

Please cite the Published Version

Bogota, Andrea Avila (2018) Home-based exercise in patients with coronary heart disease: effects on physical fitness and physical activity. Doctoral thesis (PhD), Manchester Metropolitan University and KU Leuven.

Downloaded from: <https://e-space.mmu.ac.uk/622064/>

Usage rights:  Creative Commons: Attribution-Noncommercial-No Derivative Works 4.0

Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from <https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines>)

**HOME-BASED EXERCISE IN PATIENTS
WITH CORONARY HEART DISEASE:
EFFECTS ON PHYSICAL FITNESS AND
PHYSICAL ACTIVITY**

Andrea Avila Bogota

PhD 2018

HOME-BASED EXERCISE IN PATIENTS WITH CORONARY HEART DISEASE: EFFECTS ON PHYSICAL FITNESS AND PHYSICAL ACTIVITY

Andrea Avila Bogota

**A thesis submitted in partial fulfilment of the requirements of the
Manchester Metropolitan University for the degree of Doctor of
Philosophy**

**Manchester Metropolitan University
School of Healthcare Science
Faculty of Science and Engineering
Division of Physiology & Reconstructive Science
In collaboration with KU Leuven**

2018

The work presented in this thesis was carried out as part of a joint doctorate at the Faculty of Kinesiology and Rehabilitation Sciences, Katholieke Universiteit Leuven, Belgium and the Faculty of Science and Engineering, Manchester Metropolitan University, United Kingdom. This research was funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate Program (2011-2015).



TABLE OF CONTENTS

Summary/Samenvatting	1
Chapter 1 General introduction	7
Chapter 2 A Randomized Controlled Study Comparing Home-Based Training with Tele-monitoring Guidance versus Centre-Based Training in Patients with Coronary Heart Disease: Rationale and Design of the Tele-rehabilitation in Coronary Heart Disease (TRiCH) Study	31
Chapter 3 Home-Based Rehabilitation with Tele-monitoring Guidance for Patients with Coronary Artery Disease (Short-Term Results of the TRiCH Study): Randomized Controlled Trial	47
Chapter 4 Home-based exercise with tele-monitoring guidance in patients with coronary artery disease; Does it improve long-term physical fitness?	77
Chapter 5 Validation of four physical activity trackers in a phase III cardiac rehabilitation population	105
Chapter 6 General discussion	135
Appendices	
The effect of acute supplementation with resveratrol on flow-mediated dilation and oxygen consumption kinetics in older coronary artery disease patients: intervention dependent effects.	161
Appositions	167
About the author	168
List of abbreviations	172
Scientific acknowledgments	174
Acknowledgments	175

SUMMARY

Coronary arterial disease is responsible for approximately 18 million deaths worldwide including more than four million in Europe. Although mortality is decreasing, its prevalence is rising. After a cardiac event, secondary prevention plans such as cardiac rehabilitation are recommended. Cardiac rehabilitation is a multidisciplinary program that includes dietary modification, lipid control, smoking cessation, psychological counselling, pharmacological therapies and structural exercise training as the core component. Its effects on reducing mortality, prevention of hospital readmissions and improvement of quality of life are highly proved. However, it is still underutilized partially because one model does not fit all patients. Hence, innovative ways of delivering cardiac rehabilitation have been studied. One of those technologies is tele-monitoring; through cardiac tele-rehabilitation some traditional barriers of cardiac rehabilitation programs can be address and it represents an alternative or a supplement to conventional centre-based services. Thus, patients would not be restricted to the hospital or rehabilitation centre and could be controlled at a distance.

Cardiac tele-rehabilitation has shown to be as effective as traditional centre-based cardiac rehabilitation on early stages of the program. However, the information regarding the maintenance phase is scarce. Thus, the main purpose of this doctoral research was to investigate the short and long-term effectiveness of a home-based exercise program guided through tele-monitoring in patients starting the maintenance phase (phase III) of cardiac rehabilitation compared to a centre-based group as well as a control group through an intervention study (**TRiCH = Tele-rehabilitation in Coronary Heart Disease study**).

From our results in the short-term (3 months) we can conclude that a home-based cardiac rehabilitation program with tele-monitoring guidance is as effective as centre-based cardiac rehabilitation for improving exercise capacity measured as peak exercise capacity (VO_2P).

During the intervention, exercise capacity increased in home-based and centre-based groups with on average 4 to 5% with clinical significance while it remained

stable in the control group. In the long-term, we did not obtain further increases although exercise capacity remained stable in all three groups. This result might be related to the maintenance of physical activity levels of our population. In the TRiCH study, 85% of patients meet the guidelines of the World Health Organization of at least 150 minutes of physical activity per week at a moderate intensity.

Being physically active is one of the cornerstones on lifestyle changes for primary and secondary prevention of coronary artery disease and new technologies are useful tracking patient's training. During the development of this PhD research, facing the wide variety of tracking products available to the public, we explored the accuracy of some devices. Our interest was also increased by the scarcity of published literature related to validity and reliability of such devices. We concluded that Fitbit Charge HR and MIO Fuse are valid and reliable to measure number of steps in a cardiac population, however, when it comes to energy expenditure we documented a noteworthy inability including also the SenseWear Armband Mini and the Actiheart to estimate it accurately.

Nutrition is also considered a part of the lifestyle changes for coronary artery disease patients and a number of nutritional supplements have flooded the market in a similar manner as that of activity trackers. Resveratrol is a natural antioxidant present in red wine that has proved beneficial effects in the cardiovascular system of animals (specially rats), however, when it comes to human studies, few information has been published. Based on the cardio protective effect shown in animal models we intended to study if an acute supplementation with high doses of RV would improve endothelial function measured through flow-mediated dilation in cardiac patients on phase III of cardiac rehabilitation. We concluded that resveratrol impaired flow mediated dilation in patients who underwent percutaneous coronary intervention. However, given the few number of participants, our results must be interpreted cautiously.

SAMENVATTING

Coronair arterieel lijden is verantwoordelijk voor ongeveer 18 miljoen sterfgevallen wereldwijd, waarvan meer dan vier miljoen in Europa. Ondanks dat de mortaliteitscijfers dalen, blijft de prevalentie van coronair arterieel lijden stijgen. Na het doormaken van een cardiaal event, is het aangewezen om een secundair preventieprogramma zoals cardiale revalidatie, te volgen. Een cardiaal revalidatieprogramma is van nature multidisciplinair, maar de kern bestaat uit gestructureerde training. Verder omvat het nog voedingsadvies, controle van het lipidenprofiel, rookstopbegeleiding en het op punt stellen van de medicamenteuze therapie. De effecten van cardiale revalidatie op het verlagen van de mortaliteit, het voorkomen van nieuwe ziekenhuisopnames en het verhogen van de levenskwaliteit, zijn al uitvoerig aangetoond. Nochtans wordt cardiale revalidatie de dag van vandaag nog onderbenut. Het feit dat cardiale revalidatie een schoentje is dat niet iedereen past, zit daar zeker voor iets tussen. Daarom wordt er ijverig gezocht naar nieuwe manieren om cardiale revalidatie aan te kunnen bieden. Eén van die manieren is het gebruik van technologie onder de vorm van telemonitoring. Door telemonitoring kunnen sommige barrières overwonnen worden die anders de deelname aan cardiale revalidatie zouden verhinderen. Op die manier kan telerevalidatie gezien worden als zowel een alternatief alsook een aanvulling op de traditionele ambulante cardiale revalidatie. De patiënt hoeft dus niet meer afhankelijk te zijn van een ziekenhuis of revalidatiecentrum voor een groot deel van zijn revalidatie en kan van op een afstand in de gaten gehouden worden.

Het is al aangetoond dat cardiale telerevalidatie even effectief kan zijn als traditionele hartrevalidatie wanneer gekeken wordt naar de eerste fases van het programma. Over de langetermijneffecten is echter nog weinig geweten. Daarom was het hoofddoel van dit doctoraatsproject om zowel de effecten op korte als langere termijn te onderzoeken van een trainingsprogramma dat door de patiënt in de thuisomgeving werd uitgevoerd en gebruik maakte van telemonitoring. Het betrof patiënten die met succes een revalidatieprogramma in het ziekenhuis hadden doorlopen en de onderhoudsfase (fase III) van cardiale revalidatie ingingen. De telemonitoring groep werd vergeleken met een groep die langer in het ziekenhuis

trainde alsook met een controle groep d.m.v. een interventiestudie (TRiCH = TeleRehabilitation in Coronary Heart Disease study).

Uit de resultaten op korte termijn (3 maanden) concluderen we dat thuisrevalidatie met telemonitoring even effectief is als een langere trainingsperiode in het ziekenhuis wanneer het aankomt op het verbeteren van de inspanningscapaciteit. De inspanningscapaciteit (IC) werd gemeten door zuurstofconsumptie tijdens een maximale inspanningsproef op de fiets. Tijdens de interventie steeg de IC in deze groepen met 4-5%, wat klinisch significant is. De IC bleef constant in de controlegroep. Op lange termijn (1 jaar) zagen we geen verdere stijging van de IC, maar de waarden bleven wel constant in alle drie de groepen. Dit kan te wijten zijn aan het behoud van goede hoeveelheden fysieke activiteit in onze steekproef. Van de deelnemers aan de TRiCH studie, voldeed 85% aan de richtlijnen voor fysieke activiteit zoals opgesteld door de Wereld Gezondheid Organisatie waarbij een minimum van 150 minuten matig intense inspanning per week wordt nagestreefd.

Fysiek actief zijn is één van de hoekstenen van primaire en secundaire preventie van coronair arterieel lijden. Nieuw ontwikkelde technologieën kunnen nuttig zijn om dit gedrag van de patiënt te monitoren. Tijdens de totstandkoming van dit doctoraatsproject werden we geconfronteerd met een grote variëteit van beschikbare producten en daarom hebben we de accuraatheid van enkele van deze monitors onderzocht. Deze onderneming werd gesteund door de vaststelling dat er maar zeer weinig wetenschappelijke literatuur omtrent de validiteit en betrouwbaarheid van zulke apparaten bestond. Uit ons onderzoek kwam naar voor dat de Fitbit Charge HR en MIO Fuse valide en betrouwbaar zijn om het aantal stappen te meten in een populatie met hartproblemen. Echter, wanneer het aankomt op het meten van het energieverbruik merkten we noemenswaardige tekortkomingen bij voornoemde apparaten, maar ook bij de SenseWear Armband en de Actiheart.

Zoals al eerder aangehaald is voedingsadvies ook een belangrijke component in de multidisciplinaire hartrevalidatie. Een groot aantal voedingssupplementen hebben de markt op een gelijkaardige manier overspoelt zoals dat ook bij fysieke

activiteitsmonitors gebeurd. Resveratrol (RV) is een natuurlijk antioxidant dat veel voorkomt in rode wijn en waarvan de positieve effecten op het cardiovasculair systeem zijn aangetoond bij dieren (vooral ratten). Wanneer het aankomt op mensen is er echter maar weinig informatie beschikbaar. Daarom onderzochten we of acute hoge doses RV supplementatie de endotheelfunctie bij hartpatiënten in fase III van de hartrevalidatie kon verbeteren. Dit deden we door middel van een flow-mediated dilatatie meting (FMD). Onze resultaten toonden aan dat RV de FMD verslechterde bij patiënten die een percutane coronaire interventie hadden gehad. Het is wel zo dat onze studiepopulatie heel klein was waardoor de resultaten met enige voorzichtigheid geïnterpreteerd dienen te worden.

Chapter 1

General introduction

Cardiovascular disease is defined by the World Health Organization as a group of disorders of the heart and blood vessels and include coronary artery disease (CAD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (1). Cardiovascular diseases (CVD) remain the leading contributor to global mortality and morbidity. Globally, it is responsible for approximately a third of all yearly deaths, with mortality rates in high-income countries ranging from 20% to 50% (2).

Notable progresses have been observed in the treatment of CVD. As a result, a decline in age-standardized CAD and CVD mortality has been observed in many European countries since the 1970s being most prominent in the more affluent countries, illustrating the potential for premature death prevention and prolonged healthy life expectancy (3). Despite these progresses, incidence of new and recurrent CAD remains high (4), and is expected to increase health care costs, work disability and reduce quality of life (4). Furthermore, global deaths from CVD have risen by 41% between 1990 and 2013 (5), with ischemic heart disease becoming the leading cause of global deaths and stroke risen to third position (6). In Europe, more than 4 million people die from CVD across the continent every year, with more than 1.4 million dying prematurely, before 75 years of age (7). In several eastern European countries, CVD and CAD mortality remains high.

Pathophysiology of Coronary Artery Disease (CAD)

The underlying pathophysiologic mechanisms of coronary heart disease or coronary artery disease (CAD) begin with the process of atherosclerosis, which develops and progresses for decades prior to an acute event. Atherosclerosis can be considered as a low-grade inflammatory state of the intima (inner lining) of medium-sized arteries, accelerated by risk factors such as high blood pressure, smoking, high cholesterol, diabetes, and genetics (8). In the case of coronary atherosclerosis, this slow progression leads to a gradual thickening of the inner layer of the coronary arteries, which in time narrow the lumen of the artery to various degrees, leading to acute syndromes such as myocardial infarction (AMI) and sudden cardiac death

(SCD). Atherosclerosis is more common in the proximal segments of the major coronary arteries often at arterial bifurcation points affecting the flow in the artery (8).

Risk factors

An estimated 75% to 90% incidence of CAD in a variety of populations can be explained by antecedent exposure to conventional lifestyle risk factors, including poor dietary habits, physical inactivity, and cigarette smoking (9). Risk factors for CAD can be divided into modifiable (hypertension, diabetes mellitus, smoking, physical inactivity, dyslipidaemia, obesity, stress and diet) and non-modifiable risk factors (gender, age, and family history) (10).

Modifiable risk factors

Cigarette smoking increases the risk of morbidity and mortality from ischemic heart disease compared with not smokers; this risk falls immediately after stopping smoking, although it may take more than 20 years, before the risks associated with smoking are completely reversed (11). However, the global prevalence of tobacco smoking in people aged 15 years and older has declined from 27% in 2000 to 21% in 2013, being largest in developed countries (12). With the decline of cigarette smoking, dyslipidaemia has become the number one modifiable risk factor for CAD (13).

