change after 24 weeks when compared to baseline (P = .09), and decreased from week 6 [22.86 ± 0.66 ml/kg/min] to week 24 [22.15 ± 0.77 ml/min*kg] (P = .02), after an initial non-significant increase. Between-group analysis of aerobic capacity was significant after 24 weeks (P < .001) in favor for the intervention group. VT1 (W), OUES (ml/min/(log ml/min)) and Watt (% pred) changed similarly over time.

Table 2. Cardiopulmonary exercise test parameters at baseline, 6 weeks and 24 weeks follow-up period.

				Within-group				Between-group			
Intervention	Week 1	Week 6	Week 24	*P*	*P*	*P*	*P*	*P*	*P*	*P*	*P*
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Overall	Δ 6-1	Δ 24-6	Δ 24-1	Overall	Δ 6-1	Δ 24-6	Δ 24-1
VO2 peak (ml/min*kg)	22.46 (± 6.43)	23.91 (± 6.74)	24.46 (± 7.57)	.01	.08	.38	.01	<.001	.19	.01	<.001
HR max (% pred)	79 (± 13)	80 (± 12)	83 (± 12)	.047	.99	.36	.05	.53	NA	NA	NA
Watt (W)	152 (± 48)	163 (± 52)	165 (± 53)	.01	.02	.81	.01	.01	.90	.01	.02
Watt (pred%)	103 (± 23)	110 (± 27)	116 (± 27)	<.001	.01	.27	<.001	<.001	.83	.01	.01
VT1 (W)	69 (± 24)	75 (± 25)	81 (± 26)	<.001	.74	<.001	<.001	<.001	.80	<.001	<.001
VT1 (bpm)	93 (± 17)	91 (± 15)	96 (± 15)	.01	.99	.01	.08	.01	.35	.01	.047
OUES (ml/min/log(ml/min))	2,067 (± 518)	2,241 (± 545)	2,272 (± 579)	<.001	.02	.045	<.001	.1	NA	NA	NA

Weight (kg)	83.3 (± 18.2)	83.2 (± 17.4)	83.0 (± 17.3)	.69	NA	NA	NA	.45	NA	NA	NA
BMI (kg/m2)	28 (± 5)	28 (± 5)	28 (± 5)	.63	NA	NA	NA	.60	NA	NA	NA
DBP rest (mmHg)	82 (± 19)	81 (± 21)	77.24 (± 21.13)	.48	NA	NA	NA	.67	NA	NA	NA
SBP rest (mmHg)	126 (± 21)	129 (± 30)	150 (± 14)	.26	NA	NA	NA	.30	NA	NA	NA
Control											
VO2 peak (ml/min*kg)	22.72 (± 6.05)	22.86 (± 5.37)	22.15 (± 5.83)	.02	.99	.02	.09				
HR max (% pred)	77 (± 12)	79 (± 13)	79 (± 12)	.43	NA	NA	NA				
Watt (W)	150 (± 49)	158 (± 50)	152 (± 53)	.01	<.001	.02	.99				
Watt (pred%)	105 (± 26)	108 (± 26)	104 (± 27)	.01	<.001	.01	.99				
VT1 (W)	83 (± 34)	88 (± 34)	76 (± 31)	<.001	.20	<.001	.01				
VT1 (bpm)	95 (± 15)	96 (± 15)	95 (± 17)	.53	NA	NA	NA				
OUES (ml/min/log(ml/min))	2,493 (± 2,338)	2,264 (± 637)	2,142 (± 636)	.25	NA	NA	NA				
Weight (kg)	82.7 (± 13.4)	82.5 (± 13.3)	82.5 (± 13.9)	.18	NA	NA	NA				
BMI (kg/m2)	28 (± 4)	28 (± 4)	27 (± 5)	.51	NA	NA	NA				

DBP rest (mmHg)	84 (± 21)	78 (± 19)	79 (± 17)	.33	NA	NA	NA				
SBP rest (mmHg)	129 (± 25)	127 (± 23)	129 (± 21)	.57	NA	NA	NA				

Physical activity

Sensitivity analysis of accelerometric step data confirmed similar activity patterns for both groups, regardless of the thresholds. > 2,000 total daily steps or ≥ 8 daily measurement hours were used as thresholds for further analysis. In the intervention group total daily steps increased from baseline (Mdn: 7,448) to both 6 weeks (Mdn: 7,799) and 24 weeks (Mdn: 8,233), however no changes were significant (P = .24). In the control group, total daily steps showed an initial increasing trend from baseline (Mdn: 5,678) to week 6 (Mdn: 6,630), but declined afterwards (Mdn: 5,265) (p = .85). Total daily steps were positively correlated with VO2peak (ml/min*kg) at baseline (rs = 0.330, P = .01), after 6 weeks (rs = 0.237, P = .03) and 24 weeks (rs = 0.485, P < .001).

Self-reported physical activity (by IPAQ questionnaire) was converted to MET-min/week of vigorous and/or moderate and/or walking activities for the leisure time domain and all domains together respectively. Summed vigorous-moderate-walking activity (VMW) leisure increased significantly in the intervention group ($\chi 2$ F (2) = 13.66, P = .01) during study period. In the control group VMW leisure (MET-min/week) did not change ($\chi 2$ F (2) = 0.646, P = .72), however it showed a downward trend. Between-group analysis confirmed a difference between the intervention group and control group in favor of the intervention group (U = 1,830, z = 3.336, P = .01). Contrary to the VMW activities, total sitting time (min/week) decreased significantly during study period in the intervention group ($\chi 2$ F (2) = 19.89, P < .001). In the control group, total siting time (min/week) did not change overall ($\chi 2$ F (2) = 3.67, P = .16). Control patients tended to decrease sitting time during the first 6 weeks, but increased their sitting time back again after 6 weeks study period. Between-group analysis confirmed a difference between the intervention group and control group for self-reported total sitting time (U = 1,360, z = -2.427, P = .02).

Cardiovascular risk factors

In the intervention group, no significant within-group differences were found for weight (P = .69), BMI (P = .63), diastolic blood pressure (P = .48) and systolic blood pressure (P = .26). The same was true for the control group (P = .18 for weight, P = .51 for BMI, P = .33 for diastolic blood pressure and P = .57 for systolic blood pressure). No between-group differences were found for these outcomes.

Fasting glucose levels, HbA1c and LDL-cholesterol did not change during study period in the intervention group (P = .67, P = .18 and P = .20), nor in the control group (P = .25, P = .51 and P

= .31). Total cholesterol levels increased in both treatment groups, but no between-group differences were found (P = .97).

Quality of life

Intervention group patients showed a significant improvement in perceived health-related quality of life (QoL) for the physical subscale from baseline (2.23 ± 0.08) to the end of study period (2.52 ± 0.07) ($\chi 2$ F (2) = 15.35, P < .001). The standardized response mean of .43 indicated a small to moderate effect size. Their global QoL score also improved significantly ($\chi 2$ F (2) = 14.04, P < .001). The standardized response mean of .43 indicated a small to moderate effect size. The QoL of the control group patients did not change during study period for the physical subscale ($\chi 2$ F (2) = 6.32, P = .05), the emotional subscale ($\chi 2$ F (2) = 0.456, P = .80) or the global scale ($\chi 2$ F (2) = 3.11, P = .21). Between-group analysis confirmed that globally the intervention group's QoL improved more compared to the control group (U = 2,407, z = 2.805, P = .01).

Cardiovascular rehospitalisations

The proportional hazards assumption was valid as assessed using the log-log plot and comparing curves for the different strata. 23 participants were rehospitalized for cardiovascular reasons (7 for intervention group, 16 for control group). The reasons for rehospitalisation were in-stent restenosis (n = 2), atypical thoracic pain (n = 1), ventricular arrhythmia (n = 1), supraventricular arrhythmia (n = 1), pericarditis (n = 1) and peripheral artery disease (n = 1) for the intervention group. In the control group, rehospitalisations were due to in-stent restenosis (n = 1), acute coronary syndrome (n = 2), stable angina (n = 6), atypical thoracic pain (n = 2), ventricular arrhythmia (n = 1), supraventricular arrhythmia (n = 1), atrial fibrillation ablation (n = 1), CRT-D replacement (n = 1) and peripheral artery disease (n = 1). The average [95% CI] time to first cardiovascular rehospitalisation was 502 [469-535] days for the intervention group and 445 [400-491] days for the control group (p = 0.045, HR 0.415 [0.170-1.009]) (Figure 3).

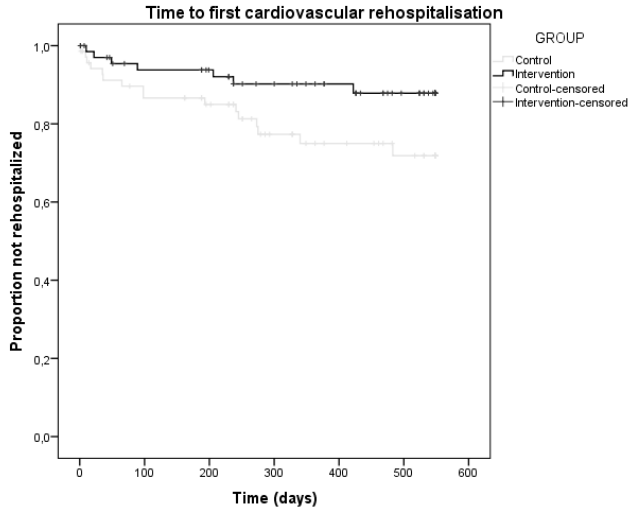

Figure 3. Time to first cardiovascular rehospitalisation after randomization.

Cost-effectiveness

The total average cost per patient (intervention plus health care costs) was significantly lower in the intervention group (2156 ± 126 €) than in the control group (2720 ± 276 €, U = 3068, z = 2.582, p = 0.01, r = 0.22 (i.e. small to medium effect) (Table 3). The cost-effectiveness analysis demonstrated that overall, the addition of the telerehabilitation program to center-based CR (intervention group) was both cost-saving and more effective than the center-based CR alone (control group) . Dividing the overall incremental average cost per patient (-564.40 €) by the baseline adjusted differential incremental QALY's (0.026 QALY's) yielded an ICER of -21,707 €/QALY. The distribution of the points in the cost-effectiveness scatter plot (Figure 4) further illustrated aforementioned findings.

Table 3. Incremental cost (intervention minus control) per quality adjusted life year.

		Control group (n=70)			Intervention group (n=69)	
Description of resource	Average cost per unit (€)	Average number of units	Average cost per participant (€)	Average cost per unit (€)	Average number of units	Average cost per participant (€)
Intervention costs						
Standard CR (RIZIV)	1372.95	1	1372.95	1372.95	1	1372.95
Standard CR (patient)	152.55	1	152.55	152.55	1	152.55
Study nurse	33.36	0	0	33.36	2	66.72
Accelerometer	39.95	0	0	39.95	1	39.95
Web page service	9.95	0	0	9.95	6	59.7
Info brochure	2.5	0	0	2.5	1	2.5
Health care costs						
CV rehospitalisations cost (RIZIV)	2301.91	0.37	851.71	1551.68	0.17	263.79
CV rehospitalisation cost (patient)	249.52	0.37	92.33	85.56	0.17	14.54

Specialist visit cost (RIZIV)	24.74	1.8	44.53	24.74	1.37	33.89
Specialist visit cost (patient)	12	1.8	21.6	12	1.37	16.44
Diagnostics cost (RIZIV)	35.83	4.63	165.90	33.51	3.57	119.62
Diagnostics cost (patient)	4.027	4.63	18.64	3.69	3.57	13.16
Total average cost per patient			2720.21			2155.81
Incremental cost (I-C) (€): -564						
Average QALY's baseline			0.77			0.74
Average change in QALY's			-0,09			0.06
Adjusted mean QALY [a]			0.36			0.39
Adjusted differential incremental QALY's gained [b]: 0.03						
ICER = [Cost I-Cost C]/[Effectiveness I- Effectiveness C] (€/QALY): -21,707						
Comments: Intervention more effective and efficient						

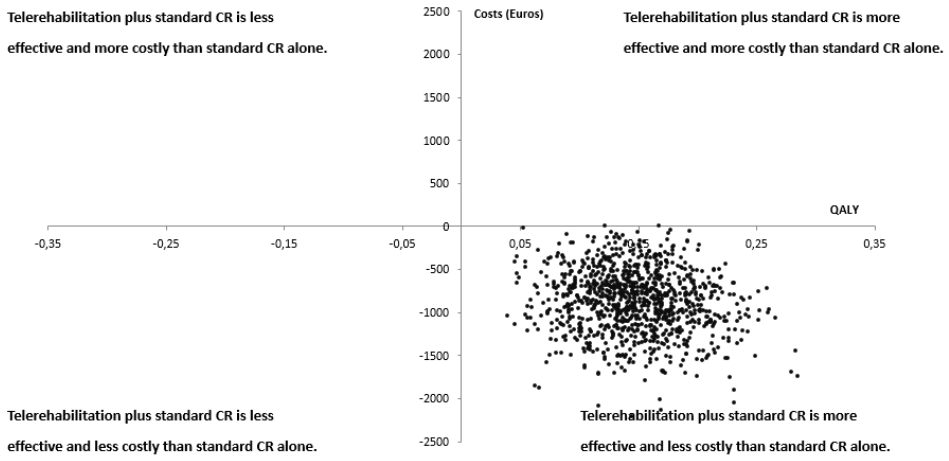

Figure 4. Cost-effectiveness plane scatter plot of the incremental cost (Euros) and incremental quality-adjusted life years (QALY) gained, based on the bootstrap resampling method. Each point in the scatter plot represents 1 bootstrap iteration. 1000 bootstrap iterations were carried out. CR: cardiac rehabilitation.

Discussion

The present study showed that an additional 6-month patient-specific, comprehensive telerehabilitation program can lead to a bigger improvement in both physical fitness (VO2peak) and associated health-related quality of life, compared to center-based cardiac rehabilitation alone. The real difference between both groups occurred after center-based cardiac rehabilitation was completed. Peak oxygen uptake (VO2peak (ml/min*kg)), daily total step count and IPAQ's self-reported VMW activities (MET-min/week) increased from baseline to 6 weeks in both treatment groups. They additionally increased between week 6 and 24 in the intervention group, but decreased in the control group. Control group patients participated in the center-based cardiac rehabilitation during the first 6 weeks of study period only, probably explaining their initial improvement in outcome measures. The observed findings imply that control group patients return to prior lifestyle behavior after center-based cardiac rehabilitation, while intervention group patients further maintain and ameliorate acquired behavioral change. The cost-utility analysis showed that overall, the addition of the cardiac telerehabilitation program to conventional center-based CR, was more cost-efficient as compared to center-based CR alone. The main reason for this finding was the observation of a reduced cardiovascular readmission rate in the intervention group.

Recent literature findings confirmed telehealth interventions such as telemonitoring to be feasible and effective for heart failure patients [15-18]. Furthermore, two systematic reviews on cardiac tele-interventions were published [5,6] . We reported on cardiac telerehabilitation in CAD and CHF patients with a total of 13,248 patients enrolled in 37 studies, and a mean follow-up period of 9 months. We concluded that telerehabilitation was associated with significantly lower lack of adherence to physical activity guidelines (Odds Ratio (OR) = 0.56, 95 % CI: 0.45-0.69) [19-27]. Huang et al. however, found no statistically significant difference between telehealth interventions and center-based cardiac rehabilitation for exercise capacity (standardized mean difference (SMD) = −0.01, 95 % CI: −0.12-0.10), weight (SMD = -0.13, 95% CI: -0.30-0.05), systolic and diastolic blood pressure (mean difference (MD) -1.27, 95% CI: -3.67-1.13 and MD 1.00, 95% CI: -0.42-2.43, respectively) and lipid profile. Another very recent systematic review on digital health interventions (DHIs) of Widmer et al., concluded that DHIs can improve cardiovascular risk factors such as weight loss, blood pressure and LDL-cholesterol in patients seeking primary prevention of CVD [28]. In contrary they found no consistent reductions in the aforementioned risk factors in secondary prevention studies.

The somewhat contrary findings between the review of Frederix et al., the results of the current Telerehab III trial (ISRCTN29243064) showing effectiveness of cardiac tele-interventions on exercise capacity and the review of Huang et al. which showed no effect on exercise capacity, could be attributed to differences in intervention group programs. It appears that a comprehensive tele-intervention, including at least physical activity telemonitoring and telecoaching is necessary. The feedback provided by the tele-intervention should be patient-specific in order to increase success rates.

In this Telerehab III trial (ISRCTN29243064), we found no significant effect of the additional cardiac telerehabilitation program on weight loss, blood pressure, lipid profile and/or glycemic control. This is consistent with the findings of Huang et al. and Widmer et al. DHIs seem to be able to improve cardiovascular risk factors in primary prevention but not secondary prevention programs. Future research should focus on furthering our understanding of the variables determining this success of DHIs in primary prevention populations, contrary to secondary prevention populations.

The intervention group patients could see and follow-up their own transmitted activity data by logging onto the Telerehab III webpage as many times as they preferred. On average, they transmitted their activity data and logged onto the webpage 1.0 ± 0.3 times per week. Some patients' their frequency of data transmission increased during study period, the frequency of others remained stable. There were almost no patients of whom the frequency of data transmission decreased during study period.

The reason for the increasing frequency of data transmission, seen for some of the intervention patients remains unclear. In this trial, all intervention patients received feedback messages with the same frequency (once weekly). However, it would be interesting to investigate if the patients' frequency of data transmission would be different for different frequencies of sent feedback messages.

The strength of Telerehab III is that it, contrary to most analyzed trials in the review of Huang et al., provided intervention group patients with a comprehensive, patient-specific telerehabilitation program focusing on multiple core components (exercise training, nutritional counseling, smoking cessation). Both telecoaching and telemonitoring strategies were included, exercise training programs and dietary prescriptions were based on initial maximal cardiopulmonary exercise testing, BMI and individual cardiovascular risk factor profile.

A limitation of this study was that Telerehab III was initially designed to recruit a broad cardiac patient population (including both CAD, CHF with reduced EF and CHF with preserved EF). However, as shown by the baseline clinical characteristics (Table 1), only a minority of CHF patients eventually participated (5.8 % and 7.1 % in the intervention group and control group respectively). This reduced the generalizability of study findings to CHF patients.

Finally, in Telerehab III one part-time (caregiver) was responsible for control of feedback content and one part-time (technical assistant) for system/service operability. In a routine application setting similar staff requirements would be sufficient.

Conclusion

This paper showed the addition of the cardiac telerehabilitation program to conventional center-based cardiac rehabilitation to be more effective than center-based cardiac rehabilitation alone in improving VO2peak, self-reported physical activity and associated QoL at 24 weeks. We plan to conduct a follow-up trial of Telerehab III to assess whether the intervention-related health benefits persist 2 years after study termination. The current findings answer to the European Heart

Network's question to profoundly well-document and evaluate critical eHealth interventions before large-scale deployment in the health care system. Future research should focus on even more elaborate comprehensive telerehabilitation programs, that have the potential to improve not only aerobic capacity, physical activity level and quality of life, but also improve the patient's cardiovascular risk factor profile (weight, blood pressure, lipids and glycaemia control).

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References

[1] Scharf, Petra. 2015. European Heart Network, fighting heart disease and stroke. http://www.ehnheart.org/cvd-statistics.html. Archived at: http://www.webcitation.org/6YwSAyrVl

[2] Montalescot G, Sechtem U, Achenbach S. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34: 2949-3003. PMID: 23996286

[3] McMurray JJ, Adamopoulos S, Anker SD. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart 2012; 33: 1787-1847. PMID: 22611136

[4] Hansen D, Dendale P, Raskin A, et al. Long-term effect of rehabilitation in coronary artery disease patients : randomized clinical trial of the impact of exercise volume. Clin Rehabil 2010;24:319–27. PMID: 20176771

[5] Frederix I, Vanhees L, Dendale P, et al. A review of telerehabilitation for cardiac patients. J Telemed Telecare 2015; 21(1): 45-53. PMID: 25475219

[6] Huang K, Liu W, He D, et al. Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: A systematic review and meta-analysis. Eur J Prev Cardiol 2014 [Epub ahead of print]. PMID: 25488550

[7] Scharf, Petra. 2015. European Heart Network, fighting heart disease and stroke. EHN Paper on eHealth. http://www.ehnheart.org/patients/papers/publication/698-ehn-paper-on-ehealth.html. Archived at: http://www.webcitation.org/6YwSKmss8

[8] Frederix I, Hansen D, et al. Telerehab III: a multi-center randomized, controlled trial investigating the long-term effectiveness of a comprehensive cardiac telerehabilitation program. Rationale and study design. BMC Cardiovasc Disord 2015; 15(1): 29. PMID: 25948479

[9] Frederix I, Van Driessche N, Hansen D, et al. Increasing the medium-term benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients. Eur J Prev Cardiol 2015; 22(2): 150-158. PMID: 24249840

[10] Van Vlaenderen, Ilse. 2015. Cardiale revalidatie: klinische doeltreffendheid en gebruik in België. KCE rapport 140A. https://kce.fgov.be/sites/default/files/page_documents/kce_140a_cardiale_revalidatie.pd. Archived at: http://www.webcitation.org/6YwSh6Snn

[11] Ross RM. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med 2003; 167: 211-277. PMID: 12738602

[12] Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol 1996;28:1567–72. PMID: 8917273

[13] Warren J, Ekelund U, Besson H, et al, Experts Panel. Assessment of physical activity – a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil 2010; 17(2): 127-139. PMID: 20215971

[14] Oldridge N, Höfer S, McGee H, et al. The HeartQol: Part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol 2014; 21(1): 98-106. PMID: 22822180

[15] Agboola S, Jethwani K, Khateeb K, et al. Heart failure remote monitoring: evidence from the retrospective evaluation of a real-world remote monitoring program. J Med Internet Res 2015; 22;17. PMID: 25903278

[16] Kitsiou S, Paré G, Jaana M. Effects of home telemonitoring interventions on patients with chronic heart failure: an overview of systematic reviews. J Med Internet Res 2015; 12;17. PMID: 25768664

[17] Seto E, Leonard K, Cafazzo J, et al. Mobile phone-based telemonitoring for heart failure management: a randomized controlled trial. J Med Internet Res 2012;14(1). PMID: 22356799

[18] Zan S, Agboola S, Moore S, et al. Patient engagement with a mobile web-based telemonitoring system for heart failure self-management: a pilot study. JMIR Mhealth Uhealth 2015;3(2). PMID: 25842282

[19] Barnason S, Zimmerman L, Nieveen J, et al. Influence of a symptom management telehealth intervention on older adults' early recovery outcomes after coronary artery bypass surgery. Heart Lung 2009;38:364–76. PMID: 19755186

[20] Hanssen T, Nordrehaug J, Eide G, et al. Does a telephone follow-up intervention for patients discharged with acute myocardial infarction have long-term effects on health-related quality of life? A randomised controlled trial. J Clin Nurs 2009;18:1334–45. PMID: 19220616

[21] Redfern J, Briffa T, Ellis E, et al. Choice of secondary prevention improves risk factors after acute coronary syndrome: 1-year follow-up of the CHOICE (Choice of Health Options In prevention of Cardiovascular Events) randomised controlled trial. Heart 2009;95:468–75. PMID: 18801781

[22] Jelinek M, Vale M, Liew D, et al. The COACH program produces sustained improvements in cardiovascular risk factors and adherence to recommended medications-two years follow-up. Heart Lung Circ 2009;18:388–92. PMID: 19648058

[23] De Lusignan S, Wells S, Johnson P, et al. Compliance and effectiveness of 1 year's home telemonitoring. The report of a pilot study of patients with chronic heart failure. Eur J Heart Fail 2001;3:723–30. PMID: 11738225

[24]Clark R, Tideman P, Tirimacco R, et al. A pilot study of the feasibility of an Internet-based electronic Outpatient Cardiac Rehabilitation (eOCR) program in rural primary care. Heart Lung Circ 2013;22:352–9. PMID: 23294762

[25] Piotrowicz E, Baranowski R, Bilinska M, et al. A new model of home-based telemonitored cardiac rehabilitation in patients with heart failure: effectiveness, quality of life, and adherence. Eur J Heart Fail 2010;12:164–71. PMID: 20042423

[26] Koehler F, Winkler S, Schieber M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation 2011;123:1873–80. PMID: 21444883

[27] Kraal J, Peek N, Van den Akker-Van Marle M, et al. Effects of home-based training with telemonitoring guidance in low to moderate risk patients entering cardiac rehabilitation: short-term results of the FIT@Home study. Eur J Prev Cardiol 2014; 2(25): 26-31. PMID: 25354951

[28] Widmer R, Collins N, Collins S, et al. Digital Health Interventions for the Prevention of Cardiovascular Disease: A Systematic Review and Meta-analysis. Mayo Clin Proc 2015; 90:469-480. PMID: 25841251

Chapter 07

Telerehab III Long-term:

Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits

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Abstract

Background. Finding innovative and cost-efficient care strategies that induce long-term health benefits in cardiac patients constitutes a big challenge today. The aim of this Telerehab III follow-up study was to assess whether a 6-month additional cardiac telerehabilitation program could induce long-term health benefits and remain cost-efficient after the tele-intervention ended.

Methods and results. 126 cardiac patients first completed the multi-center, randomized controlled telerehabilitation trial (Telerehab III, time points: t0 to t1). They consequently entered the follow-up study(t1) with evaluations 2 years later(t2). A quantitative analysis of peak aerobic capacity (VO2 peak, primary endpoint), IPAQ self-reported physical activity and HeartQoL quality of life (secondary endpoints) was performed. The incremental cost-effectiveness ratio was calculated. Even though a decline in VO2 peak (24 ± 8 ml/[min*kg] at t1 and 22 ± 6 ml/[min*kg] at t2,p=< 0.001) was observed within the tele-intervention group patients, overall they did better than the no tele-intervention group (p=0.032). Dividing the incremental cost (- 878€/patient) by the differential incremental QALYs (0.22QALYs) yielded an incremental cost-effectiveness ratio of – 3,993 €/QALY.

Conclusions. A combined telerehabilitation and center-based program, followed by transitional telerehabilitation induced persistent health benefits and remained cost-efficient up to two years after the end of the intervention. Partial decline of the benefits originally achieved, did occur once the tele-intervention ended. Healthcare professionals should reflect on how innovative cost-efficient care models could be implemented in standard care. Future research should focus on key behavior change techniques in technology-based interventions that enable full persistence of long-term behavior change and health benefits.

Introduction

The European Association of Preventive Cardiology in collaboration with the Acute Cardiovascular Care Association and the Council on Cardiovascular Nursing and Allied Professions described in their ESC Secondary Prevention after Acute Myocardial Infarction awareness campaign the possible role of novel care delivery strategies such as cardiac telerehabilitation [1-3]. They identified cardiac telerehabilitation as a supplement and/or alternative to conventional center-based services. Telerehabilitation is defined as the remote delivery of rehabilitation services via telecommunication technologies, including the phone, the internet and videoconference communication between the patient and healthcare provider. It encompasses a comprehensive program with multiple components such as telemonitoring, telecoaching and e-learning [5]. Two recent systematic reviews pooled primary studies comparing cardiac telerehabilitation with center-based CR and concluded the former to be non-inferior to the latter [6,7]. Huang et al. reviewed the effectiveness of mainly phone-based telehealth interventions versus center-based care in 1,546 low to moderate risk CAD patients [6]. They found no difference between the former and latter care delivery strategy for exercise capacity, cardiovascular risk factors, mortality, quality of life and psychosocial state. Hwang et al. compared remote rehabilitation with on-site care delivery in 908 CAD, CHF and/or respiratory disease patients [7]. Telerehabilitation was shown to be as effective as center-

based cardiac rehabilitation (CR) in terms of exercise capacity and quality of life. None of the included studies in these reviews however, assessed the effectiveness of an initial combination of telerehabilitation and center-based CR, followed by transitional telerehabilitation alone. A cost-effectiveness analysis, evaluating the cost-efficiency of telerehabilitation was rarely performed. Given the current healthcare era of budgetary constraints on the one hand and a large number of cardiovascular disease patients on the other hand, these types of analyses are encouraged. In the Telerehab III trial, we previously showed that supplementary cardiac telerehabilitation was more effective, when compared to conventional center-based CR alone [8,9]. With this Telerehab III follow-up study, we assessed whether an initially combined telerehabilitation and center-based program, followed by transitional telerehabilitation (6 months telerehabilitation program) could induce long-term health benefits and remain cost-efficient once the tele-intervention has been stopped.