The crucial role of dyslipidaemia, especially hypercholesterolaemia, in the development of CVD is well documented with pathology, genetic, intervention and observational studies (14). Most cholesterol is normally carried in LDL-C (14), and an elevated low-density lipoprotein (LDL) cholesterol levels account for approximately half the population-attributable risk of an acute cardiac event (15) and around one quarter of the risk of stroke (16). Hypertriglyceridaemia is also a significant independent risk factor, although the risk is associated bigger with moderate hypertriglyceridaemia that with very severe hypertriglyceridaemia [$>10\text{mmol/L}$] (14).

High blood pressure is a major public-health challenge globally; it is estimated to be responsible for 7.5 million deaths annually, and is predicted to increase with

population aging and growth (17); elevated blood pressure is considered the most significant global risk factor for cardiovascular morbidity and mortality and exhibits the highest prevalence in the world, although being approachable by different antihypertensive treatments (18).

Over the past three decades, the burden of diabetes mellitus (DM) has increased from 30 million in 1985 to 382 by 2014, with current trends indicating a raising in the numbers (19), estimating that by the year 2035, one in ten persons will have DM (592 million worldwide) (20). A close link exists between DM and CVD, being the direct cost of DM attribute to macro and micro vascular complications; furthermore, there is an increased risk of CVD mortality in diabetic patients with a relative risk ranging from 1 to 3 in men and from 2 to 5 in women compare to those without DM (21). These traditional risk factors are established as mediators between obesity and atherosclerotic vascular disease, making obesity a common risk factor for several CVD (22).

Excess body weight is estimated to cause approximately 3 million deaths every year (23) and although weight management is fundamental in the treatment of CVD prevention, the majority of obese individuals do not achieve sufficient and sustained weight loss. Thus, there is a great emphasis on controlling the traditional CVD risk factors resulting from obesity as a strategy for reduction in CV risk (24). The main dietary factors that impact CV mortality include trans-fat, saturated fat, salt and insufficient vegetables and fruits; in fact, insufficient intake of fruit and vegetables is estimated to cause approximately 11% of ischaemic heart disease deaths and 9% of stroke deaths worldwide (12). Diverse dietary patterns can be adopted where a high predominance of vegetables and fruits, wholegrain cereals and low-fat protein sources would have more importance that the precise proportions of total energy obtained by the major macronutrients. In the same line, salt intake should be restricted, and limiting saturated and trans fats and alcohol consumption, plus monitoring of carbohydrate consumption and an increase in dietary fibre should be recommended (14).

A wide variety of stressors including mental, social and work stress could also influence the presence of CVD through a general adaptation syndrome (25). This syndrome has been described in earlier research and consists of three phases, being “fight or flight” response the first phase, which prepares the organism for the challenge of the stressful stimuli. The second phase represents the chronic adaptation to the stressful stimuli, and the last phase constitutes a state of fatigue, where the adaptive system begins to fail (25). Selye’s hypothesis that excessive mental stress leads to systemic stress, that manifest in peripheral tissues and that these psychological modulations are closely associated with the pathogenesis of CVD are now well accepted (26). In fact, psychosocial stress and/or depression are stronger risk factors for myocardial infarction than traditional risk factors such as hypertension or obesity (27). Figure 1 describes the mechanism(s) underlying the exacerbation of CVD due to mental stress.

Currently, data are limited on trends in physical inactivity worldwide (12); however, in 2010, 23% of adults older than 18 years of age were insufficiently physically active having a prevalence of 33% of physical inactivity in high-income countries (1). Physical inactivity has a deleterious effect comparable to smoking or obesity (28), in fact, Wen and Wu (29) estimated that because of the remarkably high prevalence of physical inactivity, a sedentary lifestyle kills more people worldwide than smoking. In addition to the relationship between level of physical activity and CVD, the concept of sedentary time and sedentary behaviour has recently emerged as a new risk factor for morbidity and mortality (30). Consequently, even when not achieving recommended physical activity levels, getting the population out of their sedentary behaviours would, at least theoretically have a huge public health effect on morbidity and mortality from CVD (31).

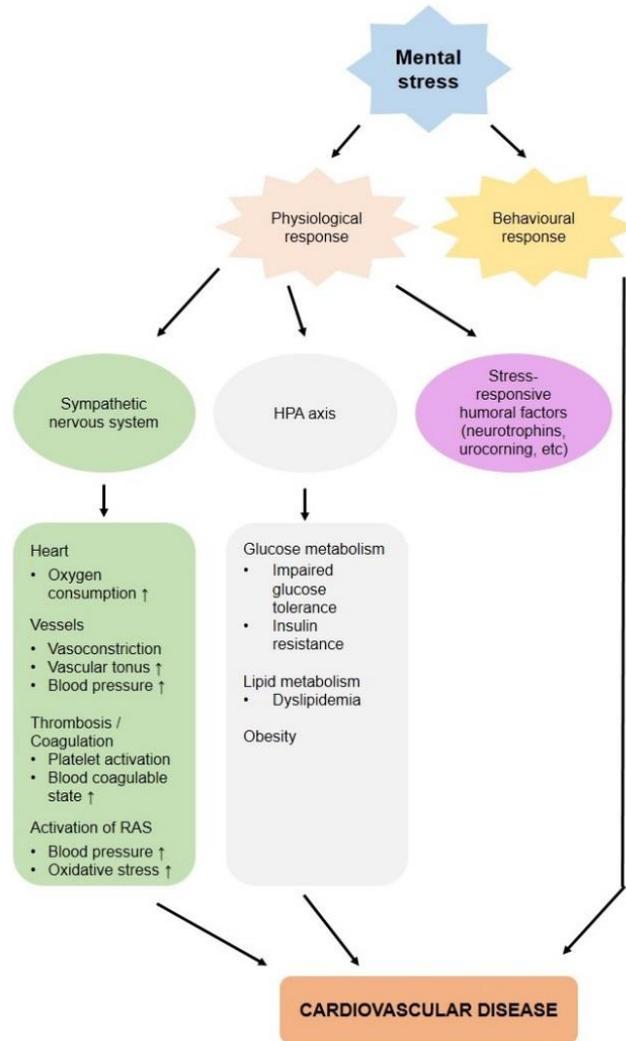


Figure 1. Mental stress induces two kinds of responses: physiological and behavioural. Physiologically, the sympathetic nervous system and HPA axis are activated. Follow this activation, a wide variety of cellular events are involved in the pathogenesis of CVD. Additionally, various stress-responsive humoral factors are regulated, including neurotrophins and urocortin. Adapted from Inoue et al (26).

Non-modifiable risk factors

Importantly, 10% to 15% of patients with CAD have no apparent major CAD risk factors. Family and twin studies suggest a strong genetic influence on premature CAD. Results from the Framingham Offspring Study demonstrate that, after correction for known risk factors, parental CVD was associated with a 1.7 and 2.0-fold increased risk for women and men, respectively (32). The risk also varies

considerably between ethnicity. South Asians and sub-Saharan Africans have a higher risk, while Chinese and South Americans have a lower risk of CVD (14). Finally, numerous studies have shown that CAD occurs more frequently in men than in women (7.9 and 5.1% in men and women >20 years old, respectively) (33). This trend however, reverses in older age (>75 years), possibly due to menopause and related hormonal changes in women (34). Figure 2 resumes the main risk factors associated with cardiovascular disease.

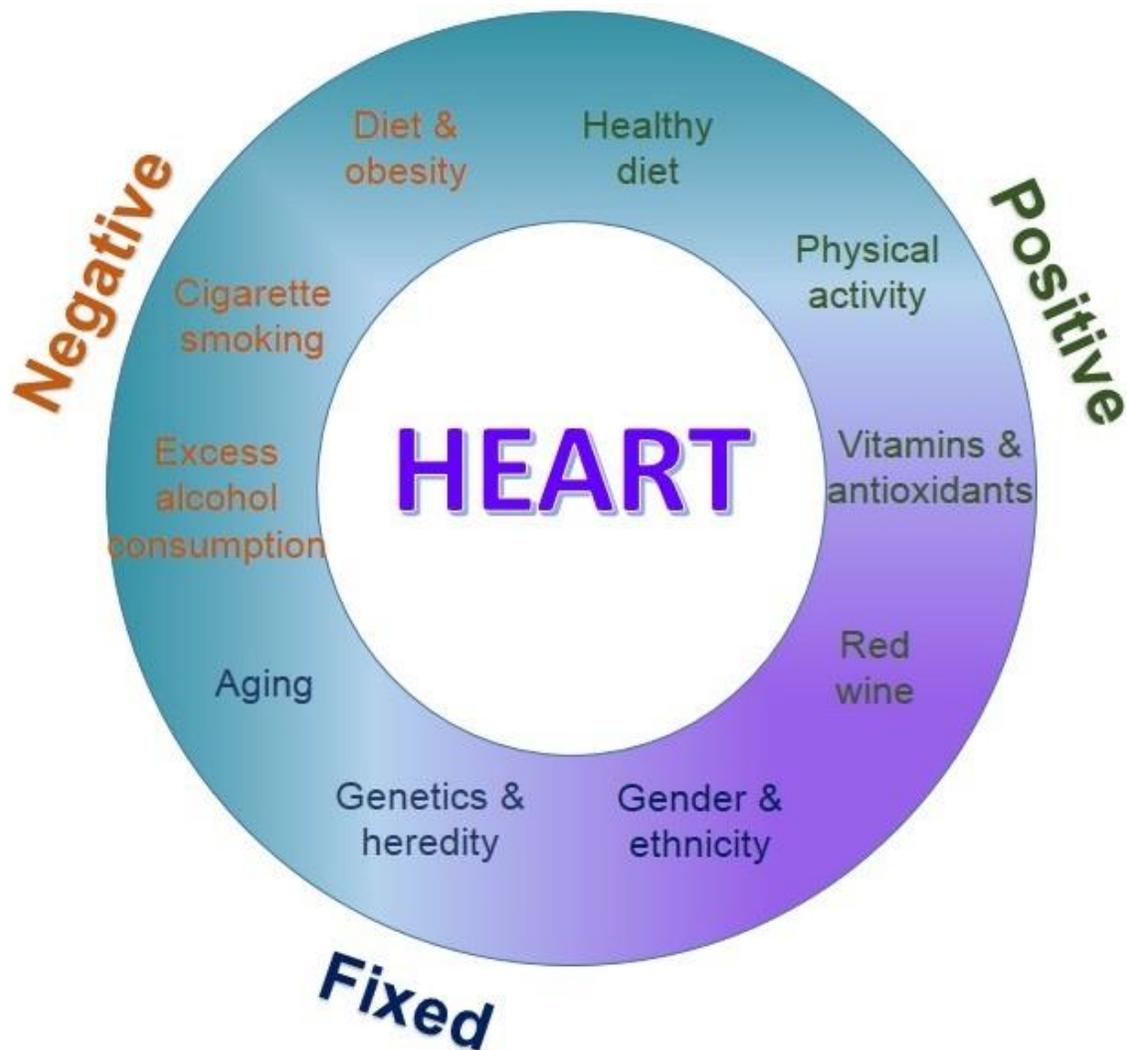


Figure 2. The individual development of CVD can be modified by a number of risk factors. These fall into two categories: modifiable and not-modifiable risk factors. As modifiable risk factors, these may have both a negative (increase risk) and a positive (lowered disease risk) impact on the likelihood of an individual developing of CVD. Adapted from Laher (35).

Diagnosis

These traditional risk factors (smoking, hypertension, diabetes, hyperlipidemia, physical inactivity) together with a family history of myocardial infarction before the age 60 years, increase the likelihood of CAD.

The medical history identifies relevant comorbidities and should include details of patient diet, physical activity, and relevant social history including tobacco and alcohol use and family history of heart disease (36). Physical examination is often not able to reveal CAD, however, examination remains essential because these findings may be important in determining the risks and benefits of a comprehensive treatment strategy and the need for additional investigations (37).

Currently the guidelines recommend a systematic approach to CV risk assessment targeting populations at higher risk such as those with family history of premature CVD (14). Non-invasive cardiac investigation could include standard laboratory biochemical testing, a resting ECG, an ambulatory ECG monitoring as well as a resting echocardiography and in selected patients a chest X-ray (38).

Treatment

The aim of the management of CVD is to reduce symptoms, improve prognosis and prevent future CV events. The management of CVD patients encompasses lifestyle modification, control of CVD risk factors, evidence-based pharmacological therapy and patient education (39).

Patients with CAD are considered at very high risk for cardiovascular events and statin treatment should be considered, irrespectively of low density lipoprotein cholesterol (LDL-C) levels (39). The goals of treatment include LDL-C below 1.8mmol/L or >50% LDL-C reduction if target level cannot be reached (39).

It is recommended that SBP be lowered to <140 mmHg and DBP to <90 mmHg in stable CAD patients with hypertension (39). Provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in the majority of patients (40). Most patients will require (in addition to lifestyle modifications) drug therapy in order to achieve optimal BP control. Currently, five

major drug classes are recommended for the treatment of hypertension: ACE inhibitors (angiotensin-converting enzyme), ARBs (angiotensin receptor blocker), beta-blockers, CCBs (calcium channel blockers), and diuretics (thiazides and thiazide-like diuretics such as chlortalidone and indapamide) (40).

Diabetes mellitus increases the progression of CAD and should be managed carefully. Currently, a glycated hemoglobin (HbA1c) <7.0% and <6.5 – 6.9% on individual bases is recommended (39).

Latest advances in techniques, equipment, stent and adjuvant therapy have established PCI as a routine and safe procedure in patients with stable CAD and a suitable coronary anatomy (38). The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, the expected benefit on prognosis and/or symptoms and the amount of related ischaemia (38). Revascularization can also be considered as a first-line treatment in post-myocardial infarction, angina/ischaemia, multivessel disease, left ventricular dysfunction and/or large ischaemic territory, left main stenosis (38). The indications for PCI and CABG in stable CAD patients have been clearly described by Windecker et al (41). Stable CAD patients treated with PCI irrespective of the type of metallic stent implanted, should have a dual antiplatelet therapy between 1 to 6 months depending on the bleeding risk. Insufficient data exist for patients treated with CABG, thus dual antiplatelet therapy is not recommended (42).