Methods

Study design and study population

This paper presents the results of Telerehab III's long-term follow-up study. Telerehab III (ISRCTN29243064) was a multi-center, prospective randomized controlled trial conducted in both Jessa Hospital (Hasselt), East Limburg Hospital (Genk) and St. Franciscus Hospital (Heusden-Zolder) in Belgium. The study protocol and short-term results were described previously in detail [10]. Briefly, 140 patients with coronary artery disease (CAD) and/or chronic heart failure (CHF) were included after eligibility screening and randomization (time point: t0). A central computerized randomization system, randomly assigned (1:1) them to a 6-month internet-based telerehabilitation program in addition to center-based rehabilitation (intervention group) or center-based rehabilitation alone (control group). After Telerehab III (time point: t1), 126 of them entered the long-term follow-up study (Figure 1). The follow-up study was conducted according to the principles stated in the Declaration of Helsinki (reviewed version 2008), local and national regulations. Its study protocol (15.83/cardio15.12) was approved by Jessa Ethics Committee. Written informed consent was obtained from all patients prior to enrollment. The Telerehab III follow-up study adheres to the relevant CONSORT standards of reporting.

Study intervention

Study intervention: the intervention group. The intervention group patients were randomized and enrolled at time point t0 (Figure 1), when they were half-way their classical 12-week center-based CR program. They then received the remaining 6 weeks of center-based CR and in addition 6 months of cardiac telerehabilitation (the Telerehab phase) (between time points: t0 and t1). During the initial 6 weeks of the Telerehab phase, patients thus received both center-based CR and telerehabilitation. In cardiac telerehabilitation, patients were provided with patient-specific exercise training prescriptions. They were instructed to self-monitor their activities by a commercially available accelerometer. They regularly uploaded the registered activity data to a secure Dutch

webpage (telemonitoring). Based on the uploaded data, a semi-automatic telecoaching system provided the patients weekly feedback on their performance via e-mail and/or SMS in Dutch. In addition, patients received weekly dietary and smoking cessation advice also by email and/or SMS in Dutch. The dietary telecoaching system included a module for arterial hypertension, diabetes mellitus, obesity and a healthy module. Patient cardiovascular risk factor profiling at the start of the study determined which dietary module was used for them. The Telerehab phase was followed by the long-term follow-up phase (between time points: t1 and t2), during which no tele-intervention was provided. The follow-up phase ended after the long-term follow-up study visit in 2016 (at time point: t2).

Study intervention: the control group. The control group patients were randomized and enrolled at time point t0 (Figure 1), when they were half-way their classical 12-week center-based CR program. They initially received the remaining 6 weeks of center-based CR (the No Telerehab phase), between time points t0 and t1. They never received telerehabilitation. The No Telerehab phase was followed by the follow-up phase (between time points: t1 and t2), during which no intervention was provided. The follow-up phase ended after the long-term follow-up study visit in 2016 (at time point: t2).

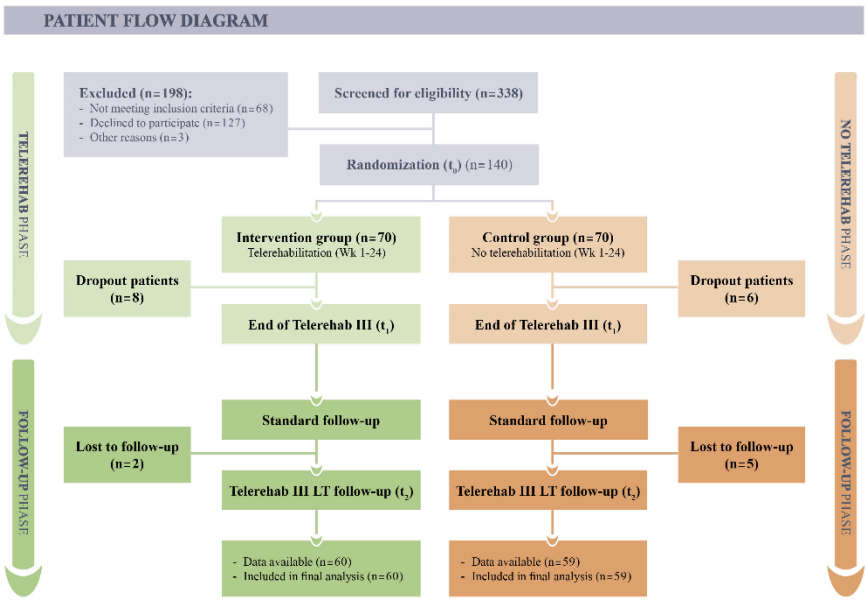

Figure 1. Patient flow diagram.

LT: long-term, t: time. Between the time points t0 and t1, the intervention group patients received cardiac telerehabilitation (Telerehab phase) whereas the control group patients did not (No Telerehab phase). During the Follow-up phase (t1 – t2), intervention and control group patients were followed-up but received no intervention.

Baseline demographics

The following demographical variables were documented at baseline: i. patient age (years), ii. patient gender (male, female), iii. ethnicity (Caucasian, black), iv. level of education (primary school, secondary school, university level), v. language (Dutch native, Dutch non-native), vi. smoking behavior (current smoker, prior smoker, non-smoker), vii. presence and/or absence of obesity, viii. presence and/or absence of diabetes mellitus, ix. presence and/or absence of hyperlipidemia, x. presence and/or absence of arterial hypertension, xi. presence and/or absence of familial history of cardiovascular disease, xii. presence and/or absence of peripheral artery disease, xiii. type of cardiac pathology (CAD, HFrEF, HFpEF), xiv. left ventricular EF, xv. presence and/or absence of atrial fibrillation.

Outcomes measurements

The primary endpoint was peak aerobic capacity (VO2 peak), measured during cardiopulmonary exercise testing (Jaeger MS-CPX) with breath-by-breath gas exchange analysis [11].

The secondary endpoints included self-reported physical activity, cardiovascular risk factor profile, self-reported health-related quality of life and cardiovascular readmission rate. The self-reported physical activity was assessed by the offline International Physical Activity Questionnaire (IPAQ) [12]. Metabolic equivalent task (MET) minutes were calculated by multiplying the minutes of a specific activity performed with predefined MET scores to weigh each activity by its energy requirement. A MET score of 3.3 METs was used for walking, 4.0 METs for moderate physical activity, and 8.0 METs for vigorous physical activity according to prior research [12]. Self-reported physical activity was converted to MET-min/week of vigorous and/or moderate and/or walking activities for all domains together. Fasting glycaemia, hemoglobin A1c (HbA1c), total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol/HDL-cholesterol ratio were measured by blood sampling. These biochemical markers, together with the patient's systolic blood pressure (SBP) and the diastolic blood pressure (DBP) constituted the cardiovascular risk factor profile. The 14-item offline HeartQoL questionnaire was used to assess health-related quality of life (HRQL) [13]. Mean (SD) and median [Q25-Q75] scores were calculated for both the physical (10-item) and the emotional (4-item) subscale. The proportion of patients at the floor (floor effect defined as the lowest possible score on the questionnaire) and at the ceiling (ceiling effect defined as the best possible score) was determined to assess sensitivity to positive and negative changes in HRQL. All outcome measurements were assessed by trial investigators (blinded to treatment allocation) at time points t0, t1 and t2.

Both day procedures, emergency visits (< 24 h) and hospital admissions (> 24h) were defined as readmissions. The principal study investigator retrieved all readmissions from the electronic health records in the recruiting hospitals. All identified readmissions were subsequently cross-checked with those on file in the patients' medical insurance records as confirmation. A Clinical Endpoint Committee (CEC), composed of three cardiologists from three different hospitals (not including the recruiting test beds), classified all readmissions to cardiovascular or non-cardiovascular. As independent assessors, blinded to treatment allocation, they provided physician reported diagnoses. The number of days lost due to cardiovascular readmissions, the proportion of actual to

theoretical days alive and out of hospital, and the time to first cardiovascular readmission were calculated.

Cost-effectiveness

The cost-utility analysis was performed from a patient and healthcare perspective. Quality adjusted life years (QALYs) were used as utility measure. Patient self-reported EQ-5D questionnaire scores were used and converted to QALYs (14). Both healthcare resource and intervention costs were included in the total cost calculation. Productivity losses were not taken into account, since the vast majority of study participants was retired. The combination of cardiovascular readmission costs, the costs due to cardiologist follow-up visits and performed diagnostic tests, constituted the healthcare costs. The readmission costs were derived from their invoices, which were retrieved from the hospitals' financial departments. The National Sickness and Invalidity Insurance Institution (RIZIV/INAMI) nomenclature-based tariffs quantified cardiologist follow-up visit and diagnostic test denominations. Intervention costs were defined as the aggregated costs of the center-based CR and the telerehabilitation program (for intervention group patients only). The RIZIV/INAMI's (dd. 01/2015) nomenclature code no. 771212 was used to determine the center-based CR cost.

Costs and outcomes (utilities) were compared, by calculation of the incremental cost-effectiveness ratio (ICER) (ICER = (Cost intervention group – Cost control group)/(Effectiveness intervention group-Effectiveness control group)). The incremental cost represents the difference in total average cost per patient between the intervention and control group. The incremental effectiveness was determined as the difference in average QALY change between the intervention and control group.

Statistical analysis

Data analysis was performed using SPSS v. 22 (SPSS Inc, Chicago, IL, USA), according to the intention-to-treat principle by assigned treatment group. All available data were used. No data imputation was performed for missing values, assuming that the reason for missing values was not related to the condition of the patient, nor to the treatment received. The sample size for Telerehab III (N = 140) was calculated based on the a priori sample size calculation to detect a 20% effect size in the primary outcome measurement (VO2 peak) between the intervention and the control group at the end of the (No)Telerehab phase (with a statistical power of 95% for a 2-sided t-test, working with type I error level of 0.05 and a dropout rate of 30%) [11]. The Shapiro-Wilk test was used to assess whether normal distribution was present. Nonparametric tests were used in case the normality assumption was violated. Independent t tests (parametric) or Mann-Whitney U tests (nonparametric) were used for between-group analyses. Repeated measures ANOVA (parametric) or Friedman's ANOVA (nonparametric) compared multiple dependent means. In case of significant Friedman's ANOVA tests, follow-up tests were performed to assess differences between each pair of time points. Bonferroni corrections were applied to correct for multiple testing. Data were

presented as both mean ± SD and median [Q25-Q75] in the supplementary appendices for reasons of completeness. P-values < 0.05 (two-sided) were considered statistically significant. Effect sizes for the HeartQoL questionnaire were reported using the standardized response mean methodology (standardized response mean=[A-B]/D, where A and B are the mean scores at time 2 and time 1, respectively, and D represents the score change standard deviation) [13]. Cumulative survival curves for the time-to-first cardiovascular readmission were constructed according to the Kaplan-Meier method. The difference between the two curves was assessed with the log-rank test statistic. The log-log plot and the comparison of curves for the different strata was used to confirm that the proportional hazards assumption was valid. The Cox regression model was applied to calculate the hazard ratio (HR), with treatment as the only covariate. Censoring was applied when the follow-up period terminated before the first cardiovascular readmission occurred.

Results

In total, 126 out of the initial 140 patients entered the long-term follow-up study (the dropout reasons were: technical problems (N = 1), logistic problems (N = 7), loss of interest (N = 1), new pathology (N = 1), other (N = 4)). 60 patients in the intervention group and 59 patients in the control group completed the follow-up phase. Intervention group patients (N = 62) (61 ± 9 years) were predominantly male (84%, N = 52). They suffered from hyperlipidemia (74%, N = 46) and arterial hypertension (56%, N = 35) in the majority of the cases. 45% (N = 28) of them smoked and 53% (N = 33) had a family history of cardiovascular disease. Control group patients (N = 64) (61 ± 8 years) were predominantly male (80%, N = 51). They suffered from hyperlipidemia (80%, N = 51) and arterial hypertension (63%, N = 40) in the majority of cases. 39% (N = 25) of them smoked and 53% (N = 34) had a family history of cardiovascular disease. Intervention group patients primarily suffered from CAD (n = 60, 96.8%), 1 (1.6%) and 1 (1.6%) were included for CHF with reduced and preserved ejection fraction, respectively. Control group patients also predominantly had CAD (n = 60, 94%), 4 (6%) and 0 (0%) suffered from CHF with reduced and preserved ejection fraction, respectively. The time between time point t0 and t2 was (mean ± SD, Median [IQR]) 816 ± 86, 821 [127] days in the intervention group and 831 ± 99, 846 [119] days in the control group, which was not different between both groups (U = 1638, z = - 0.552, p = 0.581).

Aerobic capacity

In the intervention group, VO2 peak increased during the Telerehab phase (t0: 22 ± 6 ml/[min*kg], t1: 24 ± 8 ml/[min*kg]) (χ2Friedman (2) = 0.500 , p = 0.043). It decreased between the end of the Telerehab phase (t1: 24 ± 8 ml/[min*kg]) and the end of the follow-up phase (t2: 22 ± 6 ml/[min*kg]) (χ2Friedman (2) = 0.938, p = < 0.001). The VO2 peak of the control group patients decreased progressively from the start of the No Telerehab phase (t0: 23 ± 6 ml/[min*kg]), to the end of the No Telerehab phase (t1: 22 ± 6 ml/[min*kg]) and to the end of the follow-up phase (t2: 20 ± 6 ml/[min*kg]) (χ2Friedman (2) = 31.080, p < 0.001). Overall

between-group analysis of aerobic capacity was significant in favor of the intervention group (U = 1936, z = 2.139, p = 0.032).

Physical activity

During the Telerehab phase, the summed vigorous and/or moderate and/or walking activities increased in the intervention group (t0: 6676 ± 8898 MET-min/week, t1: 7821 ± 6740 MET-min/week) (χ2Friedman (2) = 0.518, p = 0.018). It showed a non-significant downward trend during the Follow-up phase (t1: 7821 ± 6740 MET-min/week, t2: 6327 ± 6955 MET-min/week) (χ2Friedman (2) = 0.125, p = 1.000) (Figure 2). The summed vigorous and/or moderate and/or walking activities of control group patients decreased progressively from the start of the No Telerehab phase (t0: 8135 ± 8891 MET-min/week), to the end the No Telerehab phase (t1: 7200 ± 7720 MET-min/week) and to the end of the follow-up phase (t2: 5831 ± 6117 MET-min/week) (χ2Friedman (2) = 11.577, p = 0.003). Overall between-group analysis of the summed vigorous and/or moderate and/or walking activities was significant in favor of the intervention group (U = 1940, z = 2.566, p = 0.010).

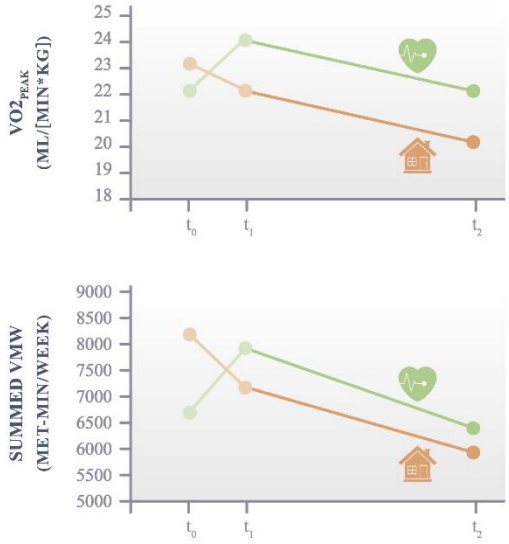

Figure 2. Line charts depicting mean VO2 peak (ml/[min*kg]) and mean vigorous-moderate-walking (VMW) activity for all domains (MET-min/week) for the start of the (No) Telerehab phase (t0), the end of the (No) Telerehab phase (t1) and the end of the follow-up phase (t2). The intervention group is represented by the heart icon and the control group by the cardiac rehabilitation center icon.

Cardiovascular risk factor profile

Overall, glycemic control did not change in the intervention group ($\chi 2F$ (2) = 0.927, p = 0.317), nor did it in the control group ($\chi 2$Friedman (2) = 4.521, p = 0.104). Total cholesterol levels increased progressively between the start of the (No) Telerehab phase, the end of the (No) Telerehab phase and the end of the follow-up phase in both the intervention and control group (t0: 136 ± 31 mg/dl, t1: 143 ± 28 mg/dl, t2: 149 ± 31 mg/dl, $\chi 2$Friedman (2) = 8.640, p = 0.013 and t0: 145 ± 42 mg/dl, t1: 154 ± 41 mg/dl, t2: 152 ± 43 mg/dl, $\chi 2$Friedman (2) = 8.317, p = 0.016 respectively).

Health-related quality of life

In the intervention group, the perceived HRQL for the physical subscale improved progressively from the start of the Telerehab phase (t0: 2.23 ± 0.67), to the end of the Telerehab phase (t1: 2.52 ± 0.52) and the end of the follow-up phase (t2: 2.72 ± 0.51) ($\chi 2$Friedman (2) = 32.000, p < 0.001). The standardized response mean of 0.29 (between t1 and t2) indicated a small effect size. The HRQL (physical subscale) of the control group patients did not change significantly between the start of the No Telerehab phase (t0: 2.27 ± 0.61), the end of the No Telerehab phase (t1: 2.28 ± 0.63), and the end of the follow-up phase (t2: 2.36 ± 0.69) ($\chi 2$Friedman (2) = 0.603, p = 0.740). Overall, between-group analysis confirmed that the intervention group's HRQL improved more than the control group (U = 2083, z = 2.808, p = 0.005).

Cardiovascular readmissions

At the end of the follow-up phase (t2), 92 cardiovascular readmissions were documented (60 in the control group, 32 in the intervention group) (U = 2,131, z = -1.600, p = 0.110). The average (95% confidence interval [CI]) time to first cardiovascular readmission was 1,014 [920–1,108] days for the intervention group and 894 [784–1,005] days for the control group (p = 0.155, HR 0.655 (0.364-1.178)) (Figure 3). The number of days lost due to cardiovascular readmissions in the intervention group (1.20 ± 0.27) was not significantly different from that in the control group (1.89 ± 0.39), U = 2,151, z = -1.496, p = 0.135. The proportion of actual to theoretical maximal days alive and out of hospital was not different in the intervention group, compared with the control group, U = 2,745, z = 1.470, p = 0.142.

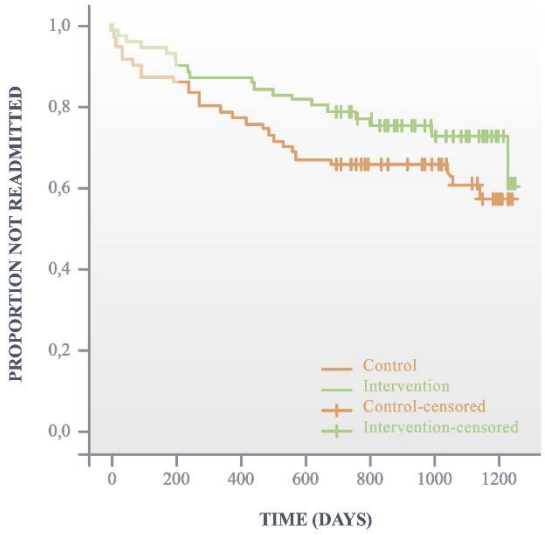

Figure 3. Time to first cardiovascular readmission.

Cost-effectiveness

The total average cost per patient in the intervention group was 3262 € ± 339 €, compared to 4140 € ± 513 € in the control group (Table 1). In the intervention group the quality-adjusted life years increased (average ΔQALY 0.07), in the control group they decreased (average ΔQALY -0.15). Dividing the overall incremental average cost per patient (- 878 €) by the incremental QALYs (0.22 QALYs) yielded an ICER of – 3993 €/QALY. The distribution of the points in the cost-effectiveness scatter plot (Figure 4) further illustrates that, the addition of the telerehabilitation program to center-based CR (intervention group) remained both cost-saving and more effective than center-based CR alone (control group) even after stopping the intervention (time point: t2).

Table 1. Incremental cost (intervention minus control) per quality adjusted life year.

	Control group			Intervention group		
Description of resource	Average cost per unit (€)	Average number of units	Average cost per participant (€)	Average cost per unit (€)	Average number of units	Average cost per participant (€)
Intervention costs						
Standard CR (RIZIV)	1373	1	1373	1373	1	1373
Standard CR (patient)	153	1	153	153	1	153
Study nurse	33	0	0	33	2	67
Accelerometer	40	0	0	40	1	40

Web page service	10	0	0	10	6	60
Info brochure	3	0	0	3	1	3
Healthcare costs						
CV rehospitalisations cost (RIZIV)	2106	0.9	1811	2383	0.5	1096
CV rehospitalisation cost (patient)	356	0.9	306	200	0.5	92
Specialist visit cost (RIZIV)	25	3.7	92	25	2.8	68
Specialist visit cost (patient)	12	3.7	45	12	2.8	33
Diagnostics cost (RIZIV)	35	9.3	324	34	7.3	250
Diagnostics cost (patient)	4	9.3	36	4	7.3	28
Total average cost per patient			4140			3262
Incremental cost (I-C) (€)	-878					
Average change in QALYs			-0.15			0.07
Incremental QALYs: 0.22						
ICER=(Cost I – Cost C)/(Effectiveness I – Effectiveness C) (€/QALY): -3993						
Comments: intervention more effective and efficient						

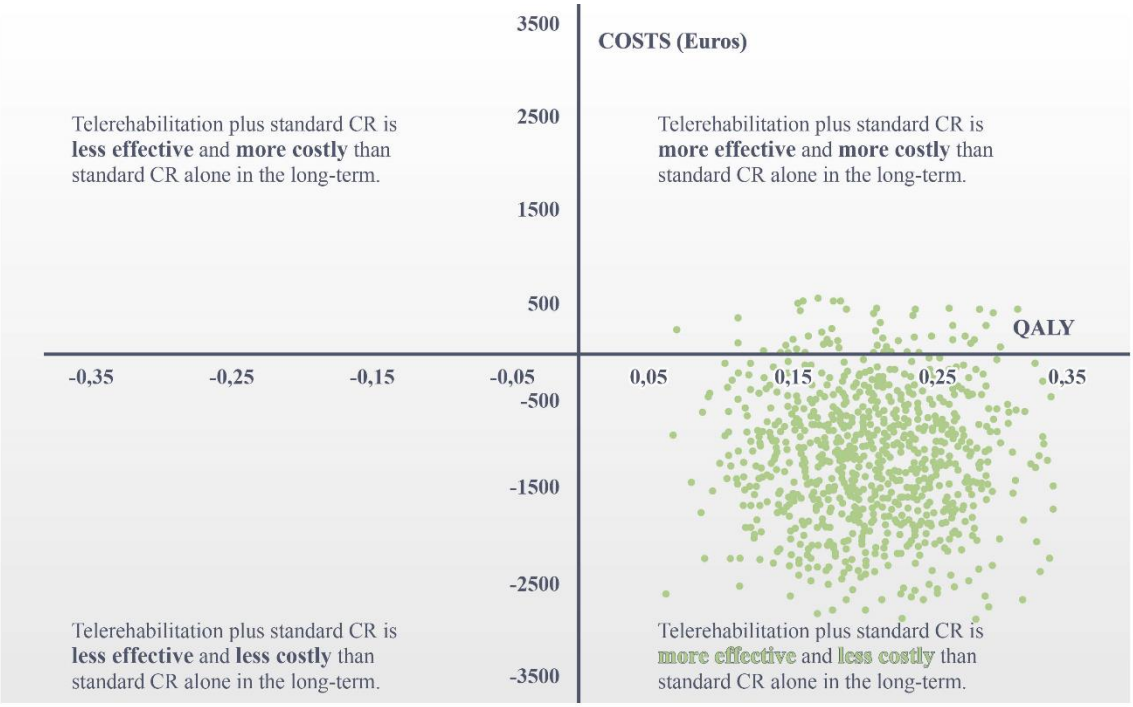

Figure 4. Cost-effectiveness plane scatter plot of incremental cost (€) and incremental quality-adjusted life years (QALYs), based on the bootstrap resampling method. CR: cardiac rehabilitation.

Discussion

This long-term follow-up study of Telerehab III showed that a firstly combined telerehabilitation and center-based program, followed by transitional telerehabilitation (6 months telerehabilitation program) can induce persistent health benefits, when compared to conventional center-based CR alone. During the follow-up phase however, the benefits demonstrated at the end of the Telerehab phase, were not fully maintained. Intervention group patients tend to partially relapse once the tele-intervention has been stopped, reflected by a partial loss of the improvements in both VO2 peak and the daily physical activities.

The difficulty of maintaining long-term lifestyle behavior change and its derived health benefits has been described previously [15]. Replacing an operant unhealthy lifestyle behavior with a new more healthy lifestyle behavior while the first is being extinguished can still allow relapse to occur. Extinction of the prior behavior can be thought of as producing a kind of behavioral inhibition. That is, the original behavior is still in the memory system. Although it is inhibited by the intervention (i.e. (tele-)rehabilitation program), it is ready to return under certain conditions. Furthermore, operant behaviors are always context-dependent to some extent [16]. It suggests that any new healthy behavior that a patient might have learned, might be disrupted merely by the change of context [17]. As evidenced by the Telerehab III long-term follow-up study, context change (i.e. termination of supervised cardiac telerehabilitation) resulted in partial relapse. Other hypothesized explanations for the lack of long-term behavior change persistence are i. lack of caregiver supervision/interaction, ii. lack of self-monitoring and its derived insight in the patient's clinical

state, iii. lack of self-efficacy to sustain a healthy lifestyle, iv. shifting/changing decisional balance prone to relapse [18]. The identification of the key health behavior change techniques in technology-enabled interventions that can assure complete long-term persistence of behavior change however still remain largely unkown. Furthermore, future research should investigate whether a long-term, semi-automatic telerehabilitation program (with reduced supervisory caregiver intensity) could prevent the partial relapse documented in this long-term follow-up study.

The Telerehab III long-term follow-up study has several strengths, differentiating it from prior research in the field. To the authors' knowledge, it is the first trial assessing the long-term persistence of health benefits derived from a 6-months supplemental cardiac telerehabilitation program. Previous research on CR has recently been aggregated in two systematic reviews [6,7]. Huang et al. reviewed the effectiveness of telehealth interventions versus center-based care in 1,546 low to moderate risk CAD patients and the former to be non-inferior to the latter for exercise capacity, systolic and diastolic blood pressure, lipid profile and mortality [6]. Hwang et al. compared remote rehabilitation with on-site care delivery in 908 cardiopulmonary disease patients and found the former to be equally effective as the latter for exercise capacity and quality of life. Contrasting the primary studies in these two reviews is that the Telerehab III study and its long-term follow-up study assessed the cost-effectiveness of supplemental cardiac telerehabilitation to center-based CR. Another novelty of the Telerehab III follow-up study is that it assesses the long-term benefits of an initial combined telerehabilitation and center-based CR program, followed by transitional telerehabilitation (6 months telerehabilitation program) once the tele-intervention has been ended. It addresses one of the biggest challenges in chronic cardiovascular care: "How to successfully make the transition from a supervised CR program to the patients' daily life easier, getting better outcomes and adherence to healthy lifestyle in the long-term?". This contrasts prior telerehabilitation related evidence, that lacks data regarding long-term persistence of derived benefits. The Telerehab III follow-up study included a predefined and EUnetHTA compliant health technology assessment type cost-utility analysis. Study data on use of healthcare services were derived from administrative records rather than patient self-report, thereby avoiding recall bias. The quality of life data were collected directly from the patients by the use of a validated tool [14]. The importance of including a cost-utility analysis is underscored by the fact that large-scale deployment of innovative care strategies is impossible without prior proof of its cost-efficiency.