Cardiac rehabilitation (CR) is a central element in contemporary CVD management that aims to optimize cardiovascular risk reduction, facilitate adoption and adherence to healthy behaviours, reduce disability and promote an active lifestyle (43). Following a cardiac event, secondary prevention by means of cardiac rehabilitation (CR) is a Class IA recommendation in the treatment of patients with CAD by the European Society of Cardiology (ESC) (44), the American Heart Association and the American College of Cardiology (45).

CR is a multifaceted and multidisciplinary intervention, which improves functional capacity, recovery and psychosocial well-being. It has been shown to be a cost-effective intervention following an acute coronary event and chronic heart failure, as

it improves prognosis by reducing recurrent hospitalization and health care expenditures, while prolonging life (45).

The World Health Organization has offered a definition of CR that summarizes very well its objectives: i.e. the sum of activities required to influence favorably the underlying cause of the disease, as well as to ensure the patient the best possible physical, mental and social conditions, so that they may, by their own efforts, preserve or resume when lost, as normal a place as possible in the life of the community (World Health Organization; 1993) (46).

CR focusses on secondary prevention which relies on early detection of the disease process and application of interventions to prevent the progression of disease (47). Over the past decade, secondary prevention and CR programs have moved on from being simple interventions to much more complex services that include more comprehensive professional lifestyle interventions based on behavioural models of change (i.e. smoking cessation, healthy food choices and exercise training) with different. Risk factor management in terms of effective control of blood pressure, lipids and glucose to defined targets, and the appropriate prescription and adherence to cardio-protective drugs are now integral parts of this approach. Finally, the psychosocial and vocational supports required to help patients regain a life as full as possible are also provided (48). Nonetheless, international clinical guidelines consistently identify exercise as a central element of CR (49). Four previous meta-analyses of the effects of exercise-based interventions in patients with CAD reported a statistically significant benefit in patients receiving exercise compared with usual medical care, with a reduction in total and cardiac mortality ranging from 20% to 32% (49). Current components of CR can be seen in Figure 3.

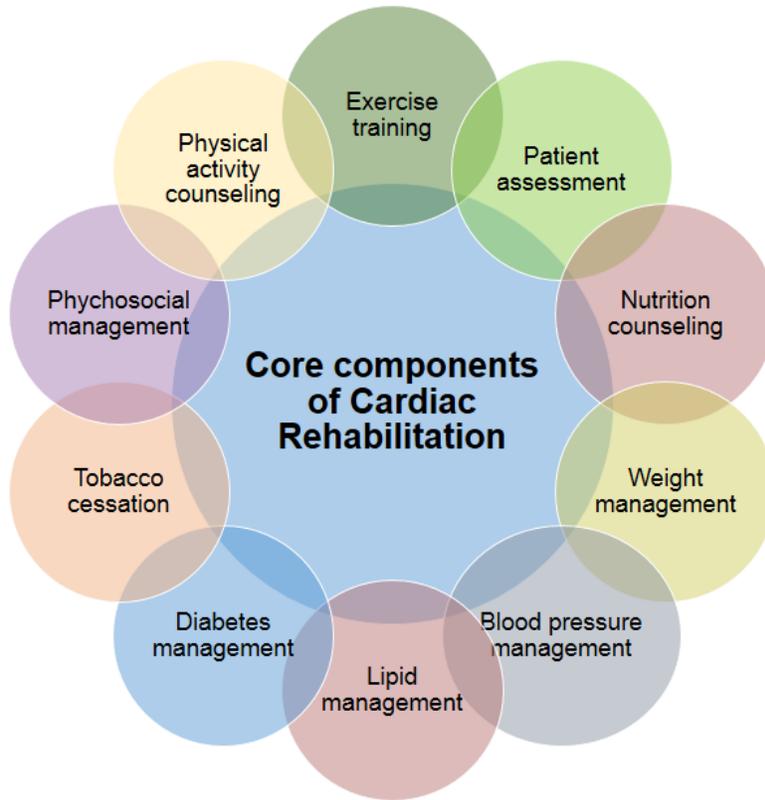


Figure 3. Core components of CR/secondary prevention programs. Adapted from Sandesara et al (9).

Phases of CR

Traditionally, CR is divided into three phases. All phases of CR aim to facilitate recovery and to prevent a new cardiovascular event (47).

Phase I or the inpatient phase initiates while the patient is still in the hospital. It consists of early progressive mobilization once the patient is stable to a level of activity required to perform simple household tasks. Inpatient CR programmes are mostly limited to early mobilization to make self-care possible by discharge, and brief counselling about the nature of the illness, risk factors management, the treatment and follow-up planning (47).

Phase II is a supervised ambulatory outpatient programme lasting usually between 3 to 6 months which consists of outpatient monitored exercise and aggressive risk

factor reduction. Yet, in many countries (especially in Europe), residential programs of 3 to 4 weeks duration are offered (47).

Phase III is a lifetime maintenance phase in which physical fitness is a cornerstone and additional risk-factor reduction are emphasized. It consists of home or gymnasium-based exercise with the goal of continuing the risk factor modification and exercise programme learned during phase II (47).

Referral of CR

Despite the well-known benefits of CR, referral and uptake of supervised centre-based (CB) CR are inadequate (50). Based on data from the EuroAspire study of CVD management, 44.8% of CR-eligible patients are being referred to a CR program whereas only 36.5% participates in a CR program (51). In 2007 a Belgian report suggested that only 15-30% of patients for whom CR may be beneficial, use this service (52). These rates have not improved since the 2002 publication of the Carinex project (53). There are common aspects affecting participation and adherence to CR programs. In fact, predictors of poor participation in CR have been widely studied through quantitative analysis and include distance from CR centre, lower socioeconomic status, female gender, ethnicity and older age (54). Regarding accessibility, proximity to a health centre offering CR programs, plays an important role in participation and adherence (55). Patients regularly choose not to attend the rehabilitation sessions in the hospital due to ill-health, a lack of transport, time and scheduling commitments associated with returning to work and / or reimbursement problems (56). Furthermore, in many countries, legislation with regard to CR is inadequate or non-existing; there is a lack in reimbursement and know-how with regard to implementation of guidelines that could support the referral and access to CR (57).

Long-term benefits are even more disappointing, mainly due to low CR uptake, low adherence rates (2) and the lack of resources regarding phase III CR. Evidence is emerging that most patients fail to achieve secondary prevention targets in the long term; in fact, many patients need support to maintain physical activity as well as other health related lifestyle changes. Thus, whereas phase III ought to support the

benefits obtained in phase II; it appears to be somewhat “invisible” today. In many countries, the impression is that implementation of phase III is led by patients instead of health care providers (58). Consequently, although most cardiac patients adopt healthier lifestyles during CR, many relapse into old habits when returning to everyday life. Excluding medication adherence, that seems to be improved after enrolment in CR (59), research on the maintenance of other CR benefits shows that up to 60% of patients after a centre-based CR program relapse over the first six months (60). Hansen et al. showed that only one out of four patients with CAD adhere to the recommended physical activity level of CR at 18 months follow-up (56). In the same line, Twadella et al (61), proved that CR patients receiving dietary intervention achieve a higher median intake of recommended food items (low-fat sausage, margarine, cheese, wholemeal bread) and lower median consumption of high-fat and not recommended food items (French fries, milk, eggs, white bread, cake) compared with their dietary habits 1 year before their enrolment. However, this change was not maintained up to 1 year after CR.

Alternative models for CR

Currently CR delivery approaches do not suit everyone and new innovative ways are needed to match patient preferences in order to improve uptake and compliance to a life-long physically active lifestyle among cardiac patients (62, 63) after completion of hospital-based CR (4). Different strategies for secondary prevention range from multidisciplinary and specialized modalities in the hospital setting to family-based interventions in the long term (57). While there is no general consent upon definition of home or community-based CR, several guidelines recommend delivery of the same established core components of in-hospital CR program, including structured exercise, patient education and counselling (64). In home-based CR, a patient comes in the CR centre for an initial assessment, where patient safety for independent exercise is established and an exercise prescription is developed. Then, exercise training is performed without formal supervision, and regular contact through different technologies are made to deliver other components or review exercise (64). On the other hand, community-based CR exploit community exercise

facilities where CR staff go and deliver comprehensive services (64). It is estimated that 15% of patients in Australia (65), 12% in New Zealand (66), 28% in Europe (53), and 38% in Mexico (67) participate in some form of alternative model of CR.

Supervised-CR programs

CR programs differ considerably worldwide and across randomized controlled trials in duration (one to 30 months), frequency (one to seven sessions/week) and session length (20 to 90 minutes/session), and also vary in the inclusion of exercise-only or comprehensive programmes (exercise plus psychological or education intervention or both) (68). Heran et al. found a trend towards larger reduction in total mortality (RR 0.82; 95% CI 0.67 to 1.01) in the CR group compared to the no-CR control up to six to 12 months of follow-up, and a reduction in overall mortality and cardiovascular mortality with follow-up of 12 months or more. Currently, CR is predominantly delivered in a supervised group-based model and only a small proportion provided other modes to their patients (69). Traditionally, it is assumed that a supervised group-based is the best approach for influencing outcomes; however there is an emerging trend in recent years to offer models based on facilitated self-management (69).

Community-based CR

According to Lima et al (64), community-based programs are delivered in 25 countries with an average of 20 sessions, usually supervised by an exercise physiologist or physiotherapist and involved usually a cardiologist or physiatrists. Programs are usually on the basis of choice, risk or indication and distance or transportation (64).

Home-based CR

Home-based (HB) rehabilitation programs might overcome some of the barriers for attending a centre-based (CB) CR program and target a broader range of patients who would benefit from CR (70). Meta-analyses showed that HB rehabilitation can be at least as effective as supervised rehabilitation for maintaining exercise capacity, with some evidence of higher levels of program completion and adherence up to 12

months (70). HB cardiac tele-rehabilitation seems to be a promising tool for stable CAD patients (71).

Telemedicine is the utilization of medical information transferred remotely via digital communication to improve or promote the health of patients, and is progressively becoming common practice of medicine in many areas of the world (72), in CR, recent advances in information and telecommunication technologies, such as smartphones and the internet, have enabled the advent of cardiac tele-rehabilitation programs (2).

Tele-rehabilitation is part of telemedicine and is defined as the application of telecommunication technology that provides distant support, assessment and intervention to individuals with disabilities (73). The benefits of using tele-rehabilitation include: 1) decreased travel between rural communities and specialized urban health centres; 2) improved access to specialized services; 3) better clinical support in local communities; 4) delivery of local health care in rural communities; 5) reduced feelings of isolation for rural clinicians indirect educational benefits for remote clinicians who participate in teleconsultations; 6) improved service stability in regions with high staff turnover; and 8) multimedia communication (74).

In tele-rehabilitation, the patient is monitored from a distance and receives regular feedback. Thus, patients are no longer restricted to the hospital environment as in exercise-based CR, and learn to implement the exercise in their daily routine at home (4). These new methods of health care delivering whether using mobile digital communication devices or mobile health (mHealth), may increase the number of patients treated while facilitating patient self-management and saving costs (72). Tele-rehabilitation also have the potential to increase the number of cardiac rehabilitation components delivered to the patients. Different models of HB cardiac tele-rehabilitation have been present, the use of heart rate monitors are considered the less sophisticated as well as the trans telephonic electrocardiographic monitoring, whereas more advanced systems are using tele-ECG-monitoring via a remote device and real-time ECG and voice trans telephonic monitoring (71).

The use of wearable physical activity trackers also offers great promise to researchers and clinicians aiming to promote a physical active lifestyle and have the potential to affect physical activity behaviour of patients (75). A recent report found that 77% of adults over 65 years old owned a mobile phone and over half (59%) used the Internet (76). Furthermore, since 2011, there has been a 30% increase in ownership of smartphones with nearly 62% of smartphone owners reporting using their cell phone to seek health information within the past year (77). Hence, the introduction of a home-based exercise therapy with tele-monitoring guidance carries the potential to improve compliance to exercise-based CR today.

However many challenges remain to increase the benefits of CR programs. Therefore, the particular aim of this PhD-project was:

- To evaluate the short (3-months) and longer-term (one-year) effectiveness of a home-based exercise program in patients completing a phase II centre-based CR program

The majority of exercise intervention studies in CAD patients examined the effects of short (up to 3 months) CR programs and follow-up studies reported poor long-term adherence to physical activity recommendations and a decline in exercise capacity (78), however the majority of these interventions have not undergone rigorous trials for efficacy (77). Consequently, in **chapter 1** we describe the research protocol of the Tele-Rehabilitation In Coronary Heart disease (TRiCH-study). In **chapter 2** we report on the short-term effect of a home-based CR program with tele-monitoring guidance on physical fitness and other secondary outcomes in CAD patients following completion of a centre-based CR program. **Chapter 3** evaluates the added benefit in the longer-term (i.e. one year after completion of ambulatory CR program) of a home-based program with tele-monitoring guidance on physical fitness and its effectiveness to a prolonged centre-based (CB) CR intervention. It is worth clarifying that although CR includes core components such as nutritional counselling, risk factor management, psychosocial management on top of physical

activity training; this PhD research focussed exclusively on exercise training with tele-monitoring support.

Finally despite the widespread adoption and potential application of monitor tracking devices in health care, there is little information about their accuracy and reliability (79). Since living a physically active lifestyle has profound and multiple benefits not only in healthy young individuals but also in older adults and specially populations living with chronic illnesses like CVD, **chapter 4** determines the validity and reliability of some consumer and more research based physical activity devices to assess energy expenditure (EE) and step count in a phase III CR population under well-controlled laboratory conditions; this in an effort to increase the understanding of the precision of several assessment tools available in the market and commonly used to evaluate physical activity behaviour in the CAD population.

Completing the particular aims of this PhD-project and as part of the requirements of the joint doctorate program “MOVE-AGE”, Manchester Metropolitan University joined the fellowship as a “host” university and a project was developed between both institutions. The consumption of Mediterranean-style diets, which are rich in resveratrol, are associated with a reduced risk of cardiovascular mortality in humans (80). Thus, our aim was to determine the acute effect of supplementation with high doses of resveratrol, a nutraceutical supplement, on endothelial function and oxygen consumption in patients with coronary artery disease. The research developed between both institutions is part of the **appendices** of the present document.

REFERENCES

1. Global Status Report on noncommunicable diseases 2014: WHO (World Health Organization); 2014.
2. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *European Journal of Preventive Cardiology*. 2016;23(16):1715-33.
3. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren WM AC, Benlian P, Boysen G, Cifkova R, Deaton C. European Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*. 2012;33(13):1635-701.
4. Alves AJ, Viana JL, Cavalcante SL, Oliveira NL, Duarte JA, Mota J, et al. Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated. *World journal of cardiology*. 2016;8(10):575.
5. Schwalm JD, McKee M, Huffman MD, Yusuf S. Resource Effective Strategies to Prevent and Treat Cardiovascular Disease. *Circulation*. 2016;133(8):742.
6. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. *The New England Journal of Medicine*. 2015;372(14):1333-41.
7. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *European heart journal*. 2016;37(42):3232.
8. Ambrose JA, Singh M. Pathophysiology of coronary artery disease leading to acute coronary syndromes. *F1000prime reports*. 2015;7:08.
9. Sandesara PB, Lambert CT, Gordon NF, Fletcher GF, Franklin BA, Wenger NK, et al. Cardiac Rehabilitation and Risk Reduction: Time to "Rebrand and Reinvigorate". *Journal of the American College of Cardiology*. 2015;65(4):389-95.
10. Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. *Atherosclerosis*. 2015;239(1):260-7.
11. Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM. Secondary prevention in coronary heart disease: baseline survey of provision in general practice. *Bmj*. 1998;316(7142):1430-4.
12. Mendis S. Global progress in prevention of cardiovascular disease. *Cardiovasc Diagn Ther*. 2017;7(Suppl 1):S32-s8.
13. Hendrani AD, Adesiyun T, Quispe R, Jones SR, Stone NJ, Blumenthal RS, et al. Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies. *World J Cardiol*. 2016;8(2):201-10.
14. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, 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): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol*. 23. England2016. p. NP1-NP96.
15. Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, et al. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. *Circulation*. 2005;112(23):3554-61.

16. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376(9735):112-23.
17. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015;241(1):211-8.
18. Bohm M, Mahfoud F. High blood pressure in coronary artery disease: when to start treating and what to target? *Eur Heart J*. 2018.
19. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-53.
20. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes*. 2015;6(13):1246-58.
21. Rivellese AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. *Nutr Metab Cardiovasc Dis*. 2010;20(6):474-80.
22. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, et al. Obesity and Subtypes of Incident Cardiovascular Disease. *J Am Heart Assoc*. 2016;5(8).
23. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360(9343):1347-60.
24. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, et al. Long-term weight loss maintenance in the United States. *Int J Obes (Lond)*. 2010;34(11):1644-54.
25. Selye H, Fortier C. Adaptive reaction to stress. *Psychosomatic medicine*. 1950;12(3):149-57.
26. Inoue N. Stress and atherosclerotic cardiovascular disease. *J Atheroscler Thromb*. 2014;21(5):391-401.
27. Clouse RE, Lustman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. *Psychosom Med*. 2003;65(3):376-83.
28. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219-29.
29. Wen CP, Wu X. Stressing harms of physical inactivity to promote exercise. *Lancet*. 2012;380(9838):192-3.
30. Bouchard C, Blair SN, Katzmarzyk PT. Less Sitting, More Physical Activity, or Higher Fitness? *Mayo Clinic Proceedings*. 2015;90(11):1533-40.
31. Despres JP. Physical Activity, Sedentary Behaviours, and Cardiovascular Health: When Will Cardiorespiratory Fitness Become a Vital Sign? *Can J Cardiol*. 2016;32(4):505-13.
32. Anderson TJ, Gregoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 29. England: 2013 Canadian Cardiovascular Society. Published by Elsevier Inc; 2013. p. 151-67.

33. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 129. United States 2014. p. 399-410.
34. Shlyakhto E. Gendered Innovations in the Study of Cardiovascular Diseases. *Adv Exp Med Biol*. 2018;1065:655-75.
35. *Systems Biology of Free Radicals and Antioxidants* edited by Ismail Laher: Berlin, Heidelberg : Springer Berlin Heidelberg : Imprint Springer; 2014.
36. Cagle SD, Jr., Cooperstein N. Coronary Artery Disease: Diagnosis and Management. *Prim Care*. 2018;45(1):45-61.
37. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic Coronary Artery Disease: Diagnosis and Management. *Mayo Clinic Proceedings*. 2009;84(12):1130-46.
38. Safri Z. Management of coronary artery disease. 2018.
39. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease. *European Heart Journal*. 2013;34(38):2949-3003.
40. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-104.
41. Stephan Windecker, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Rev Esp Cardiol (Engl Ed)*. 2015;68(2):144.
42. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. Special article 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Rev Esp Cardiol (Engl Ed)*. 2018;71(1):42.
43. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. (AHA/AACVPR Scientific Statement). *Circulation*. 2007;115(20):2675.
44. Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, et al. Effect of comprehensive cardiac telerehabilitation on one-year cardiovascular rehospitalization rate, medical costs and quality of life: A cost-effectiveness analysis. *European journal of preventive cardiology*. 2016;23(7):674-82.
45. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2010;17(1):1-17.
46. Brown RA. Rehabilitation of patients with cardiovascular diseases. Report of a WHO expert committee. *World Health Organ Tech Rep Ser*. 1964;270:3-46.
47. Mampuya WM. Cardiac rehabilitation past, present and future: an overview. *Cardiovascular diagnosis and therapy*. 2012;2(1):38.

48. Piepoli M CU, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, Dendale P, Doherty P, Gaita D, Höfer S, McGee H, Mendes M, Niebauer J, Pogossova N, Garcia-Porrero E, Rauch B, Schmid J, Giannuzzi P. 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. *European Journal of Preventive Cardiology*. 2014;21(6):664-81.
49. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *The American Journal of Medicine*. 2004;116(10):682-92.
50. Rawstorn JC, Gant N, Direito A, Beckmann C, Maddison R. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. *Heart*. 2016;102(15):1183-92.
51. Humphrey R, Guazzi M, Niebauer J. Cardiac Rehabilitation in Europe. *Progress in Cardiovascular Diseases*. 2014;56(5):551-6.
52. De Vos C, Li X, Van Vlaenderen I, Saka O, Dendale P, Eyssen M, et al. Participating or not in a cardiac rehabilitation programme: factors influencing a patient's decision. *European Journal of Preventive Cardiology*. 2013;20(2):341-8.
53. Vanhees LEMJ, McGee H, Dugmore D, Schepers D, Daele Pv. A representative study of cardiac rehabilitation activities in European Union member states: the Carinex survey. *Journal of Cardiopulmonary Rehabilitation*. 2002;22(4):264-72.
54. Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A, Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *European Journal of Preventive Cardiology*. 2012;19(3):494-503.
55. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, Raposeiras S, van, T Hof A, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International Journal of Cardiology*. 2016;223:436-43.
56. Frederix I, L Vanhees L, Dendale P, Goetschalckx K. A review of telerehabilitation for cardiac patients. *Journal of Telemedicine and Telecare*. 2015;21(1):45-53.
57. Piepoli MF, Corra U, Abreu A, Cupples M, Davos C, Doherty P, et al. Challenges in secondary prevention of cardiovascular diseases: a review of the current practice. *Int J Cardiol*. 2015;180:114-9.
58. Bjarnason-Wehrens B, McGee H, Zwisler A-D, Piepoli MF, Benzer W, Schmid J-P, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2010;17(4):410.
59. Shah ND, Dunlay SM, Ting HH, Montori VM, Thomas RJ, Wagie AE, et al. Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med*. 2009;122(10):961 e7-13.

60. Janssen V, De Gucht V, Van Exel H, Maes S. Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients. *European journal of preventive cardiology*. 2013;20(3):431-41.
61. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Journal of the American College of Cardiology*. 2014;64(18):1929-49.
62. Clark RA, Conway A, Poulsen V, Keech W, Tirimacco R, Tideman P. Alternative models of cardiac rehabilitation: A systematic review. *European Journal of Preventive Cardiology*. 2015;22(1):35-74.
63. Buys R, Claes J, Walsh D, Cornelis N, Moran K, Budts W, et al. Cardiac patients show high interest in technology enabled cardiovascular rehabilitation. *BMC Medical Informatics and Decision Making*. 2016;16(1):95.
64. Lima de Melo Ghisi G, Pesah E, Turk-Adawi K, Supervia M, Lopez Jimenez F, Grace SL. Cardiac Rehabilitation Models around the Globe. *J Clin Med*. 2018;7(9).
65. Abell B, Glasziou P, Briffa T, Hoffmann T. Exercise training characteristics in cardiac rehabilitation programmes: a cross-sectional survey of Australian practice. *Open Heart*. 2016;3(1):e000374.
66. Kira G, Doolan-Noble F, Humphreys G, Williams G, O'Shaughnessy H, Devlin G. A national survey of cardiac rehabilitation services in New Zealand: 2015. *N Z Med J*. 2016;129(1435):50-8.
67. Ilarraza-Lomeli H, Garcia-Saldivia M, Rojano-Castillo J, Justiniano S, Ceron N, Aranda-Ayala ZL, et al. National Registry of Cardiac Rehabilitation Programs in Mexico II (RENAPREC II). *Arch Cardiol Mex*. 2017;87(4):270-7.
68. Anderson L, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev*. 2014(12):Cd011273.
69. Harrison AS, Doherty P. Does the mode of delivery in routine cardiac rehabilitation have an association with cardiovascular risk factor outcomes? *Eur J Prev Cardiol*. 2018:2047487318798923.
70. Claes J, Buys R, Budts W, Smart N, Cornelissen VA. 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. *European Journal of Preventive Cardiology*. 2017;24(3):244-56.
71. Piotrowicz E, Piotrowicz R. Cardiac telerehabilitation: current situation and future challenges. *European Journal of Preventive Cardiology*. 2013;20(2_suppl):12-6.
72. Supervia M, Lopez-Jimenez F. mHealth and cardiovascular diseases self-management: There is still a long way ahead of us. *Eur J Prev Cardiol*. 2018;25(9):974-5.

73. Ricker JH, Rosenthal M, Garay E, DeLuca J, Germain A, Abraham-Fuchs K, et al. Telerehabilitation needs: A survey of persons with acquired brain injury. *Journal of Head Trauma Rehabilitation*. 2002;17(3):242-50.
74. Schmeler M, Schein R, Mccue M, K. B. Telerehabilitation Clinical and Vocational Applications for Assistive Technology: Research, Opportunities, and Challenges. *International Journal of Telerehabilitation*. 2009;1(1):59-72.
75. Ferguson T, Rowlands AV, Olds T, Maher C. The validity of consumer- level, activity monitors in healthy adults worn in free-living conditions: a cross-sectional study. *The international journal of behavioral nutrition and physical activity*. 2015;12(1):42.
76. Pfaeffli Dale L, Dobson R, Whittaker R, Maddison R. The effectiveness of mobile-health behaviour change interventions for cardiovascular disease self-management: A systematic review. *European Journal of Preventive Cardiology*. 2016;23(8):801-17.
77. Brager Jenna, Melissa P, Adam K. Theory Driven Mobile-Based Interventions: A Scoping Review. *Journal of Mobile Technology in Medicine*. 2017;6(3):48-65.
78. Mandic S, Stevens E, Hodge C, Brown C, Walker R, Body D, et al. Long-term effects of cardiac rehabilitation in elderly individuals with stable coronary artery disease. *Disability and Rehabilitation*. 2016;38(9):837-43.
79. Bai JY, Welk HG, Nam AY, Lee FJ, Lee MJ-M, Kim MY, et al. Comparison of Consumer and Research Monitors under Semistructured Settings. *Medicine & Science in Sports & Exercise*. 2016;48(1):151-8.
80. Ungvari Z, Labinskyy N, Mukhopadhyay P, Pinto JT, Bagi Z, Ballabh P, et al. Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. *Am J Physiol Heart Circ Physiol*. 2009;297(5):H1876-81.

Chapter 2

A Randomized Controlled Study Comparing Home-Based Training with Telemonitoring Guidance versus Center-Based Training in Patients with Coronary Heart Disease: Rationale and Design of the Telerehabilitation in Coronary Heart Disease (TRiCH) Study

Avila A, Goetschalckx K, Vanhees L, Cornelissen V.

A randomized controlled study comparing home-based training with telemonitoring guidance versus center-based training in patients with coronary heart disease: Rationale and design of the tele-rehabilitation in coronary heart disease (TRiCH) Study.

Journal of Clinical Trials. 2014;4(4):1-5.

ABSTRACT

Aerobic exercise capacity (VO_2P) and an active life style are related to long-term survival and to a reduction in cardiovascular morbidity in subjects with cardiovascular disease. However, the majority of cardiac patients do not engage enough in physical activity (PA) to obtain or maintain the benefits of a physically active lifestyle. There is a need for innovative rehabilitation methods aiming at increasing longer-term adherence and hence more sustained effects on physical fitness. One strategy might be the use of home-based training in combination with tele-monitoring guidance.

Here we describe the rationale, design and methods of the Tele-Rehabilitation in Coronary Heart disease study (TRiCH). The main objective of TRiCH is to compare the longer-term (=1 year) effects of a 3-month patient-tailored home-based cardiac rehabilitation program with tele-monitoring guidance with a supervised centre-based cardiac rehabilitation program in coronary artery disease patients (phase III).