The contemporary healthcare era is indeed characterized by increasing resource constraints on the one hand, but a large number of chronic cardiovascular disease patients on the other hand. This underscores the need for innovative care delivery strategies that enable persistent health benefits and that are cost-efficient also in the long-term. This Telerehab III follow-up study confirmed that a supplemental 6-month cardiac telerehabilitation program remains cost-efficient even 2 years after ending the tele-intervention (i.e. at the end of the follow-up phase – t2). Up until today, other research assessing the cost-effectiveness of cardiac telerehabilitation remains scarce. The Teledialog study evaluated the cost-utility of cardiac telerehabilitation in 151 CAD, CHF and/or valve surgery patients [19]. Based on the calculated ICER of > 400,000 € per QALY gained, cardiac telerehabilitation was concluded not to be cost-effective. The Birmingham Rehabilitation Uptake Maximisation Study (BRUM) [20] compared the costs of a home-based CR program using the Heart Manual with center-based care in a total of 525 CAD patients. The direct rehabilitation costs to the

health service were higher for the home-based program (mean cost 234 €), when compared to center-based care (mean cost 186 €). The discrepancy between the Teledialog, the BRUM and the Telerehab III follow-up study has several explanations. First of all contrary in BRUM and Teledialog, the telerehabilitation patients received home-based CR only and never stepped foot into a center-based CR program. This contrasts to Telerehab III in which intervention group patients initially received both center-based CR and telerehabilitation, making it harder to compare this study with BRUM and Teledialog. Differences in the telerehabilitation and center-based CR programs provided in the respective trials are a second explanation. Clear definitions and standardization of telemedical care program content and/or core components are mandatory but lacking. Future research should focus on the identification of telemedical care models that prove to be the most successful and cost-efficient at the same time. The elaboration of European guidelines, describing and defining what constitutes the ideal cardiac telerehabilitation program would be extremely valuable in this regard.

A potential limitation of our study is that it is reflective of the Belgian situation. The structure, content, duration, intensity and volume of CR however, varies widely both between and within different countries, as do the costs of healthcare. Female and black patients were relatively underrepresented, as were HFrEF/HFpEF patients compared to CAD patients. This restricts the generalizability of the study findings to other healthcare settings and patient populations, especially for the health economic calculations. It indicates the relevance of future large-scale and European-wide clinical trials assessing the efficacy and cost-efficiency of telerehabilitation in different demographical and socio-economical settings. In the follow-up study, we noted a trend towards a lower cardiovascular readmission rate in the tele-intervention group. As the study was powered to detect a difference in aerobic capacity and not cardiovascular readmission rate, this observation must be interpreted with caution and considered exploratory.

To conclude: This Telerehab III long-term follow-up study demonstrated that a 6-month cardiac telerehabilitation program added to classical CR induces a better exercise capacity, a better adherence to healthy lifestyle behaviors and quality of life, while remaining cost-efficient in the long-term, when compared to center-based CR alone. Partial decline of the achieved health benefits did occur once the tele-intervention ended. These findings have high clinical and public health policy impact. Current restrictions in healthcare budgets impose great difficulties to enable the provision of qualitative secondary prevention to all cardiac patients in an era facing a huge cardiovascular disease epidemic. Innovative care strategies, exemplified by remote tele-intervention programs, have the potential to improve cost-efficiency and to target an increasing number of eligible patients. Healthcare providers together with policy makers and other relevant stakeholders should be encouraged to reflect on how innovative cost-efficient care delivery models can be implemented in standard cardiac care. Future research efforts should focus on the key health behavior change techniques in technology-based interventions that enable full persistence of long-term behavior change. Comprehensive, large-scale and European-wide long-term clinical trials assessing cardiac telerehabilitation in varying healthcare settings are encouraged.

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References

[1] European Heart Network, www.ehnheart.org/cvd-statistics.html (27 July 2016)

[2] Task FM, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the managemenet of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34(38):2949-3003.

[3] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016 [Epub ahead of print].

[4] Piepoli MF, Corrà U, Dendale P, et al. Challenges in Secondary Prevention after Acute Myocardial Infarction: A Call for Action. Eur J Prev Cardiol 2016; [Epub ahead of print]

[5] Frederix I, Vanhees L, Dendale P, et al. A review of telerehabilitation for cardiac patients. J Telemed Telecare 2015;21(1):45-53.

[6] Huang K, Liu W, He D, et al. Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2015;22(8):959-971.

[7] Hwang R, Bruning J, Marris N, et al. A systematic review of the effects of telerehabilitation in patients with cardiopulmonary diseases. J Cardiopulm Rehabil Prev 2015;35(6):380-9.

[8] Frederix I, Hansen D, Coninx K, 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.

[9] Frederix I, Hansen D, Coninx K, et al. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization rate, medical costs and quality of life: A cost-effectiveness analysis. Eur J Prev Cardiol 2016;23(7):674-82.

[10] Frederix I, Hansen D, Coninx K, et al. Telerehab III: a multi-center randomized, controlled trial investigating the long-term effectiveness of a comprehensive cardiac telerehabilitation program – Rationale and study design. BMC Cardiovasc Disord 2015;15:29.

[11] Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167(10):1451.

[12] Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381-95.

[13] Oldridge N, Höfer S, McGee H, et al. The HeartQoL: part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol 2014;21(1):98-106.

[14] Ellis JJ, Eagle KA, Kline-Rogers EM, et al. Validation of the EQ-5D in patients with a history of acute coronary syndrome. Curr Med Res Opin 2005;21:1209-1216.

[15] Bouton ME. Why behavior change is difficult to sustain? Prev Med 2014;68:29-36.

[16] Bouton ME, Todd TP, Leon SP. Contextual control of discriminated operant behavior. J Exp Psych Anim Learn Cogn 2014;40:92-105.

[17] Todd TP, Winterbauer NE, Bouton ME. Effects of amount of acquisition and contextual generalization on the renewal of instrumental behavior after extinction. Learn Behav 2012;40:145-157.

[18] Marshall SJ, Biddle SJ. The transtheoretical model of behavior change: a meta-analysis of applications to physical activity and exercise. Ann Behav Med 2001;23(4):229-46.

[19] Kidholm K, Rasmussen MK, Andreasen JJ, et al. Cost-Utility Analysis of a Cardiac Telerehabilitation Program: The Teledialog Project. Telemed J E Health 2016;22(7):553-63

[20] Taylor RS, Watt A, Dalal HM, et al. Home-based cardiac rehabilitation versus hospital-based rehabilitation: A cost effectiveness analysis. Int J Cardiol 2007;119:196–201.

Chapter 08

FIT@Home editorial: Supporting a new era of cardiac rehabilitation at home?

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Ischemic heart disease remains prevalent in Europe: among patients surviving an acute coronary event, up to 20% suffer a repeat event in the first year [1]. Secondary prevention, by means of multidisciplinary cardiac rehabilitation (CR), is recommended by the European Society of Cardiology (ESC) to reduce morbidity and mortality[2-3]. Center-based or outpatient CR has a Class I, Level B indication for ST-segment elevation myocardial infarction (STEMI) patients[2], a Class IIa, Level A indication for non ST-segment elevation myocardial infarction (NSTEMI) patients[3]. Despite the proven effectiveness of conventional center-based programs and the ESC recommendations, long-term benefits remain disappointing due to inadequate uptake and adherence[4]. Innovations in information technologies enabled the advent of cardiac tele-rehabilitation, an innovative care delivery strategy allowing ischemic heart disease patients to rehabilitate in their own environment[5]. It was recently identified by the European Association of Preventive Cardiology as a promising new way to deliver secondary prevention[6]. The need for additional clinical research assessing (cost)effectiveness was underscored.

The FIT@Home study is a randomized, controlled clinical trial, comparing home-based (HB) with center-based (CB) CR[7] in ischemic heart disease patients (n=90). HB patients entered a 3-month exercise training program at home, supervised remotely by heart rate and physical activity telemonitoring. They received weekly feedback on training frequency, duration and intensity via telephone. The CB group patients received a 3-month CR program in the outpatient rehabilitation center. The primary endpoint was peak aerobic capacity. Secondary endpoints included Health-related Quality of Life (HRQoL), patient satisfaction and exercise training adherence. A cost-utility analysis was performed, using a societal perspective. All outcome measures were assessed at baseline, after the 3-month CR program and at one-year follow-up. The results of FIT@Home indicate that patients in both groups improved VO2 peak and HRQoL (physical subscale) from baseline to discharge from CR and to one year, without between-group differences. The average costs per patient were €3160 lower for patients in the HB group. The authors conclude that home-based training with telemonitoring guidance is a useful alternative to conventional center-based training for low-to-moderate risk ischemic heart disease patients.

In the recently published Telerehab III trial we observed a difference in favor of the patients receiving telerehabilitation[8,9]. Telerehab III was a randomized controlled clinical trial (n = 140) comparing the efficacy and cost-efficiency of a 24-week telerehabilitation program in addition to conventional CR versus conventional CR alone. The patients receiving telerehabilitation improved more in physical fitness and HRQoL and the total cost per patient was significantly lower.

These two studies nicely complement each other showing that this novel care delivery strategy has the potential to improve or replace classical center based CR: improved uptake and adherence can be expected for an intervention that does not interfere with daily life, as transport, availability, cost and return to work are often quoted as reasons not to participate.

Although these results indicate telerehabilitation to be successful for ischemic heart disease patients in research settings, we cannot predict how this will translate into clinical practice and/or affect patient outcomes and costs. As acknowledged in the ESC e-Health position statement, ensuring adequate integration of new technologies into the healthcare system is difficult[10]. In the past, the implementation of several technology-based solutions has failed due to their inherent

tendency to disrupt existing workflow patterns. Integration of telemedical care models in routine practice implies changing roles and responsibilities for healthcare staff and requires profound service redesign[11]. This underscores the importance of training programs for all caregivers to define these new responsibilities, to clarify how the new way of care delivery will change current workflow and to aid them in adopting and applying the technologies. Adequate patient education in order for them to get acquainted with the new technologies and/or to understand their position in this more patient-centric care model is paramount.

Upfront clear and detailed descriptions of the telemedical program content and its primary goal are needed in order to ascertain successful implementation. Specific, measurable, attainable and relevant outcome and/or process metrics should be defined and (re-)assessed on a regular basis to monitor improvement but also to adapt/abandon and/or remediate ineffective interventions.

Consideration of contextual factors related to the implementation of telemedical care is important. Both the FIT@Home and Telerehab III study are reflective of the situation in one country, for patients with a specific type of illness and sufficient ability to interface with the technology used. The variation in structure, content and duration of standard CR between different (non-) European countries may limit the external validity of the study findings to other healthcare settings that are geographically, demographically and socio-economically different. One should be cautious, to avoid simplistic extrapolation of reported benefits of cardiac telerehabilitation to related but differing patients populations.

There remain significant barriers to providing telemedical care: lack of reimbursement, compliance of available eHealth solutions with EU regulations for telemonitored data[12-13] and liability concerns, as well as healthcare provider resistance[14].

Future research should include large-scale and long-term European-wide clinical trials, evaluating the efficacy of cardiac telerehabilitation with hard clinical endpoints in different demographical and socio-economical settings[15]. EUnetHTA (European network for Health Technology Assessment) compliant and comprehensive economic evaluations are needed in order to prove the value of telehealth to healthcare consumers and demonstrate return on investment. An improved description of telehealth intervention components, a clear and shared taxonomy on outcome and/or process metrics and profound study of the necessary resulting workflow redesign is mandatory. As eHealth technologies comprise complex interventions, standard evaluative methodologies (such as RCT's) alone may not be sufficient to assess their impact in a complex socio-technical environment and the effect they have on the delivery of care[16]. Therefore, more comprehensive evaluation approaches, encompassing continuous evaluations throughout the lifecycle of an eHealth intervention should be encouraged[17]. Recurrent interim evaluation at the key stages provide a way to understand the implementation process better.

References

[1] Pedersen F, Butrymovich V, Kelbaek H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol 2014; 64(20):2101-2108

[2] Steg G, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-2619.

[3] Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37: 267-315.

[4] Kotseva K, Wood D, De Bacquer D, 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):636-48.

[5] Frederix I, Vanhees L, Dendale P, et al. A review of telerehabilitation for cardiac patients. J Telemed Telecare 2015;21(1):45-53.

[6] Piepoli MF, Corrà U, Dendale P, et al. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur J Prev Cardiol 2016;23(18):1994-2006.

[7] Kraal JJ, Van den Akker-Van Marle E, Abu-Hanna A, 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; [Epub ahead of print].

[8] Frederix I, Hansen D, et al. Medium-term effectiveness of a comprehensive internet-based and patient-specific telerehabilitation program with text messaging support for cardiac patients: randomzes controlled trial. J Med Internet Res 2015;17(7):e185.

[9] Frederix I, Hansen D, et al. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization arte, medical costs and quality of life: a cost-effectiveness analysis. Eur J Prev Cardiol 2016;23(7):674-82.

[10] Cowie MR, Bax J, Bruining N, et al. e-Health: a position statement of the European Society of Cardiology. Eur Heart J 2016;37:63-66.

[11] McLean S, Protti D, Sheikh A. Telehealthcare for long term conditions. BMJ 2011;342:d120.

[12] Regulation (EU) 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). [http://ec.europa.eu/justice/data-protection/reform/files/regulation_oj_en.pdf]

[13] Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications). [http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0058:en:HTML]

[14] Davidson E, Simpson C, Demiris G, et al. Integrating telehealth care-generated data with the family practice electronic medical record: qualitative exploration of the views of primary care staff. Interact J Med Res 2013;2(2):e29. doi: 10.2196/ijmr.2820.

[15] McLean S, Sheikh A, Cresswell K, et al. The impact of telehealthcare on the quality and safety of care: a systematic overview. PLoS One 2013;8(8):e71238.