The study is planned as a randomized controlled prospective trial that will randomize 105 coronary artery disease patients (40-75 yrs) who have successfully completed a three month ambulatory cardiac rehabilitation program (phase II) to one of the three groups: home-based, centre-based or a control group (usual care) on a 1:1:1 basis. The exercise programs (frequency, intensity and time of exercise) of patients randomized to home-based or centre-based will be designed according to current exercise recommendations. Patients in the control group will receive the advice to maintain a physically active lifestyle. Assessments will be performed at baseline, after 12 weeks of intervention and at one year of follow-up. The primary outcome measure is change in exercise capacity assessed by VO_2P at 3 and 12 months of follow-up. Secondary outcomes include determinants of exercise capacity, i.e. PA, endothelial function and muscle function, as well as traditional cardiovascular risk factors and quality of life.

It is hypothesized that home-based training with tele-monitoring guidance will result in higher levels of VO_2P at one year of follow-up. Enrolment started in February 2014; last enrolment is expected in November 2015.

INTRODUCTION

Cardiovascular diseases are the leading cause of death, responsible for 30% of all deaths worldwide (1). It is widely recognized that secondary cardiovascular prevention programs play a pivotal role in optimizing recovery in cardiac patients, with meta-analyses demonstrating reduced morbidity and mortality (2). Exercise is a cornerstone therapy in these Cardiac Rehabilitation programs as it has been consistently shown to increase exercise capacity and subsequently decrease cardiovascular risk factors, morbidity and all-cause mortality in patients with coronary heart disease (CHD) (3, 4). Given the strong association between higher exercise capacity and favourable prognosis in those with coronary artery disease, it should be no surprise that maintaining a physically active lifestyle is of utmost importance. However, CR is dramatically underutilized. Recent data from the EuroAspire study of cardiovascular disease management showed that only 44.8% of eligible patients had evidence of referral and 36.5% evidence of participation in rehabilitation (5). These data show that participation rates have not substantially improved since the 2002 publication of the Carinex project (6).

Barriers to participation besides low referral rates, include patient difficulty attending centre-based (CB) rehabilitation sessions and cost. Even if patients gain knowledge about the importance of physical activity (PA) and improve their exercise capacity during the structured cardiac rehabilitation programs, most fail to translate this into a lifelong physically active lifestyle (7). Hansen et al., (8) demonstrated that only 27% of patients that participated in an centre-based program adhered to the minimal PA level that is required to obtain significant health benefits at 18 months following the ambulatory rehabilitation program. In line, Reid et al. found a significant decrease in habitual PA during long-term follow up after hospital discharge in patients with coronary artery disease (9). Therefore, graduation from a supervised to an unsupervised environment constitutes a pivotal event that is often associated with a decline in PA and fitness levels resulting in a worsening of cardiovascular risk profile (10, 11).

There is a need for innovative rehabilitation methods aiming at increasing longer-term adherence to a physically active lifestyle and hence more sustained effects on health related physical fitness, and in the end morbidity and mortality. One strategy might be the use of home-based (HB) training in combination with tele-monitoring guidance. It has been demonstrated that self-regulatory techniques create empowerment and perceived control and might have longer lasting effects on PA improvements. That is, individuals who develop their own PA plans are more likely to adhere to them than those who have a structured exercise plan imposed (7). A recent meta-analysis already demonstrated that HB cardiac rehabilitation in low to moderate-risk cardiac patients is safe, and has at least equal short-term clinical effects as CB cardiac rehabilitation (12, 13). Therefore, HB cardiac rehabilitation has been used more and more for certain patient groups to overcome the previous cited barriers and to promote patient self-efficacy for independent exercise. However, its effects on long-term physical fitness and activity levels as compared to CB programs remain inconclusive (13).

To our knowledge, our study is the first to investigate clinical effects of HB cardiac rehabilitation with tele-monitoring guidance compared to CB cardiac rehabilitation in a randomized controlled design in patients with coronary artery disease (CAD) in the maintenance phase (WHO Phase III) following the supervised outpatient ambulatory rehabilitation program (Phase II) (14). The aim of this paper is to describe the rationale, design, and protocol of the Tele Rehabilitation in Coronary Heart disease study, TRiCH.

OBJECTIVES AND HYPOTHESES

The main objective of our trial is to compare the longer-term (=1 year) effects of a 3-month patient-tailored HB cardiac rehabilitation program with tele-monitoring guidance in CAD patients (phase III) with a supervised CB cardiac rehabilitation program. The primary outcome measure is exercise capacity, measured as peak oxygen uptake (VO_{2P}) at 12 months. VO_{2P} was chosen as the primary endpoint because it is the most important predictor of cardiovascular morbidity and mortality in patients with CAD (15, 16). We hypothesize that patients randomized to

a HB training cardiac rehabilitation program with tele-monitoring guidance will demonstrate higher levels of PA at 1-year follow up, resulting in higher levels of physical fitness, compared to patients who have been enrolled to the CB cardiac rehabilitation program or control-group.

Secondary outcome measures include determinants of exercise capacity (17, 18), i.e. PA, muscle function and endothelial function, health related quality of life (HRQoL) and traditional cardiovascular risk factors.

The second objective of this study is to determine whether HB cardiac rehabilitation versus CB cardiac rehabilitation has a differential effect in improving physical fitness, and the secondary endpoints specified above, in the short-term (3 months) in CAD patients (phase III). It is hypothesized that the effect of HB cardiac rehabilitation will have a larger effect compared to advice only (control group), but that the effect will be similar to a CB cardiac rehabilitation.

METHODS

Trial design and participants

The TRiCH study is planned as a randomized controlled clinical trial with a parallel group design at the University Hospital Leuven (Leuven, Belgium). Participants will be randomly assigned to one of the three groups: Home-based, Centre-based, or control group on a 1:1:1 basis. Primary and secondary outcome measures will be assessed at baseline, after the 3-month intervention period and at 12 months of follow-up. Participants will be 105 CAD patients who have been referred after acute myocardial infarction (AMI), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to the ambulatory rehabilitation program of the University Hospital Leuven and who have successfully completed this 3-month program (phase II). Inclusion and exclusion criteria of patients are shown in Table 1.

The sample size calculation was based on our primary outcome, VO_2P at 12 months. Assuming a difference of 4 ml/min/kg (effect size=0.65) between both exercise groups at follow-up, which has been shown earlier to be of clinical importance (19),

a total sample size of 105 patients is required with a power of 0.80 and a two-sided p-value of 0.05.

The study protocol has been approved by the medical ethical committee of the UZ Leuven/ KU Leuven. Clinical trial registration: NCT02047942.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Patients with CAD (post-PCI, post-MI, post-CABG).	Significant undercurrent illness last 6 weeks.
Patients on optimal medical treatment and stable with regard to symptoms and pharmacotherapy for at least 6 weeks.	Known severe ventricular arrhythmia with functional or prognostic significance; significant myocardial ischemia, hemodynamic deterioration or exercise-induced arrhythmia at screening or heart disease that limits exercise.
Patients who have successfully completed the 3-months ambulatory CB cardiac rehabilitation program.	Co-morbidity that may significantly influence one-year prognosis any, active cancer.
Patients over 40 and under 75 years old.	Severe psychological and/or cognitive disorders that limit exercise.
Access to internet facilities or PC at home	

Participant recruitment

In a first step, eligible patients will be contacted in the last weeks of their in hospital ambulatory cardiac rehabilitation program (phase II) and will be provided oral information about the TRiCH study. Agreeing subjects will then receive written information material and are invited for a screening maximal cycle exercise test. If no exclusion criteria are present patients will be asked to give written informed consent, according to principles of Good Clinical Practice and the Declaration of Helsinki, before randomization.

Randomization and Blinding

A randomization schedule will be prepared by the principle investigator (AA) using a computer random generator (Random.org). After signing the informed consent and registration of the patient in the trial, the random allocation will be provided to the investigator following a phone call. It is inherently not possible to blind participants

and physiotherapists delivering the supervised training sessions as the control group is not receiving any intervention and the intervention groups will undergo their respective training programs in different environments (i.e. home vs hospital setting). However, the investigator analysing the data will be blinded to group allocation.

Intervention

Patients randomized to CB cardiac rehabilitation will continue their training at the outpatient clinic of UZ Leuven under supervision of physiotherapists. Participants will be asked to perform three exercise sessions per week with duration of 90 minutes per session. Each session consists of endurance training (cycling, running, arm ergometry, rowing and dynamic callisthenics) followed by relaxation. The endurance exercise workload is individually controlled by clinical and heart rate monitoring. Training heart rate corresponded to 70-80% of heart rate reserve. Each patient spends on average 45 minutes at the training heart rate during each session.

The HB cardiac rehabilitation group will train the first three sessions under the supervision of the research group for acquaintance with the tele-monitoring system: i.e. heart rate monitors (Garmin Forerunner 210; Garmin), data uploading (<http://connect.garmin.com/en-US/>) as well as the intensity of exercise. After these sessions, patients will receive an individualized exercise prescription to be performed in the home environment. They will be recommended to exercise for at least 150 minutes a week (preferably 6 to 7 days/week) at an individually determined target heart rate zone corresponding to moderate intensity, i.e. 70-80% of heart rate reserve (3, 20). All exercise data will be accessed by the research group on a weekly basis through the online web application. Patients in the HB cardiac rehabilitation group will receive weekly feedback by phone or e-mail. These contact moments will be used to check for adverse effects and injuries, discuss the exercise program, and discuss attendance/compliance and barriers to adherence/compliance if necessary.

Patients randomized to the control group will only receive the usual advice given to patients at the end of the phase II ambulatory CR program, i.e. the recommendation to remain physically active.

After the 3-month intervention period all groups will be encouraged to continue exercising but no contact or feedback will be provided by the research group.

Exercise Attendance and Compliance

Attendance and compliance to the training programs will be established weekly for both intervention groups. Attendance will be defined by % of weekly volume (duration*frequency) of exercise attended by the participants; compliance will be defined by the % of exercise performed at the prescribed intensity.

OUTCOME MEASURES

All patients will be evaluated at baseline, immediately after the 3-month intervention, and at 1-year of follow-up. Evaluations include measurements of cardiorespiratory fitness (VO_{2P} and submaximal measures of exercise), determinants of exercise capacity (PA, endothelial function, and muscle function), HRQoL and traditional cardiovascular risk factors. All measures will be completed by the same investigator at the same time of day for each individual patient.

Primary outcome measure

Cardiorespiratory fitness or exercise capacity. A maximal graded exercise test until volitional fatigue will be carried out using an individualized cycle (Ergometrics 800 S, Ergometrics, Bitz, BadenWürttemberg, Germany) ergometer protocol (20 watt+20 W/min or 10 watt+10 W/min) with gas analysis. Twelve-lead ECG will be recorded continuously and blood pressure will be measured every two minutes and at peak exercise. Breath-by-breath gas exchange measurements (Oxycon Pro TM Jaeger, Carefusion 234, GmbH Hoechberg, Germany) will allow on-line determination of ventilation (VE), oxygen uptake (VO_2) and carbon dioxide production (VCO_2) every 10 s. The test ends when cycling speed falls below 60 rpm or if the patient develops exercise-induced physiological signs that warrant a termination of the test (Depression of ST segment, significant arrhythmias, fall in systolic blood pressure >20mmHg from the highest value during test or hypertension >250mmHg, severe desaturation, loss of coordination, mental confusion, dizziness

or faintness) (21). After reaching maximal volitional fatigue, participants recuperate by cycling for another six minutes at 25 Watt. VO_2P will be defined as the highest 30-s average of VO_2 at the end of the test. In addition, the following submaximal exercise parameters will be determined: ventilator anaerobic threshold (VAT), oxygen uptake efficiency slope (OUES), $VeVCO_2$ slope, $VO_2/Load$ as well as the VO_2 -off time (22).

Secondary outcomes

Physical activity. PA will be objectively assessed with the Sensewear® Mini Armband (BodyMedia, Inc., Pittsburgh, PA, USA), a multisensory body monitor worn over the triceps muscle of the right arm. Patients will be asked to wear the device 24 hours a day, except during water-based activities, for a total of 7 days (23). In addition, they will be asked to record their physical activities in a logbook. Data from these sensors will then be combined with gender, age, body weight and height to estimate energy expenditure and PA intensity, using algorithms developed by the manufacturer (SenseWear professional software, version 6.1).

Muscle function. Oxygen uptake on-kinetics will be established on a separate day at least 48 hours after the maximal exercise test. Measuring oxygen uptake (VO_2) kinetics quantifies the rate of increase in VO_2 during the early phase of exercise providing information on muscle energetics, metabolic control and the determinants of the efficiency of skeletal muscle contraction. Slowed VO_2 kinetics is associated with poor exercise performance (24). This measurement will start with a 3 minutes seated rest on the bike to obtain resting VO_2 data. Next, subjects will be instructed to cycle at a rate of 70 rpm, against a resistance corresponding to 30% of peak load for 6 minutes. After 6 minutes of cycling, subjects remain seated on the bike for an additional 6 minutes, after which a second 6-minute exercise bout will be initiated (25). Subsequently, exercise-onset VO_2 kinetics will be calculated according to previously published formula (25, 26). Following the on-kinetics protocol, maximal handgrip strength will be measured by means of a JAMAR grip strength dynamometer (Lafayette Instrument, USA) using a standardized protocol (27). This will be followed by testing of the maximal isometric knee extension strength and

endurance of the right quadriceps by isokinetic testing equipment (Biodex Medical Systems Inc., 840-000 System 4, New York, USA). Each subject will have to perform a total of three voluntary maximal isometric contractions (6s) at a 60° angle of the knee, with a 60-second rest period between each test; the highest value will be taken as the maximal isometric strength or peak torque (Nm). After 1 minute of recovery, patients will perform two bouts of 25 repetitive maximal isokinetic knee extensions at 180°/s, interspersed with 2-minute recovery intervals. Endurance will be calculated in each bout ([mean peak torque of the last 8 repetitions/mean peak torque of the first 8 repetitions] times by 100). Standardized verbal instructions and encouragements will be given (28).

Endothelial Function. Brachial flow mediated dilation will be measured as previously described in our laboratory (29) and in agreement with international guidelines (30). Brachial artery images will be obtained using a Vivid 7 ultrasound system with a 12 MHz linear array transducer. The subject will be positioned supine with the right arm in a comfortable position for imaging the brachial artery. A blood pressure cuff will be placed proximal to the imaging transducer on the forearm and after a 10 minute period of supine rest, the cuff will be inflated to at least 200 mmHg or at least 50 mmHg over the systolic pressure for exactly 5 minutes. Longitudinal brachial artery images will be recorded during the final 30 seconds before the occlusion and for 150 seconds following cuff deflation. All data will be stored digital for later analysis.

Traditional cardiovascular risk factors. Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, plasma glucose and serum insulin will be analysed by the biochemical laboratory of UZ Leuven using standardized analytic methods on fasting blood samples. The HOMA index will be calculated as a measure of insulin resistance (31). Office blood pressure and heart rate will be measured in sitting position using an automatic device (OMRON M6 Comfort, Japan) after an initial rest of 5 minutes following the European Guidelines of Hypertension (32, 33). Blood pressure will be measured at least twice with 1-min intervals; if there is more than a 5 mmHg difference between the first and second reading; one extra reading

will be taken and office blood pressure will be defined as the mean of the last two measurements (33). Further, height and body mass will be measured in fasting state using a stadiometer and digital scale (Tefal PP6011) with patients barefoot and wearing light sportswear. Waist circumference will be measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest at the end of a normal expiration. Hip circumference will be assessed at the widest portion of the buttocks. Body mass will be measured to the nearest 0.1 kg, height and circumferences to the nearest 0.1 cm. Body mass index ($\text{weight}/\text{height}^2$) and waist/hip ratio will be calculated. Body fat in % and Kg will be established by bioelectric impedance (Omron BF300, Japan).

Health-related quality of life and sociodemographic data. Next to all the physiological parameters HRQoL will be assessed by means of the SF-36 health survey. This questionnaire will be used as a generic health status measure (34) and is composed of 36 questions and standardized response choices, organized into eight multi-item scales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. Finally, sociodemographic data (e.g. age, gender, education, marital status) as well as data on medical and family history and use of medication will be obtained via questionnaires.

STATISTICAL ANALYSES

Microsoft Access will be used for database management and statistical analyses will be conducted using SAS 9.3 (SAS Institute, Inc, Cary, North Carolina, USA). All primary statistical analyses will be conducted on an intention-to-treat principle according to initial randomization. Missing data will be managed using the last observation carried forward method. As a proportion of dropouts may be expected, on-treatment analysis will give the physiological effect of training. Demographic characteristics and baseline data will be summarized using descriptive statistics and baseline comparability of the three groups will be examined. Multivariate analysis of

variance will be used to assess intra and intergroup differences and interactions in the parameters studied. A p -value < 0.05 will be considered statistically significant.

DISCUSSION

Exercise-based cardiac rehabilitation is an important component of a comprehensive approach to cardiovascular disease patients. However, only a small percentage of cardiac patients are still active enough to obtain or even maintain health benefits one year after completion of an in hospital program (phase II). Tele-rehabilitation provides an alternative opportunity to improve the adherence to a physically active lifestyle. Namely, interventions that facilitate self-monitoring of behaviour change in daily life are recommended to improve activity behaviour (35). Moreover, the use of activity monitoring makes patients aware of their activity, which is likely needed for successful treatment effects (36). Therefore, we hypothesize that the use of Garmin Heart rate monitors and the Garmin online platform will make the patient more aware of his exercise behaviour. Moreover, as it allows real-time online supervision from a distant by an external health care provider who can give immediate feedback on the performed activity (duration, frequency but also intensity) and where needed motivation it is believed that this could have a more powerful influence on longer-term activity behaviour and hence physical fitness and health compared to standard care or a prolonged supervised in hospital program. Here we describe the rationale, design and methods of the TRiCH study that will compare the longer-term effect of a three month tele-rehabilitation program with a 3-month prolonged supervised in hospital program and regular practice (CG).

Acknowledgements

AA is supported by a doctoral research grant funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate programme (2011-0015). VAC is supported as a postdoctoral research fellow by Research Foundation Flanders (FWO). LV is holder of the faculty chair 'Lifestyle and Health' at the faculty of Health Care, UAS Utrecht, the Netherlands.

REFERENCES

1. Arena ER, Williams PM, Forman JD, Cahalin JL, Coke JL, Myers JJ, et al. Increasing Referral and Participation Rates to Outpatient Cardiac Rehabilitation: The Valuable Role of Healthcare Professionals in the Inpatient and Home Health Settings: A Science Advisory From the American Heart Association. *Circulation*. 2012;125(10):1321-9.
2. Kwan JG, Balady JG. Cardiac Rehabilitation 2012: Advancing the Field Through Emerging Science. *Circulation*. 2012;125(7):e369-e73.
3. Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, 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). *European Journal of Preventive Cardiology*. 2012;19(5):1005-33.
4. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *The American Journal of Medicine*. 2004;116(10):682-92.
5. Humphrey R, Guazzi M, Niebauer J. Cardiac Rehabilitation in Europe. *Progress in Cardiovascular Diseases*. 2014;56(5):551-6.
6. Vanhees LEMJ, McGee H, Dugmore D, Schepers D, Daele Pv. A representative study of cardiac rehabilitation activities in European Union member states: the Carinex survey. *Journal of Cardiopulmonary Rehabilitation*. 2002;22(4):264-72.
7. Ferrier S, Blanchard CM, Vallis M, Giacomantonio N. Behavioural interventions to increase the physical activity of cardiac patients: a review. *Eur J Cardiovasc Prev Rehabil*. 2011;18:15-32.
8. Hansen D, Dendale P, Raskin A, Schoonis A, Berger J, Vlassak I, et al. Long-term effect of rehabilitation in coronary artery disease patients: randomized clinical trial of the impact of exercise volume. *Clinical Rehabilitation*. 2010;24(4):319-27.
9. Reid RD ML, Pipe AL, Dafoe WA, Higginson LA, Wielgosz AT, McDonald PW, Plotnikoff RC, Courneya KS, Oldridge NB, Beaton LJ. Determinants of physical activity after hospitalization for coronary artery disease: the Tracking Exercise After Cardiac Hospitalization (TEACH) Study. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2006;13(4):529-37.
10. Carlson JJ, Norman GJ, Feltz DL, Franklin BA, Johnson JA, Locke SK. Self-efficacy, psychosocial factors, and exercise behavior in traditional versus modified cardiac rehabilitation. *Journal of cardiopulmonary rehabilitation*. 2001;21(6):363.
11. Brubaker PH, Warner JG, Rejeski WJ, Edwards DG, Matrazzo BA, Ribisl PM, et al. Comparison of standard- and extended-length participation in cardiac rehabilitation on body composition, functional capacity, and blood lipids. *The American Journal of Cardiology*. 1996;78(7):769-73.
12. Blair J, Corrigan H, Angus N. J, Thompson D. R, S. L. Home versus hospital-based cardiac rehabilitation: a systematic review. *Rural and Remote Health*. 2011;11(2):1-17.

13. Taylor RS, Dalal H, Jolly K, Moxham T, Zawada A. Home-based versus centre-based cardiac rehabilitation. *Cochrane database of systematic reviews* (Online). 2010(1):CD007130.
14. Vanhees L, McGee HM, Dugmore LD, Vuori I, Pentilla UR. *The Carinex Survey: current guidelines and practices in cardiac rehabilitation within Europe*. Amersfoort, editor: Acco (Leuven); 1999. 104 p.
15. Vanhees L, Fagard R, Thijs L, Staessen J, Amery A. Prognostic significance of peak exercise capacity in patients with coronary artery disease. *Journal of the American College of Cardiology*. 1994;23(2):358-63.
16. Domínguez H, Torp-Pedersen C, Koeber L, Rask-Madsen C, Domínguez C. Prognostic value of exercise testing in a cohort of patients followed for 15 years after acute myocardial infarction. *European Heart Journal*. 2001;22(4):300-6.
17. Thomaes T, Thomis M, Onkelinx S, et al. Muscular strength and diameter as determinants of aerobic power and aerobic power response to exercise training in CAD patients. *Acta Cardiologica*. 2012;67(4):399-406.
18. Onkelinx S, Cornelissen V, Defoor J, Matthijs G, Thomaes T, Coeckelberghs E, et al. The CAREGENE study: genetic variants of the endothelium and aerobic power in patients with coronary artery disease. *Acta Cardiologica: an international journal of cardiology*. 2011;66(4):407-14.
19. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise Capacity and Mortality among Men Referred for Exercise Testing. *The New England Journal of Medicine*. 2002;346(11):793-801.
20. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *European journal of preventive cardiology*. 2013;20(3):442.
21. Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth*. 2018;120(3):484-500.
22. Mezzani A, Agostoni P, Cohen-Solal A, Corra U, Jegier A, Kouidi E, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *Journal of Cardiovascular Risk*. 2009;16(3):249-67.
23. Scheers T, Philippaerts R, Lefevre J. Variability in physical activity patterns as measured by the SenseWear Armband: how many days are needed? *European Journal of Applied Physiology*. 2012;112(5):1653-62.
24. Ritti-Dias MR, Li MJ, Hollabaugh AK, Stoner SJ, Montgomery WP, Gardner WA. V.O₂ Kinetics and Clinical Factors Among Patients With Peripheral Artery Disease. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2013;33(6):411-8.
25. Hansen D, Wens I, Kosten L, Verboven K, Eijnde BO. Slowed Exercise-Onset Vo₂ Kinetics During Submaximal Endurance Exercise in Subjects With Multiple Sclerosis. *Neurorehabilitation and Neural Repair*. 2013;27(1):87-95.

26. Arena R, Humphrey R, Ann Peberdy M, Madigan M. Comparison of oxygen uptake on-kinetic calculations in heart failure. *Medicine & Science in Sports & Exercise*. 2002;34(10):1563-9.
27. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and Ageing*. 2011;40(4):423-9.
28. Ghroubi S, Chaari M, Elleuch H, Massmoudi K, Abdenadher M, Trabelssi I, et al. The isokinetic assessment of peripheral muscle function in patients with coronary artery disease: correlations with cardiorespiratory capacity. *Annales de réadaptation et de médecine physique*. 2007;50(5):295-301.
29. Onkelinx S, Cornelissen V, Goetschalckx K, Thomaes T, Verhamme P, Vanhees L. Reproducibility of different methods to measure the endothelial function. *Vascular Medicine*. 2012;17(2):79-84.
30. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force: A report of the International Brachial Artery Reactivity Task Force. *Journal of the American College of Cardiology*. 2002;39(2):257-65.
31. Wallace TM, Levy J, Matthews D. Use and abuse of HOMA modeling. *Diabetes Care* 2004. p. 1487-95.
32. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, et al. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *Journal of Hypertension*. 2005;23(4):697-701.
33. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, et al. Recommendations for Blood Pressure Measurement in Humans: An AHA Scientific Statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee. *Journal of Clinical Hypertension*. 2005;7(2):102-9.
34. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, et al. Translation, Validation, and Norming of the Dutch Language Version of the SF-36 Health Survey in Community and Chronic Disease Populations. *Journal of Clinical Epidemiology*. 1998;51(11):1055-68.
35. Langer D, Hendriks EJM, Burtin C, Probst V, van der Schans CP, Paterson WJ, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clinical Rehabilitation*. 2009;23(5):445-62.
36. Prochaska JO DC. *The transtheoretical approach: Crossing traditional boundaries of therapy*: Krieger Pub Co; Reprint edition; 1984. 204 p.

Chapter 3

Home-Based Rehabilitation with Telemonitoring Guidance for Patients with Coronary Artery Disease (Short-Term Results of the TRiCH Study): Randomized Controlled Trial

Andrea Avila; Jomme Claes; Kaatje Goetschalckx; Roselien Buys; May Azzawi; Luc
Vanhees; Veronique Cornelissen

Home-Based Rehabilitation with Telemonitoring Guidance for Patients with Coronary
Artery Disease (Short-Term Results of the TRiCH Study): Randomized Controlled Trial

Journal of Medical Internet Research 2018 | 2018 Jun 22;20(6):e225

ABSTRACT

Background: Cardiac rehabilitation is an essential part of contemporary coronary heart disease management. However, patients exiting a centre-based CR program have difficulty retaining its benefits.

Objective: We aimed to evaluate the added benefit of a home-based cardiac rehabilitation program with tele-monitoring guidance on physical fitness in patients with coronary artery disease (CAD) completing a phase II ambulatory cardiac rehabilitation program and to compare the effectiveness of this program in a prolonged centre-based cardiac rehabilitation intervention by means of a randomized controlled trial.

Methods : Between February 2014 and August 2016, 90 CAD patients (unblinded, mean age, 61.2 (SD 7.6) years; the majority of participants (80/90, 89.0%) were males; mean height, 1.73 (SD 0.7) m; mean weight, 82.9 (SD 13) kg; mean body mass index, 27.5 (SD 3.4) kg/m²) who successfully completed a 3-month ambulatory cardiac rehabilitation program were randomly allocated to one of three groups: home-based (30), centre-based (30), or control group (30) on a 1:1:1 basis. Home-based patients received a home-based exercise intervention with tele-monitoring guidance consisting of weekly emails or phone calls; centre-based patients continued the standard in-hospital cardiac rehabilitation, and control group patients received the usual care including the advice to remain physically active. All the patients underwent cardiopulmonary exercise testing for assessment of their peak oxygen uptake (VO₂P) at baseline and after a 12-week intervention period. Secondary outcomes included physical activity behaviour, anthropometric characteristics, traditional cardiovascular risk factors, and quality of life.

Results: Following 12 weeks of intervention, the increase in VO₂P was larger in the CB (P = .03) and HB (P = .04) groups than in the control group. In addition, oxygen uptake at the first (P-interaction = .03) and second (P-interaction = .03) ventilatory thresholds increased significantly more in the home-based group than in the centre-based group. No significant changes were observed in the secondary outcomes.