[16] Cresswell K, Blandfrom A, Sheikh A. Drawing on human factors engineering to reconsider paradigms for evaluating the effectiveness of health information technology. J Roy Soc Med (in press).

[17] Catwell L, Sheikh A. Evaluating eHealth interventions: the need for continuous systematic evaluation. PLoS Med 2009;6:e1000126.

Chapter 09

General discussion

General discussion

In this thesis we investigated the value of cardiac telerehabilitation in secondary prevention for ischemic heart disease.

We started this investigation by conducting a literature review of telerehabilitation interventions in patients with coronary artery disease, heart failure and/or cardiac surgery [1]. In most of the studies, the comparison of telerehabilitation with classical center-based cardiac rehabilitation yielded positive results for telerehabilitation with regard to feasibility, acceptance and efficacy. Telemedical care was favoured in terms of adherence to physical activity guidelines, and the risk for adverse events and cardiovascular readmissions. However, articles including health technology compliant cost-effectiveness analyses and/or safety assessments were scarce. Also the tele-interventions provided in the included studies mainly consisted of only one tele-component (i.e. telecoaching, telemonitoring, e-learning and/or social networking). These encouraging findings constituted the rationale for the conduct of Telerehab II [2] and Telerehab III [3] (Long-Term), the two main studies performed as part of this PhD project.

The first aim of this thesis was to assess the effectiveness of additional physical activity telemonitoring in secondary prevention for coronary artery disease patients on improving exercise tolerance levels, daily physical activity levels, and reducing adverse events. Eighty low-to-moderate risk coronary artery disease patients were elegible and included in this prospective randomized controlled clinical trial after week six of their 12-week center-based cardiac rehabilitation program. The results of Telerehab II showed that in the intervention group VO2 peak increased significantly during study period, whereas this was not the case for the control group patients. Between-group analysis confirmed a significant difference between both groups in favor of the physical activity telemonitoring group. A trend towards a lower readmission rate was noted in favor of intervention group patients with N = 4 (12.5%) readmitted patients in the telemonitoring group and N = 9 (26.5%) in the control group at 125 days of follow-up. As patient readmissions are the key drivers of the healthcare related costs, this observed trend gave rise to the speculation that physical activity telemonitoring could have the potential to be a cost-effective care delivery strategy in secondary prevention for coronary artery disease patients. Although Telerehab II showed promising results, it had some shortcomings. Only one compornent of a comprehensive cardiac telerehabilitation program (i.e. telemonitoring) was applied, focusing solely on physical activity. It could therefore be hypothesized that even more gains could have been achieved by applying a more comprehensive telerehabilitation program, including also other components (e.g. telecoaching, e-learning, social networking) and focusing not only on physical activity but also on nutitional counseling, smoking cessation, risk factor control, etc.

The second and third aim of this thesis were to evaluate the effectiveness and cost-efficiency of additional comprehensive cardiac telerehabilitation in coronary artery disease patients both at medium- and long-term follow-up. The Telerehab III (Long-term) study was designed, developed and conducted in order to achieve these aims. Telerehab III was a multi-center, Belgian, randomized, controlled clinical trial assessing comprehensive cardiac telerehabilitation in both coronary artery disease patients, as well as patients with heart failure reduced ejection fraction and preserved ejection fraction.

The results of Telerehab III showed that the aerobic capacity of the telerehabilitation group patients increased significantly from baseline to 24 weeks, where this was not the case in the control group. Between-group analysis was significant in favor of the intervention group. As a secondary endpoint and surrogate marker for aerobic capacity, the IPAQ self-reported physical activity data were also collected and assessed. It was shown that summed vigorous-moderate-walking leisure activities increased significantly in the intervention group, but did not change in the control group. A pattern similar to that of aerobic capacity.

Cardiovascular risk factor profiling, including the measurement of weight, systolic blood pressure, diastolic blood pressure, HbA1c, fasting glucose and lipid levels, was also performed during the Telerehab III follow-up visits. The 14-item HeartQol questionnaire was used to assess patients' health-related quality of life at the respective patient visits. Results of the data on cardiovascular risk factors indicated that additional cardiac telerehabilitation did not have a significantly favorable effect on weight, systolic blood pressure, diastolic blood pressure, fasting glucose, HbA1c and LDL-cholesterol. Intervention group patients did show a significant improvement in health-related quality of life for the physical subscale, control group patients did not.

In total 23 patients were rehospitalized for cardiovascular reasons (N = 7, 10% in the intervention group, N = 16, 23% in the control group). The numer of days lost due to cardiovascular readmissions was significantly lower in the intervention group. The cost-utility analysis, indicated additional cardiac telerehabilitation to be cost-effective when compared to classical center-based cardiac rehabilitation alone (ICER = - 21,707 €/QALY).

Telerehab III Long-term represented the long-term follow-up study of Telerehab III. No interventions were provided nor to intervention group, nor to control group patients during the follow-up study. This follow-up study showed that a firstly combined telerehabilitation and center-based program, followed by transitional telerehabilitation (6 months telerehabilitation program) can induce persistent health benefits, when compared to conventional center-based cardiac rehabilitation alone. During the follow-up phase however, the benefits demonstrated at the end of the Telerehab phase, were not fully maintained. Intervention group patients tend to partially relapse once the tele-intervention has been stopped, reflected by a partial loss of the improvements in both VO2 peak and the daily physical activities [3].

The majority of other similar research studies on telerehabilitation in IHD have recently been summarized in three systematic reviews and meta-analyses [4-6]. *Rawstorn J, et al.* compiled in his review 11 studies (N = 1189) assessing the benefits of telehealth, exercise-based cardiac rehabilitation on exercise capacity and cardiovascular risk factors, when compared to traditional cardiac rehabilitation in IHD patients [5]. Telehealth, exercise-based cardiac rehabilitation was shown to be non-inferior for improving maximal aerobic exercise capacity, systolic blood pressure, total cholesterol, HDL-cholesterol and triglycerides, when compared to center-based cardiac rehabilitation. *Huang K, et al.* performed a similar review, comparing the effectiveness of telehealth intervention delivered cardiac rehabilitation with center-based cardiac rehabilitation in IHD [4]. 9 studies (N = 1546) were included in the review. Telehealth intervention delivered cardiac rehabilitation was defined as a structured community- or home-based exercise program, delivered by any form of follow-up technology (telephone, computer, internet, or video-conferencing).

Primary endpoints included short-term all-cause mortality, cardiovascular risk factors, exercise capacity and health-realted quality of life. Telehealth intervention delivered cardiac rehabilitation appeared to be not significantly inferior in low to moderate risk IHD patients for the predefined outcome measures. It was concluded that telehealth interventions offer alternative care delivery models for cardiac rehabilitation especially for patients with restricted access to the classical cardiac rehabilitation centers. *Claes J, et al.* pooled in their systematic review all relevant studies comparing home-based and center-based exercise cardiac rehabilitation interventions in IHD [6]. Primary endpoints were exercise capacity and physical activity at long-term follow-up (defined as ≥ 12 months), differentiating it from the two other reviews. The main conclusion was that there were only very few studies eligible for inclusion in the review, hence rendering it difficult to draw general conclusions about the long-term efficacy of home-based cardiac rehabilitation.

A general reflection and comparison between the Telerehab II and III results on the one side and the other recently published reviews on the other side learns us some interesting findings. Both the Telerehab II and III trial investigated the (cost-)efficiency of additional cardiac telerehabilitation, whereas in the reviews most of the time a head-to-head comparison of telerehabilitation versus center-based rehabilitation was conducted. The tele-program content in the reviews mainly focused on physical activity telemonitoring, whereas in Telerehab III a more comprehensive approach was applied. The long-term follow-op of Telerehab III, can be differentiated from the studies included in the reviews that predominantly report study data in a short- to medium-term.

What do we learn from all this evidence?

The first thing we learned is that low- to moderate- risk IHD patients treated with center-based cardiac rehabilitation and in addition telerehabilitation, perform better than the same patients receiving only center-based cardiac rehabilitation with respect to aerobic capacity, physical activity level and cardiovascular readmission rate. The long-term benefits of additional cardiac telerehabilitation, partially disappear once the tele-intervention is stopped. Head-to-head comparison of center-based cardiac rehabilitation and telerehabilitation in IHD patients shows the latter to be non-inferior to the former. Research assessing the long-term benefits of cardiac telerehabilitation, and studies that include cost-effectiveness evaluations remain scarce.

Contemporary challenges

As described in this thesis, additional cardiac telerehabilitation has been proven to be effective and cost-efficient in the medium-term for IHD patients. In the contemporary era of budgetary constraints, it can thus be perceived as a valuable new care delivery strategy. Several challenges however currently limit its large-scale deployment in clinical practice.

In the majority of European countries, e-health care applications are not yet reimbursed, preventing the widespread adoption of these innovative care delivery strategies. The World Health Organization (WHO)’s e-health report confirmed that in the WHO European region, 50% of its member states identified insufficient funding as a main barrier for e-health adoption [7]. The

European Commission stated in its e-health Action Plan 2012-2020 however, to put a focus on funding of e-health services, tackling the reimbursement challenge [8].

Physicians' resistance to e-health application in daily practice is another challenge, currently hindering its large-scale adoption. Theoretically, innovations in the field of information and telecommunication technologies, allow for easier daily patient monitoring and follow-up when compared to traditional care involving face-to-face contact. Contrasting this is the perception of healthcare staff that too much time will have to be devoted to review all incoming patient data, resulting in an increased workload [9]. Dedicated telemonitoring nurses and/or physiotherpists can aid within this regard. Lack of the adequate infrastructure, lack of financial incentives and/or patient data safety and security issues, are also sometimes quoted as barriers for healthcare provider adoption [10].

Not only physicians, but also patients are sometimes reluctant to the use of e-health applications. As telemedical care is characterized by fewer face-to-face time, it is often perceived as too inpersonal in nature and hence inferior to traditional care [11]. Lack of appropriate patient training and education about how to use the telemonitoring sensors, m-healths apps, etc. is an additional barrier. Concerns related to patient personal data leakages to private industrial partners render some patients afraid to use e-health applications.

Telerehabilitation in secondary prevention of IHD has been proven effective in a research setting. However, its actual implementation in clinical practice will result in significantly altered workflow patterns. It implies amongst other things changing roles and responsibilities of both patients and healthcare providers. It is therefore impossible to predict how its implementation in daily clinical practice will be.

Compliance of e-health applications to relevant personal sensitive data regulations hinders its adoption. Regulation 2016/679 [12], the General Data Protection Regulation, will come into action on May 25, 2018. This regulation defines how personal sensitive data need to be handled, and what restrictions apply. The ePrivacy directive (2002/58/EC) [13], describes the personal sensitive data risks and protection mechanisms, focusing on data minimization and purpose limitation.

Most e-health solutions are still stand-alone solutions, not capable to communicate with the patients' electronic medical records. Interoperability difficulties between different e-health devices/solutions are still existant today. Data standardization and addressing the other technical constraints, typical for e-health apps is a prerequisite for large-scale deployment.

Future research

This thesis assessed the efficacy and cost-efficiency of additional cardiac telerehabilitation in secondary prevention for IHD. The core clinical trials of this PhD, Telerehab II & Telerehab III (Long-term), were Belgian prospective, randomized cotrolled clinical trials. The Telerehab II study focused mainly on physical activity telemonitoring. In Telerehab III, a more comprehensive e-health program with both physical activity telemonitoring and nutritional/smoking cessation

telecoaching was investigated. The studies performed however, are only the first avenue to future scientific research in the field.

Since both Telerehab II and Telerehab III included only Belgian recruiting hospitals, one can argue that its results are reflective only of the Belgian situation. In order to enable generalizability of study results to other (European) countries with different socio-demographical characteristics, future research should include larger-scale, European-wide clinical trials with hard clinical endpoints [14]. Clinical trials with longer follow-up periods are also encouraged given the risk of attrition.

Telerehabilitation in its most comprehensive format focuses on all cardiac rehabilitation core components (exercise training, nutritional & vocational counselling, cardiovascular risk factor control, patient education, psychosocial management) and includes both telemonitoring, telecoaching, e-learning and social interaction. In contrast to (physical activity) telemonitoring and telecoaching, the role of e-learning has only rarely been assessed in IHD. Given the importance of patient education, future research should evaluate e-learning strategies. The eEduHeart 1 study will be one of the first milestone studies in this regard [15]. eEduHeart 1 is a multi-center, prospective, randomized controlled clinical trial (N = 1000 patients) assessing the efficacy of an e-learning program in IHD. The primary study endpoint is health-realted quality of life. Secondary endpoints include disease-related knowledge, e-learning platform usage and feasibility.

Prior research in the field of telerehabilitation in general, included primarily classical randomized, controlled clinical trials (RCT's) [4-6]. As e-health technologies comprise complex interventions, standard evaluative methodologies (such as RCT's) alone may not be sufficient to assess their impact in a complex socio-technical environment and the effect they have on the delivery of care [16]. More comprehensive evaluation approaches, encompassing continuous evaluations throughout the lifecycle of an e-health intervention and big data should be encouraged [17]. Implementation research and recurrent interim evaluations at the key stages provide a way to evaluate the implementation process better.

Physical activity telemonitoring constituted an important part of the tele-intervention in both the Telerehab II and III study. A commercially available motion sensor (i.e. accelerometer) was used in both studies. Today a lot of different motion sensors are commercially available, and it is difficult for a clinician/researcher to differentiate between the sensors (in terms of data quality and accuracy). Based on the findings of my own prior research [1], I know that in general accelerometers are more accurate than pedometers and should be used preferentially in clinical trials/practice. However, profound assessments that compare the vast amount of available sensors and validate them in relation to patient self-reported physical activities (e.g. by IPAQ questionnaires) is lacking today. Future research efforts should try to address this issue, since accuracy and valdation of wearables to measure activity is highly relevant.