Conclusions: Adding a home-based exercise program with tele-monitoring guidance following completion of a phase II ambulatory cardiac rehabilitation program results in further improvement of physical fitness and is equally as effective as prolonging a centre-based cardiac rehabilitation in patients with CAD.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): NCT02047942.

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading contributor to global premature mortality and morbidity. In Europe, more than 4 million people die from CVD every year, with more than 1.4 million dying before the age of 75 years (1). Today, secondary prevention of CVD, including CAD, by means of cardiac rehabilitation is considered a class IA recommendation by the European Society of Cardiology, American Heart Association, and American College of Cardiology (2). Cardiac rehabilitation is now recognized as an essential part of contemporary CAD management that has significantly contributed to the observed reduction in cardiovascular mortality and disability by facilitating the adoption of and adherence to healthy behaviours and promoting an active lifestyle (3). However, the majority of patients fail to achieve secondary prevention targets in the long term (4). Many patients receiving CB cardiac rehabilitation adopt healthier lifestyles but relapse into old habits when returning to everyday life. After completion of a structured, supervised, exercise-based cardiac rehabilitation program without any extended support or follow-up, the assumption, of both the participant and cardiac rehabilitation staff, is that the patient will be able to self-maintain these appropriate health behaviours and optimal CVD risk profile. Unfortunately, studies have shown that patients exiting CB cardiac rehabilitation have difficulty retaining the positive benefits derived from their participation (5). Moreover, previous reports indicate decreased exercise adherence and increased body weight and serum lipid levels as early as 6 months after cardiac rehabilitation (4, 6).

Consequently, there is a need for innovative cardiac rehabilitation methods to increase long-term adherence to a physically active lifestyle that will result in more sustained effects on health-related physical fitness and cardiovascular health, thus, reducing morbidity and mortality (7). One attractive strategy is the use of HB exercise training in combination with tele-monitoring guidance. HB programs may overcome barriers associated with participation in a CB exercise program, and they have been shown to provide comparable long-term effects on mortality, recurrent coronary event risk, and cardiovascular risk factors in patients with CVD (8). This has been

attributed partly to the fact that HB interventions focus more on the development of self-regulatory techniques that create empowerment and perceived control, resulting in longer lasting effects on PA improvements (9). That is, individuals who develop their own PA plans are more likely to adhere to these plans than those who have a structured exercise plan imposed on them (9). The use of information and communication technology to augment HB programs also enables the provision of additional feedback, education, and counselling (8).

A recent meta-analysis by Buckingham et al (10) found no significant differences in the short-term (<12 months) or long-term (>12 months) patient outcomes including exercise capacity, modifiable risk factors (blood pressure, blood lipid concentrations, and smoking), HRQoL, and cardiac events (mortality, coronary revascularization, and hospital readmissions) among patients participating in home-based or centre-based phase II cardiac rehabilitation. However, there is little evidence about the added benefits of a HB exercise program for patients being discharged from CB cardiac rehabilitation compared with advice only.

In this paper, we report on the secondary objective of the TeleRehabilitation in Coronary Heart disease (TRiCH) study. We aimed to investigate the short-term effect of a HB cardiac rehabilitation program with tele-monitoring guidance on physical fitness and other secondary outcomes in CHD patients following completion of a CB cardiac rehabilitation program. We also aimed to compare the effectiveness of this program with that of a prolonged CB cardiac rehabilitation program by means of a randomized controlled trial (NCT02047942). The longer-term results of the TRiCH study will be published in a second report.

METHODS

Study Design

We conducted a randomized controlled trial using a three-arm, parallel group design among 90 low-to-moderate risk CAD patients completing a phase II cardiac rehabilitation program at the University Hospital Leuven (Belgium). The study

protocol was approved by the medical ethical committee of the UZ Leuven/KU Leuven. The protocol has been described in detail elsewhere (7).

Patient Population and Randomization

Patients were recruited between February 2014 and August 2016 at the University Hospital Leuven (Belgium). The eligible patients included men and women (aged between 40 and 75 years) with angiographically-documented CAD or previous myocardial infarction, on optimal medical treatment for the last 6 weeks, who successfully completed a supervised ambulatory cardiac rehabilitation program and who had access to a computer with Internet connection. The exclusion criteria included known clinically significant ventricular arrhythmia or exercise-induced arrhythmia at screening, myocardial ischemia, other cardiac diseases (valve disease with significant hemodynamic consequences, hypertrophic cardiomyopathy, etc), significant illness for the last 6 weeks, co-morbidity that might represent a significant influence on 1-year prognosis (eg, cancer), and co-morbidity that limits exercise testing and/or training. The criteria for ischemia on the electrocardiogram during exercise included horizontal or downsloping ST depression ≥ 1 mm at 80 ms after the J-point or any ST depression > 1 mm at 80 ms after the J-point (11). The eligible patients were contacted in the last weeks of their in-hospital ambulatory cardiac rehabilitation program (phase II) and were provided verbal information about the TRiCH study. Agreeing patients subsequently received written information and were asked to provide written informed consent according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Procedures

All the agreeing patients who had completed 40 sessions of their ambulatory cardiac rehabilitation program (phase II) were included and were subsequently randomized in a 1:1:1 ratio to one of three groups: HB group, CB group, or a CG (usual care) by means of a web-based random number generator.

The HB cardiac rehabilitation group received training for the first three sessions under the supervision of the investigator. During this period, the patients received an

individualized aerobic exercise prescription recommending at least 150 min of exercise per week (preferably 6-7 days/week) at an individually determined target heart rate corresponding to a moderate intensity (ie, 70%-80% of heart rate reserve (HRR)) in their home environment during the 12-week intervention. Furthermore, this group received instructions on how to use the heart rate monitor (Garmin Forerunner 210, Wichita USA) and how to upload their exercise data to the Garmin platform (12). This application was used to review the training data by both the patient and the investigator (13). Patients received feedback via phone or email once a week according to their preferences. These contact moments were used for the following purposes: 1) to check for adverse events and injuries, 2) to provide feedback on performed exercise during the preceding week, 3) to discuss the exercise program regarding duration and intensity, and 4) to discuss adherence and barriers to adherence if necessary.

Patients randomized to CB cardiac rehabilitation continued their exercise program at the outpatient clinic of UZ Leuven under the direct supervision of physiotherapists. The patients were asked to perform three exercise sessions per week totalling approximately 150 min of endurance exercise. Each training session consisted of predominantly endurance training (2×7 min of cycling, 2×7 min of treadmill walking/running, 7 min of arm ergometry or rowing, and 2×7 min of dynamic calisthenics) and was followed by relaxation. The endurance exercise workload was individually controlled by heart rate monitoring, which was performed by palpation by the physiotherapist during the last minute of each round of exercise. Exercise load was adjusted to maintain target heart rate (70%-80% of the HRR). Patients randomized to the CG received usual care including the standard advice to remain physically active.

Primary outcome measure

Cardiorespiratory fitness or exercise capacity. Primary outcome was change in the exercise capacity following the intervention. Exercise capacity (defined as the maximum amount of physical exertion that a patient could sustain) (14) was determined at baseline and at the end of the intervention using a maximally graded

test on a bicycle with breath-by-breath respiratory gas analysis (Ergometrics 800S, Ergometrics, Bitz, Baden-Württemberg, Germany). Peak exercise capacity was defined as the 30-s average oxygen uptake (VO_2) at the highest workload (7). Ventilatory thresholds (VTs), peak respiratory exchange ratio, and peak heart rate were also established (7).

Secondary outcome measures

Physical activity. Daily physical activity, measured using a Sensewear® Mini Armband (BodyMedia, Inc., Pittsburgh, PA, USA). Steps, sedentary time (duration of sedentary activity at an intensity of ≤ 1.5 metabolic equivalents of task [METs], min), active energy expenditure (physical activity at an intensity of ≥ 3 METs, kcal), and duration of moderate and vigorous physical activity (≥ 3 METs, min) were used in the analyses (15).

Muscle function. Oxygen uptake on-kinetics were established at least 48 h after the maximal exercise test and was calculated algebraically and expressed as mean response time (7). Sitting-rising test (SRT), handgrip strength (JAMAR grip strength dynamometer), and quadriceps maximal isometric knee extension strength and endurance (Biodex Medical Systems Inc., 840-000 System 4, New York, USA) were obtained.

Traditional cardiovascular risk factors. Anthropometric measures (body mass index, waist and hip circumference) and biochemical parameters of a fasting blood sample (glucose, total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides). Additionally, homeostasis assessment model (HOMA) (16) index was calculated using the following formula: fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5. Low HOMA-IR values indicated high insulin sensitivity, whereas high HOMA-IR values indicated low insulin sensitivity (insulin resistance). For this study, patients with HOMA-IR ≥ 3.8 were considered to be insulin resistant (17).

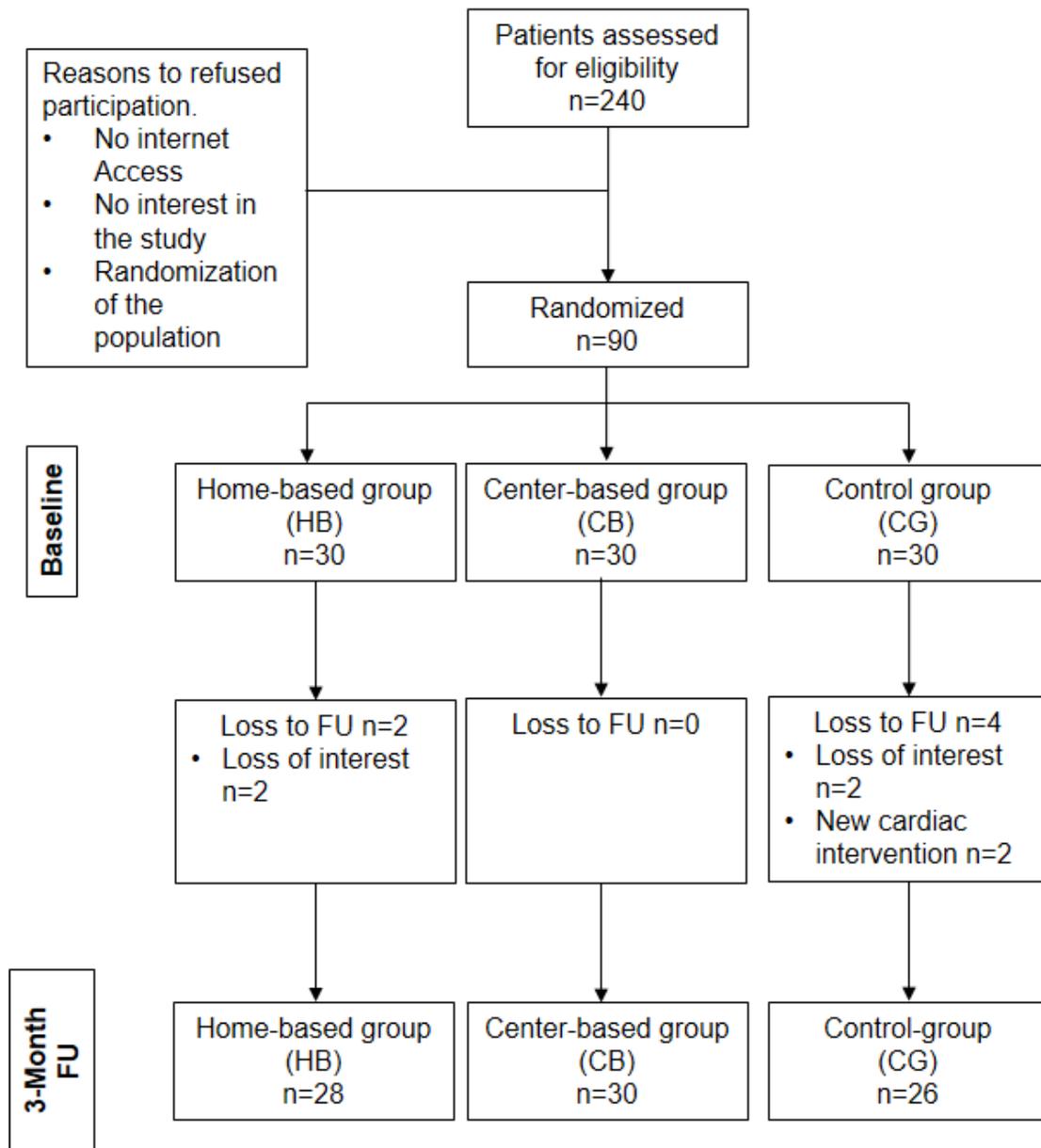
Health-related quality of life. Finally, HRQoL was obtained by means of the standard version of the Short Form 36 (7).

STATISTICAL ANALYSES

All data were expressed as mean \pm SD or median, range, or percentages (for categorical variables). Statistical analyses were performed using SPSS (version 20; SPSS for windows; SPSS Inc., Chicago, IL). Shapiro–Wilk test was used to assess normality. At baseline, the groups were compared using one-way analysis of variance or chi-square tests. For follow-up data, a linear mixed modelling method was used to evaluate time, group, and time \times group interaction effects. The analysis was complemented with a matrix syntax code including a least significant difference post-hoc test when a significant time \times group interaction identified a group that significantly differed over time. An intention-to-treat analysis was performed on the primary outcome (peak VO_2 [VO_{2P}]), and on-treatment analysis was used for secondary outcomes. Spearman correlation coefficients (ρ) were calculated between VO_{2P} and active energy expenditure and physical activity duration at 12 weeks. A probability level of $P \leq 0.05$ was considered significant.

RESULTS

A total of 90 CAD patients agreed to participate and were randomized to HB group ($n = 30$), CB group ($n=30$), and CG ($n=30$). Figure 4 shows the flow of patients throughout the study. Six patients, (4 men: CG, $n=4$; HB, $n=2$) dropped out during the 3-month intervention period. Reasons for dropout included loss of interest (CG, $n=2$; HB, $n=2$) and a new cardiac intervention (ie, percutaneous coronary intervention) (CG, $n=2$). No serious adverse events related to exercise occurred in any of the groups.

Figure 1. Flow of patients throughout the study.