Conclusion

In this thesis we have evaluated the medium-term effectiveness of additional physical activity telemonitoring (Telerehab II). We also assessed the medium- and long-term effectiveness and cost-efficiency of additional comprehensive cardiac telerehabilitation (Telerehab III Long-term) in secondary prevention for IHD, when compared to center-based cardiac rehabilitation alone. We showed that additional physical activity telemontoring is more effective to improve an IHD patient's physical fitness, compared to traditional care alone. Additional comprehensive cardiac telerehabilitation is superior to only center-based cardiac rehabilitation on improving physical fitness, quality of life and on reducing cardiovascular events. It is an innovative and cost-efficient mode of healthcare delivery in secondary prevention of IHD. Long-term efficacy and cost-efficiency data indicate that the attained benefits partially disappear once the tele-intervention is no longer provided.

The contemporary healthcare era is characterized by an increasing prevalence of diseases that need chronical management, but budgetary constraints on the other hand. We believe that our work is important because it has provided the avenue towards novel remote care strategies that can be applied to address the patients not able and/or willing to attend center-based/hospital-based care, hopefully decreasing the global burden of cardiovascular disease.

References

[1] Frederix I, Dendale P, Berger J, et al. Comparison of two motion sensors for use in cardiac telerehabilitation. J Telemed Telecare. 2011;17(5):231-4. PMID: 21565845

[2] Frederix I, Van Driessche N, Hansen D, et al. Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients. Eur J Prev Cardiol. 2015 Feb;22(2):150-8. PMID: 24249840

[3] Frederix I, Solmi F, Piepoli MF, et al. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. Eur J Prev Cardiol. 2017 Nov;24(16):1708-1717. PMID: 28925749

[4] Huang K, Liu W, He D, et al. Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: A systematic review and meta-analysis. Eur J Prev Cardiol 2015;22(8):959-71. PMID: 25488550

[5] Rawstorn JC, Gant N, Direito A, et al. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. Heart 2016;102(15):1183-92. PMID: 26936337

[6] Claes J, Buys R, Budts W, et al. Longer-term effects of home-based exercise interventions on exercise capacity and physical activity in coronary artery disease patients: A systematic review and meta-analysis. Eur J Prev Cardiol 2017;24(3):244-256. PMID: 27798366

[7] WHO Regional Office for Europe. From innovation to implementation - e-Health in the WHO European Region. 2016. Available at: (http://www.euro.who.int/en/health-topics/Health-systems/e-health/publications/2016/from-innovation-to-implementation-e-Health-in-the-who-european-region-2016).

[8] European Commission. e-Health Action Plan 2012–2020. Innovative healthcare for the 21st century. 2012; 736 final. Available at: ⟨https://ec.europa.eu/digital-single-market/en/news/e-Health-action-plan-2012-2020-innovative-healthcare-21st-century⟩.

[9] Volpp KG, Mohta NS. Patient Engagement Survey: How to hardwire engagement into care delivery processes? NEMJ Catalyst 2017; Insights Report, May 2017.

[10] Villalba-Mora E, Casas I, Lupianez-Villaneuva F, et al. Adoption of health information technologies by physicians for clinical practice: The Andalusian case. International Journal of Medical Informatics 2015;84:477-485. doi: 10.1016/j.ijmedinf.2015.03.002. PMID: 25823578

[11] Ware P, Bartlett SJ, Paré G, et al. Using e-Health Technologies: Interests, Preferences, and Concerns of Older Adults. Interact J Med Res 2017; 6:e3. doi: 10.2196/ijmr.4447. PMID: 28336506

[12] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN

[13] Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications).

[14] McLean S, Sheikh A, Cresswell K, et al. The impact of telehealthcare on the quality and safety of care: a systematic overview. PLoS One 2013;8(8):e71238.

[15] Frederix I, Vandenberk T, Janssen L, et al. eEduHeart I: A Multicenter, Randomized, Controlled Trial Investigating the Effectiveness of a Cardiac Web-Based eLearning Platform - Rationale and Study Design. Cardiology. 2017;136(3):157-163. PMID: 27657799

[16] Cresswell K, Blandfrom A, Sheikh A. Drawing on human factors engineering to reconsider paradigms for evaluating the effectiveness of health information technology. J Roy Soc Med (in press).

[17] Catwell L, Sheikh A. Evaluating eHealth interventions: the need for continuous systematic evaluation. PLoS Med 2009;6:e1000126.

Appendices

Nederlandse samenvatting

Hart- en vaatziekten zijn wereldwijd een van de voornaamste oorzaken van morbiditeit en mortaliteit. Kransslagaderlijden is één van de belangrijkste hartaandoeningen gegeven zijn prevalentie en ernst. Ondanks het feit van de beschikbaarheid van op richtlijnen gebaseerde en evidence-based farmacologische alsook niet-farmacologische behandelingen, zijn de lange termijn uitkomsten voor patiënten met kransslagaderlijden vaak teleurstellend. Een deel van de verklaring hiervoor ligt bij het gebrek aan het volgen van een hartrevalidatie programma. Patiënten opteren vaak om niet deel te nemen aan deze programma's wegens tijdgebrek, andere professionele verplichtingen,…. .

Technologische vooruitgangen in de afgelopen jaren, hebben het mogelijk gemaakt om patiënten te volgen en behandelen van op afstand d.m.v. zogenaamde e-health. e-Health betekent het gebruik van informatie- en communicatie technologie om zorgverlening mogelijk te maken. Telerevalidatie of ook, revalidatie op afstand, is een vorm van e-health zorgverlening en is het onderwerp van deze thesis.

Telerevalidatie biedt het voordeel dat de hartpatiënt van op afstand kan opgevolgd en begeleid worden. Hij/zij is in dit kader niet langer genoodzaakt naar het revalidatie centrum te komen en/of zich te houden aan de openingsuren ervan. Telerevalidatie is een nieuwe vorm van secundaire preventie die recent nog door de Europese Vereniging van Preventieve Cardiologie werd geïdentificeerd als een veelbelovende zorgmodaliteit.

Dit doctoraat, is een van de eerste grote inspanningen om de (lange termijn) kosten-effectiviteit van cardiale telerevalidatie in patiënten met kransslagaderlijden die behoren tot de lage en/of matige risico groep te analyseren. Meer specifiek werden volgende zaken onderzocht:

i. De effectiviteit van additionale telemonitoring van fysieke activiteit in kader van secundaire preventie van patiënten met kransslagaderlijden op fysieke conditie, fysieke activiteit, en heropnames in het ziekenhuis.

ii. De (kosten-)effectiviteit van additionele veelomvattende telerevalidatie in kader van secundaire preventie van patiënten met kransslagaderlijden op fysieke conditie, levenskwaliteit, cardiovasculaire risico factoren, en heropnames in het ziekenhuis.

In het eerste deel van deze thesis (hoofdstukken 2, 3 en 4) wordt beschreven voor welke patiënten secundaire preventie en dus hartrevalidatie is aangeraden, en wat de rationale is voor de toepassing van telerevalidatie in de klinische praktijk. In hoofdstuk 4 wordt de voorafgaandelijk beschikbare literatuur betreffende het onderwerp van deze thesis samengevat.

Het centrale deel van deze thesis (hoofdstukken 5, 6 en 7) bevat de resultaten van de Telerehab II en Telerehab III studie, de twee belangrijkste studies die in kader van dit doctoraat werden verricht. Hoofdstuk 5 beschrijft Telerehab II. Dit was een prospectieve, mono-centrische, gerandomizeerde en gecontroleerde klinische studie waarin de effectiviteit van een 18-weken additioneel cardiaal telerevalidatie programma werd beoordeeld, tov een klassiek 12-weken hartrevalidatie programma. 80 patiënten met kransslagaderlijden namen deel aan deze studie. Het

telerevalidatie programma bestond grotendeels uit telemonitoring van fysieke activiteit. Het primair eindpunt was fysieke fitheid van de patiënt. De hoofdstukken 6 en 7 beschrijven de Telerehab III studie. Dit was een prospectieve, multi-centrische klinische studie waarin de (kosten-) effectiviteit van een meer alomvattend telerevalidatie programma werd onderzocht. 140 patiënten met kransslagaderlijden en/of hartfalen namen deel aan de studie.

De resultaten van de Telerehab II en III studie hebben ons geleerd dat additionele telemonitoring van fysieke activiteit in secundaire preventie van patiënten met kransslagaderlijden resulteert in een verbeterde fysieke fitheid, in vergelijking met enkel klassieke hartrevalidatie. De Telerehab III studie bevestigde deze bevinding en toonde tevens aan dat een meer alomvattend telerevalidatie programma ook de levenskwaliteit van de hartpatiënt kan verbeteren en kosten besparen voor de gezondheidszorg. Op langere termijn, wanneer het telerevalidatie programma niet meer wordt aangeboden aan de patiënt, dan gaan de initieel behaalde voordelen partieel verloren. Doch globaal doen de patiënten die additionale telerevaldiatie kregen het toch nog beter dan de patiënten die enkel een 12-weken klassiek hartrevalidatie programma kregen. Eigen aan deze studies, en wat deze differentieert van ander eerder onderzoek, is het feit dat de focus lag op additionele telerevalidatie. Ander onderzoek binnen het vakgebied concentreerde zich voornamelijk op een head-to-head vergelijking van conventionele revalidatie en telerevalidatie. Het tele-programma aangeboden in Telerehab III, was meer alomvattend dan de programma's beschreven en vergeleken in de recent gepubliceerde reviews. Het feit dat een lange termijn opvolging werd opgenomen in Telerehab III, is een ander aspect dat de eigenheid en originaliteit van mijn onderzoek illustreert.

Natuurlijk blijven er de dag van vandaag nog enkele grote uitdagingen die de implementatie van telerevalidatie (en e-health toepassingen in het algemeen) in de dagelijkse klinische praktijk bemoeilijken. Niet alle zorgverleners zijn overtuigd van het nut en de meerwaarde van deze innovatieve manieren van zorgverlening. Ze hebben angst dat alle inkomende, geregistreerde data hun werklast fel doen toenemen zonder adequate financiële vergoeding hiervoor. Patiënten zijn soms niet vertrouwd met de technologie, gebruikt voor telerevalidatie. Sommigen verkiezen nog steeds face-to-face zorgverlening met de zorgverlener. e-Health toepassingen zijn in de meeste Europese landen nog steeds niet terugbetaald, wat uiteraard implementatie op grote schaal fel tegenhoudt. Bezorgdheden betreffende de veiligheid van de data, alsook de privacy van de patiënt belemmeren de uitbouw van e-health programma's buiten het wetenschappelijke kader.

Deze thesis vormt de aanzet voor een hele mooie waaier aan toekomstig onderzoek op het gebied van e-health. De studies gerapporteerd in deze thesis reiken evidentie aan voor de (kosten)-effectiviteit van additionele cardiale telerevalidatie. Beide studies werden enkel verricht in België, doch de socio-economische situatie is zeer verschillend van land tot land. Grotere internationale studies, uitgevoerd in socio-economisch verschillende landen, kunnen in dit kader zinvol zijn. Een extrapolatie van de gevonden resultaten naar andere hartziekten is tevens niet mogelijk. Onderzoek, en dan voornamelijk in de primaire preventie van cardiovasculaire aandoeningen, is een ander toekomstpad. Tot slot is het duidelijk dat e-health zorgtoepassingen complexe interventies zijn, waarvan de meerwaarde mogelijks niet met louter klassieke gerandomiseerde,

klinische studies kan onderzocht worden. Implementatie research vormt hierbij een alternatieve onderzoeksstrategie.

Curriculum vitae & list of publications

Personal details

Name : Frederix, Ines

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Prior education

Bachelor in Medicine (2010, Hasselt University): Summa cum laude, with congratulations (90,52%)

Master in Medicine (2014, Catholic University Leuven): Summa cum laude (87,19%)

Publications: papers

Hansen D, Soors A, Deluyker V, *Frederix I,* Dendale P. Electrical support during outdoor cycling in patients with coronary artery disease: impact on exercise intensity, volume and perception of effort. Acta Cardiol. 2017 Oct 10:1-8. [Epub ahead of print] PMID: 29017395

Frederix I, Solmi F, Piepoli MF, Dendale P. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. Eur J Prev Cardiol. 2017 Nov;24(16):1708-1717. PMID: 28925749

Frederix I, Vandijck D, Hens N, De Sutter J, Dendale P. Economic and social impact of increased cardiac rehabilitation uptake and cardiac telerehabilitation in Belgium - a cost-benefit analysis. Acta Cardiol. 2017 Aug 11:1-8. [Epub ahead of print] PMID: 28799460

Frederix I, Dendale P, Schmid JP. Who needs secondary prevention? Eur J Prev Cardiol. 2017 Jun;24(3_suppl):8-13. PMID: 28618916

Frederix I, Dendale P, Sheikh A. FIT@Home editorial: Supporting a new era of cardiac rehabilitation at home? Eur J Prev Cardiol. 2017 Sep;24(14):1485-1487. PMID: 28610448

Piepoli MF, Corrà U, Dendale P, *Frederix I,* Prescott E, Schmid JP, Cupples M, Deaton C, Doherty P, Giannuzzi P, Graham I, Hansen TB, Jennings C, Landmesser U, Marques-Vidal P, Vrints C, Walker D, Bueno H, Fitzsimons D, Pelliccia A. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur Heart J Acute Cardiovasc Care. 2017 Jun;6(4):299-310. PMID: 28608759

Piepoli MF, Corrà U, Dendale P, *Frederix I,* Prescott E, Schmid JP, Cupples M, Deaton C, Doherty P, Giannuzzi P, Graham I, Hansen TB, Jennings C, Landmesser U, Marques-Vidal P, Vrints C, Walker D, Bueno H, Fitzsimons D, Pelliccia A. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur J Cardiovasc Nurs. 2017 Jun;16(5):369-380. PMID: 28565965

Frederix I, Vandenberk T, Janssen L, Geurden A, Vandervoort P, Dendale P. eEduHeart I: A Multicenter, Randomized, Controlled Trial Investigating the Effectiveness of a Cardiac Web-Based eLearning Platform - Rationale and Study Design. Cardiology. 2017;136(3):157-163. PMID: 27657799

Piepoli MF, Corrà U, Dendale P, *Frederix I,* Prescott E, Schmid JP, Cupples M, Deaton C, Doherty P, Giannuzzi P, Graham I, Hansen TB, Jennings C, Landmesser U, Marques-Vidal P, Vrints C, Walker D, Bueno H, Fitzsimons D, Pelliccia A. Challenges in secondary prevention after acute myocardial infarction: A call for action. Eur J Prev Cardiol. 2016 Dec;23(18):1994-2006. PMID: 27600690

Hansen D, Roijakkers R, Jackmaert L, Robic B, Hendrikx M, Yilmaz A, *Frederix I,* Rosseel M, Dendale P. Compromised Cardiopulmonary Exercise Capacity in Patients Early After Endoscopic Atraumatic Coronary Artery Bypass Graft: Implications for Rehabilitation. Am J Phys Med Rehabil. 2017 Feb;96(2):84-92. PMID: 27175562

Frederix I, Benit E, Verwerft J, Herbots L, Dendale P. Cardiac involvement in hypereosinophilic syndrome. Acta Cardiol. 2016 Feb;71(1):75-6. PMID: 26853257

Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, Van Craenenbroeck E, Van Driessche N, Dendale P. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization rate, medical costs and quality of life: A cost-effectiveness analysis. Eur J Prev Cardiol. 2016 May;23(7):674-82. PMID: 26289723

Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, Van Craenenbroeck E, Van Driessche N, Dendale P. 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 Jul 23;17(7):e185. PMID: 26206311

Frederix I, Hansen D, Coninx K, Vandervoort P, Van Craenenbroeck EM, Vrints C, Dendale P. Telerehab III: a multi-center randomized, controlled trial investigating the long-term effectiveness of a comprehensive cardiac telerehabilitation program--rationale and study design. BMC Cardiovasc Disord. 2015 May 7;15:29. PMID: 25948479

Frederix I, Vanhees L, Dendale P, Goetschalckx K. A review of telerehabilitation for cardiac patients. J Telemed Telecare. 2015 Jan;21(1):45-53. PMID: 25475219

Frederix I, Van Driessche N, Hansen D, Berger J, Bonne K, Alders T, Dendale P. Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients. Eur J Prev Cardiol. 2015 Feb;22(2):150-8. PMID: 24249840

Frederix I, Vanderschueren P. Septo-optic dysplasia: illustration of a case. Acta Neurol Belg. 2014 Dec;114(4):313-4. PMID: 24203814

Dendale P, *Frederix I.* The future of telerehabilitation: empowerment of patients versus long distance supervision. Eur J Prev Cardiol. 2013 Jun;20(2 Suppl):17. PMID: 23702986

Frederix I, Dendale P, Berger J, Vandereyt F, Everts S, Hansen D. Comparison of two motion sensors for use in cardiac telerehabilitation. J Telemed Telecare. 2011;17(5):231-4. PMID: 21565845

Publications: Book chapters

Frederix I, Janssen L, Geurden A, Van Craenenbroeck E, Dendale P. eLearning and Health ICT Education. A systematic review of E-Learning in cardiac rehabilitation. In: Jordanova M, Lievens F, editors. Med-e-Tel Global telemedicine and eHealth updates. Knowledge resources. 1st ed. Luxembourg: ISfTeH, 2016.

Dendale P, *Frederix I.* Rehabilitation of patients after CABG/sternotomy. In: Niebauer J, editor. Cardiac Rehabilitation Manual. 2nd ed. New York: Springer, 2016.

Dendale P, *Frederix I.* Pacemaker implantation. In: Niebauer J, editor. Cardiac Rehabilitation Manual. 2nd ed. New York: Springer, 2016.

Hansen D, *Frederix I.* Hoofdstuk 17: Cardiovasculaire pathologie in de geriatrische revalidatie. In: Cambier D, Hobbelen H, de Vries N, redactie. Geriatrie en kinésitherapie in de fysiopraktijk. 1e ed. Nederland: Bohn Stafleu van Loghum, 2016.

Schmid JP, Saner H, Dendale P, *Frederix I.* Chapter 23 Ambulatory preventive care: outpatient clinics and primary care. In: Gielen S, De Backer G, Piepoli MF, Wood D, editors. The ESC Textbook of Preventive Cardiology. 2nd ed. United Kingdom: Oxford University Press, 2016.

Publications: abstracts & posters

Frederix I. Internet of things and radio frequency identification in care taking, facts and privacy challenges. Wireless VITAE conference. Aalborg (Denmark, 2009)

Frederix I, Berger J, Hansen D, Van Driessche N, Bonne K, Alders T, Dendale P. The value of telerehabilitation in encouraging coronary artery disease patients to stay active after the acute rehabilitation phase. Europrevent conference. Dublin (Ireland, 2012)

Frederix I, Van Driessche N, Laenen V, Loverix L, Hansen D, Dendale P. Additional telerehabilitation contributes to a sustained improvement in physical fitness in coronary artery disease patients, who have completed phase 2 of cardiac rehabilitation. ESC Congress. Amsterdam (The Netherlands, 2013)

Frederix I, Van Driessche N, Hansen D, Berger J, Bonne K, Alders T, Dendale P. Cost reduction by an internet-based telerehabilitation program in coronary artery disease patients after the acute rehabilitation phase. Europrevent conference. Amsterdam (The Netherlands, 2014)

Frederix I, Dendale P. Is cardiac telerehabilitation proven to be effective? Results from a literature review. I-TRAVLE (Individualised Technology-supported and Robot-Assisted Virtual Learning Environments) symposium. Hasselt (Belgium, 2014)

Wens I, Keytsman C, *Frederix I,* Dendale P, Op't Eijnde B. Does multiple sclerosis affect cardiac function? RIMS (Rehabilitation in Multiple Sclerosis) SIG Mobility conference. Bad Wildbad (Germany, 2015)

Van hunsel T, Van der Goten K, Neyens T, Hens N, Mewis A, *Frederix I,* Dendale P. Soluble ST2 as a useful marker in the diagnosis of acute heart failure. BSC congress. Brussels (Belgium, 2016)

Schuermans B, Tack W, Dendale P, *Frederix I,* Neyens T, Hens N, Berger J. Is the number of attended cardiac rehabilitation sessions influential on prevention of recurrent ischemic cardiac disease? BSC congress. Brussels (Belgium, 2016)

Dendale M, *Frederix I,* Gielen I, Guilliams R, Dendale P. Efficacy of training programs on weight loss in obese patients at high risk for cardiovascular disease. BSC congress. Brussels (Belgium, 2016)

Jeurissen J, Verdonck B, Verweft J, Neyens T, De Klippel N, *Frederix I*, Dendale P. Left Atrial Function as Predictor of Recurrent Stroke or Paroxysmal Atrial Fibrillation in Patients with Cryptogenic Stroke. BSC congress. Brussels (Belgium, 2016)

Hansen D, Roijakkers R, Jackmaert L, Robic B, Hendrikx M, Yilmaz A, *Frederix I,* Rosseel M, Dendale P. Cardiopulmonary exercise capacity in patients early after endoscopic atraumatric CABG (endo-ACAB) surgery: implications for rehabilitation and treatment. BSC congress. Brussels (Belgium, 2016)

Frederix I, Hansen D, Soors A, Deluyker V, Dendale P. Can electrically assisted cycling be recommended in cardiac rehabilitation programs for coronary artery disease patients? Europrevent congress. Sophia Antipolis (France, 2016)

Frederix I, Janssen L, Geurden A, Dendale P. Do cardiac patients like and use an e-Learning platform as part of their secondary prevention program? Med-e-Tel congress. Luxembourg (Luxembourg, 2016)

Frederix I, Vandijck D, Hens N, De Sutter J, Dendale P. Economic and social impact of large-scale cardiac telerehabilitation implementation in Belgium. A cost-benefit analysis. Biomedica 2016, The European Life Sciences Summit. Aachen (Germany, 2016)

Kirn B, *Frederix I,* Kokalj S, Dendale P. Exploring the optimal duration of video recordings in a post-discharge eLearning platform for cardiac patients. European Congress on eCardiology and eHealth. Berlin (Germany, 2016)

Frederix I, Van Driessche N, Vandervoort P, Dendale P. Is cardiac telerehabilitation cost-efficient in the long-term? The Telerehab III 2-year follow-up study (Best Poster Award nomination). BSC congress. Brussels (Belgium, 2017)

Minten L, Smeets K, Hansen D, Neyens T, *Frederix I,* Dendale P. Exercise intervention in type 2 diabetes mellitus: impact on cardiac diastolic function. BSC congress. Brussels (Belgium, 2017)

Raymaekers V, Brenard C, Hermans L, Vanvoorden P, *Frederix I*, Dendale P. How to reliably diagnose arterial hypertension? Lessons from 24h blood pressure monitoring. BSC congress. Brussels (Belgium, 2017)

Wieringa P, Dendale P, *Frederix I,* Hansen D. The usefulness of the current long-term intensive cardiological follow-up in patients with a myocardial infarction. BSC congress. Brussels (Belgium, 2017)

Raymaekers V, Brenard C, Hermans L, Vanvoorden P*, Frederix I,* Dendale P. Predictive values based on 24h ambulatory blood pressure measurements. Europrevent Congress. Malaga (Spain, 2017)

Wouters D, Verboven AS, Vanderlinden L, Welten M, *Frederix I,* Dendale P. Do the positive effects of a telemedical care program on mortality and hospitalization readmissions in chronic heart failure patients persist in the long-term? European Congress on eCardiology and eHealth. Berlin (Germany, 2017)

Kirn B, *Frederix I,* Kokalj S, Dendale P. Your own doctor can motivate you best to learn remotely! European Congress on eCardiology and eHealth. Berlin (Germany, 2017)

Frederix I, Beckers P, Vrints C, Heidbuchel H, Dendale P, Van Craenenbroeck E. The OptimEx Telemonitoring Substudy – Study Design. OptimEx Symposium. Munich (Germany, 2017)

Hansen D, Rovelo Ruiz G, *Frederix I,* Coninx K, Dendale P. Do clinicians prescribe exercise according to clinical guidelines in patients with cardiovascular disease? Findings from the European Association of Preventive Cardiology EXPERT (EXercise Prescription in Everyday practice & Rehabilitative Training) working group survey. BSC congress. Brussels (Belgium, 2018)

Hansen D, Reekmans L, Dingenen C, *Frederix I,* Dendale P. Acute physiological impact of electrical support during cycling in patients with systolic heart failure. BSC congress. Brussels (Belgium, 2018)

Boujemaa H, Verboven K, Hendrikx M, Rummens JL, *Frederix I,* O. Eijnde B, Dendale P, Hansen D. Lean tissue mass loss after coronary artery bypass graft surgery: relation to post-operative clinical status and impact of endurance exercise-based rehabilitation. BSC congress. Brussels (Belgium, 2018)

Boujemaa H, Claessen G, Bakelants E, Yilmaz A, Robic B, *Frederix I,* Dendale P, Hansen D. Cardiopulmonary exercise performance in critical aortic valve stenosis: early impact of minimally invasive aortic valve replacement. BSC congress. Brussels (Belgium, 2018)

Verboven K, Stinkens R, Wens I, *Frederix I,* Jocken J, Blaak E, Hansen D. Coordinated regulation of adipose tissue lipid breakdown during exercise in obese individuals: a contribution of non-adrenergic mediators and the effects of exercise training. Europrevent congress. Ljubljana (Slovenia, 2018)

Publications: invited speaker sessions

Telemedicine in cardiac rehabilitation. Congres hartrevalidatie: "How to do it?!" Amersfoort (The Netherlands, 2012)

Telerehabilitation as a Method to Improve the Cardiac Patient's Physical Fitness, Preliminary Results from the Telerehab II Study. eHealth and Telemedicine in Cardiovascular Prevention & Rehabilitation, 1st European conference. Bern (Switzerland, 2013)

Telerehabilitation-state of the art. Europrevent conference. Amsterdam (The Netherlands, 2014)

Telecardiology and telerehabilitation : the future of medicine? Europrevent conference. Lisbon (Portugal, 2015)

Speaker session Mobile Health Congress. Agoria E-Health. Grimbergen (Belgium, 2014)

Cardiale telerevalidatie. CIRO+ Lunch Seminars. Horn (The Netherlands, 2015)

Cardiac Telerehabilitation, prior and current developments in the field. International congress on physiotherapy 2016. Biomedical engineering & physiotherapy. From research to clinical practice. Hôpital Erasme (ULB). Brussels (Belgium, 2016)

Impact of digital health on optimising exercise training in diabetes mellitus. Europrevent conference. Sophia Antipolis (France, 2016)

The Role of eHealth in Healthcare Systems: Evidence on the Cost Effectiveness of eHealth in cardiology. Public policy exchange-EU project. Brussels (Belgium, 2016)

Take-home messages from the BWG on Cardiovascular Prevention and Rehabilitation (BWGCPR). BSC congress. Brussels (Belgium, 2016)

Round table discussion: The importance of telemedicine. TAKE HEART congress. Rome (Italy, 2016)

CPET: What can the Cardiologist and the Pneumologist learn from the Rehabilitation Doctor? 7th Update Symposium Cardiopulmonary Exercise Testing. Aartselaar (Belgium, 2016)

Tele-rehabilitation strategy after acute coronary syndromes. ESC congress. Rome (Italy, 2016)

eEduHeart I: a multi-center randomized, controlled trial investigating the usage of a post-discharge eLearning platform for cardiac patients (YIA session). European Congress on eCardiology and eHealth. Berlin (Germany, 2016)

Telemedicine. Symposium "Diastolic Heart Failure – From Bench to bedside" Munich (Germany, 2017)

Tele-CardioRehab, the Future of Medicine? HMDP Visiting Experts FY2017. Singapore (Singapore, 2017)

Telerehabilitation for cardiovascular disease prevention. ESC Congress. Barcelona (Spain, 2017)

CPET in cardiac patients. EAPC CR Course. Bern (Switzerland, 2017)

Telerehabilitation. EAPC CR Course. Bern (Switzerland, 2017)

Practical aspects of exercise training in heart failure (HIIT, strenght training, and respiratory muscle training). EAPC CR Course. Bern (Switzerland, 2017)

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