The basic characteristics of the study population are described in Table 2. The mean age of the participants was 61.4 (SD 7.3) years (range: 42-73 years). A total of 10 (11.1%) women participated in the study, and patients were on average slightly overweight, 27.5 (SD 3.4 kg/m²). Overall, exercise capacity was normal, 101.1% (SD 21.1) compared with reference values (18). Baseline characteristics were

comparable between the groups regarding physical characteristics, reason for referral, and pharmacological therapy.

Table 2. Baseline characteristics of patients.

Characteristics	HB n = 30	CB n = 30	CG n = 30
<u>General characteristics</u>			
Age (years) \pm SD ^g	58.6 \pm 13	61.9 \pm 7.3	61.7 \pm 7.7
Female (%) ^b	4 (13)	3 (10)	3 (10)
% of Predicted peakVO ₂ ^e	99.9 \pm 23.1	99.3 \pm 20.1	105.2 \pm 20.2
<u>Reason for referral</u>			
CABG ^c (%)	18 (60)	18 (60)	20 (67)
PCI ^d (%)	12 (40)	12 (40)	10 (33)
<u>Cardiovascular risk factors (%)</u>			
Familial predisposition	12 (40)	8 (27)	13 (43)
Hypertension	14 (47)	11 (37)	17 (57)
Diabetes	12 (40)	8 (27)	4 (13)
Dyslipidemia	15 (50)	17 (57)	19 (63)

(Continued on next page)

Table 2. Baseline characteristics of patients. (Continued)

Characteristics	HB n = 30	CB n = 30	CG n = 30
Smoking			
Never-smoker	11 (37)	14 (47)	15 (50)
Ex-smoker	16 (53)	15 (50)	15 (50)
Current-smoker	3 (10)	1 (3)	0
Medication			
Anti-hypertensive ^f	23 (77)	27 (90)	24 (80)
Beta Blockers	21 (70)	23 (77)	25 (83)
Statins	28 (93)	29 (97)	28 (93)
Aspirin	29 (97)	27 (90)	29 (97)
Anti-thrombotic	19 (63)	18 (60)	23 (77)
Anti-arrhythmic	1 (3)	1 (3)	0
Hypoglycemic	4 (13)	8 (27)	4 (13)
Vasodilators	0	1 (3)	2 (7)

g: Continuous variables are expressed as means \pm SD, b: Dichotomous variables are expressed as numbers and percentages. c: coronary artery bypass graft, d: percutaneous coronary intervention, e: oxygen uptake. f: warfarine and clopidogrel.

Primary outcome measure

Changes in cardiorespiratory parameters are described in Table 3. As can be appreciated from peak respiratory exchange ratios (RER), participants in all three groups exerted a similar maximal effort at baseline and follow-up. The pattern of change in VO_2P differed significantly over time among the three groups (group \times time interaction, $P = .04$), with a larger improvement following HB ($P = .03$) and CB ($P = .04$) interventions than CG interventions. Group \times time interactions were also established for O_2 uptake at the first ventilatory threshold (VT_1) (P -interaction = .03) and the second ventilatory threshold (VT_2) (P -interaction = .03), with larger improvements in the HB group than in CG.

Table 3. Changes in cardiorespiratory parameters at baseline and 3-month follow-up.

	HB n = 28		CB n = 30		CG n = 26		P-Value		
	Baseline	3 Month	Baseline	3 Month	Baseline	3 Month	Time	Group	Interact. ^m
VO ₂ Peak (mL•kg ⁻¹ •min ⁻¹)	26.7 ± 6.55	27.8 ± 6.8 ^a	25.4 ± 7.32	26.7 ± 7.90 ^a	26.6 ± 4.97	26.4 ± 5.42	.08	.69	.04
VT ₁ ^d (mL•kg ⁻¹ •min ⁻¹)	19.5 ± 1.07	21.5 ± 1.0 ^a	19.5 ± 1.04	20.4 ± 1.04	19.9 ± 1.08	19.3 ± 1.11	.81	.06	.03
VT ₂ ^e (mL•kg ⁻¹ •min ⁻¹)	24.9 ± 5.25	26.3 ± 6.9 ^a	22.7 ± 6.95	24.2 ± 7.13	24.7 ± 5.08	22.9 ± 4.19	.41	.49	.03
Duration (s)	570 ± 136	587 ± 157	549 ± 133	552 ± 157	600 ± 126	579 ± 116	.89	.52	.23
Peak HR (bpm) ^c	140 ± 18.8	139 ± 17.8	141 ± 21.5	140 ± 21.1	140 ± 18.9	140 ± 16.6	.75	.97	.95
Peak load (Watts)	198 ± 49	200 ± 54	191 ± 50	191 ± 54	206 ± 41	197 ± 38	.39	.67	.15
Peak RER ^b	1.24 ± 0.89	1.21 ± 0.10	1.23 ± 0.80	1.24 ± 0.10	1.20 ± 0.8	1.20 ± 0.13	.47	.32	.36
Borg	15.8 ± 1.16	15.8 ± 1.33	16.2 ± 1.04	16 ± 1.17	15.9 ± 1.05	16.2 ± 1.02	.87	.45	.38

Data are presented as mean ± SD. b: Respiratory exchange ratios, c: Heart rate, d: First ventilatory threshold, e: Second ventilatory threshold, m: Interaction. ^a=P-interaction <0.05.

Changes in daily PA are shown in Table 4. PA behavior remained constant after the intervention (P -time = .73). Ninety seven percent of patients met the international guidelines of 150 minutes or more of moderate PA per week (19). In addition, a significant increase in sedentary time in the CB group (P -interaction = .02) was found. No significant correlation between change in VO_2P and change in active energy expenditure (Spearman ρ = -.14; P = .40) or change in PA duration (Spearman ρ = .09; P = .44) was found. However, a significant correlation between physical fitness and PA duration (Spearman ρ = .53; P < .001) at 12 weeks as well as with active energy expenditure (Spearman ρ = .37; P < .001) was found.

As shown in table 5, isometric handgrip strength, isometric quadriceps strength and endurance as well as exercise onset oxygen uptake on kinetics remained stable during the follow-up.

Further, cardiovascular risk factors (as can be seen in fig 5) and anthropometrics (Table 6) were similar between the groups at baseline and remained stable during the follow-up period, except for an increase in HOMA-index (P -time = .05) which was not different between the groups (P -interaction = .93).

Finally, there were no significant changes in the overall score for HRQoL (P -interaction = .57) as well as the physical (P -interaction = .50) and mental (P -interaction = .85) composite score. (See Table 7 which shows HRQoL from baseline and follow-up evaluations).

Table 4. Changes in daily physical activity at baseline and 3 months follow up.

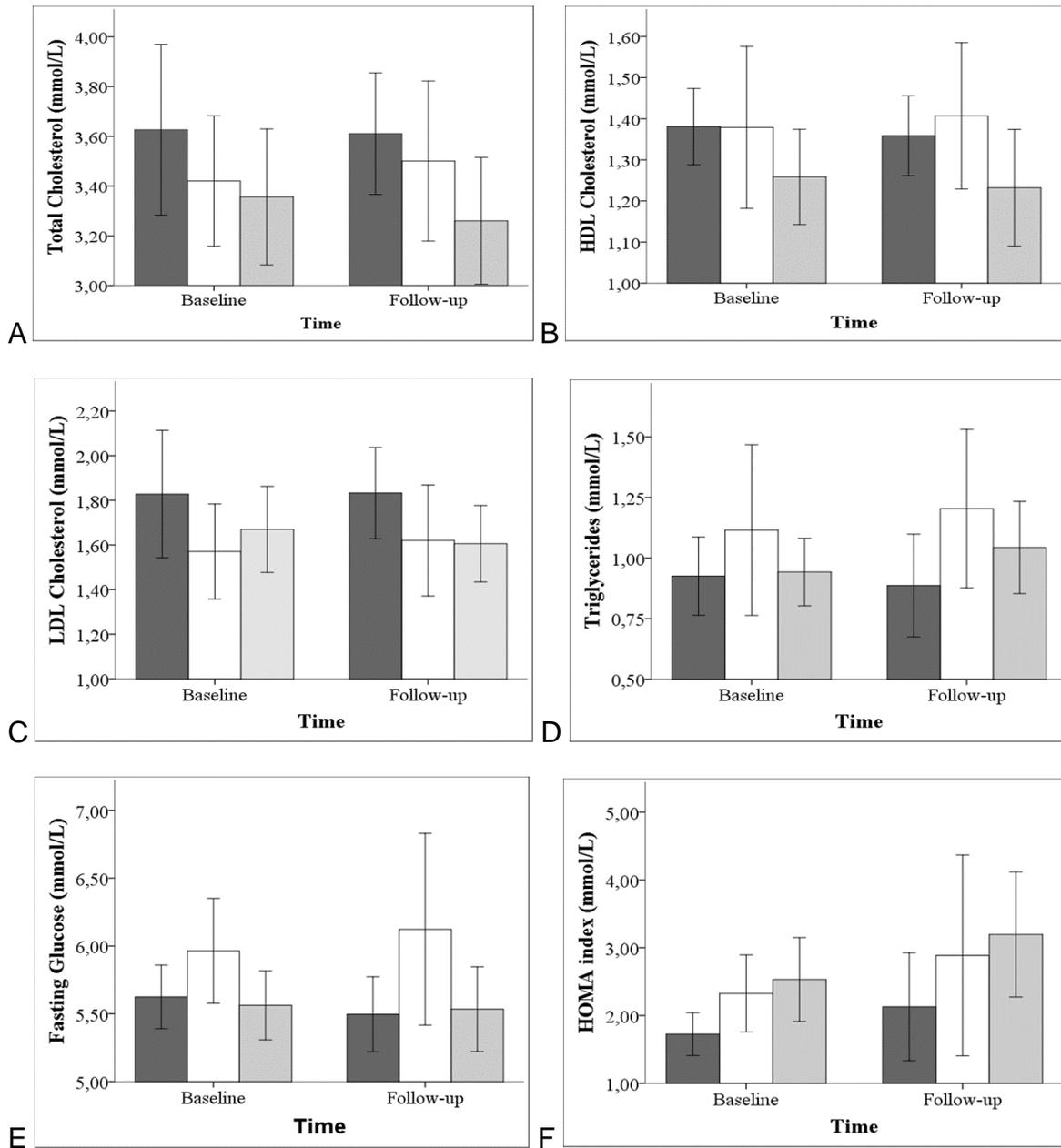
	HB n = 24		CB n = 28		CG n = 26		P Value		
	Baseline	3Month	Baseline	3Month	Baseline	3Month	Time	Group	Interact. ^m
Steps/day	7896 (2018-2554)	6469 (473-12828)	7608 (2474-3281)	7065 (489-4785)	6419 (2227-3181)	6408 (296-12041)	.18	.56	.18
Sedentary time ^c	1039 (688-1260)	1032 (790-1455)	1005 (122-1290)	1094 (857-1254) ^a	1100 (825-1355)	1062 (484-1402)	.56	.43	.02
Active EE ^{b,d}	1336 (351-3217)	1307 (661-2246)	1137 (484-2539)	1244 (549-2745)	1223 (401-2253)	1196 (181-2510)	.56	.40	.45
PA ^h duration ^e	145 (34-299)	141 (51-259)	146 (28-417)	134 (29-366)	114 (30-311)	114 (6-382)	.73	.27	.47
Moderate PA duration ^f	136 (34-238)	134 (49-241)	140 (28-391)	128 (27-348)	109 (29-303)	115 (25-368)	.57	.24	.62
Vigorous PA duration ^g	8 (0-33)	7 (0-24)	6 (0-26)	6 (0-24)	5 (0-20)	2 (0-27)	.50	.21	.59

Data are presented as mean (range) .h: physical activity, b: energy expenditure, c: ≤ 1.5 METs; min/day, d: >3METs; kcal); e: >3METs; min/day, f: 3-6 METs; min/day, g: >6 METs; min/day. a=P-interaction <0.05, m: Interaction.

Table 5. Changes in muscle strength and exercise-onset VO₂.

	HB n = 23		CB n = 29		CG n = 19		P-Value		
	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Time</u>	<u>Group</u>	<u>Interact^m</u>
<u>Muscle strength</u>									
Handgrip strength (kg)	43.1 ± 10.5	44.7±12.3	40.2 ± 8.6	41.2 ± 8.3	41.6 ± 8.3	43.8 ± 9.3	.99	.23	.23
Isometric quadriceps extension (Nm)	151.8 ± 28	164.1± 37	150.5± 44.9	155 ± 43.4	148.7 ± 30	148.8 ± 28.3	.23	.47	.86
Extension total work (180°/s (J))	1614 ± 680	1976± 718	1758 ± 756	1893±717	1694 ± 796	1906 ± 689	.09	.94	.52
<u>Exercise-Onset VO₂ kinetics</u>									
Average MRT(s)	45.5 ± 16.2	39.8± 9.3	38.7 ± 8.1	40.8 ± 9.1	39.8 ± 16.9	43.6 ± 22	.98	.64	.19

Data are presented as mean ± SD. a: Kilograms b: Mean response time, c: Nm. d: 180°/s (J). m: Interaction.

Figure 2. Cardiovascular risk factors at baseline and follow-up.

Panel A: The intervention had no effect in total cholesterol levels in any group (p interaction = .82), B: The HDL-Cholesterol did not change significantly in any group after the intervention (p interaction = .69). C: There was no significant change in the LDL-Cholesterol levels after 3-months (p interaction = .79), D: The triglycerides levels did not change significantly from baseline to 3-months control in any group (p interaction = .27), E: Fasting glucose did not change significantly in any group during the intervention (p interaction = .71), F: Homa index did not show significant differences in any group after the intervention (p interaction = .93). No significant changes were found in cardiovascular risk factors. Dark gray column: HB group, White column: CB group, Light grey column: CG.

Table 6. Outcomes at baseline and 3 months control in anthropometric parameters.

	HB n = 28		CB n = 30		CG n = 26		P-Value		
	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Time</u>	<u>Group</u>	<u>Interact^m</u>
<u>Anthropometrics</u>									
Weight(kg)	80.4 ± 10.3	79.8 ± 10.3	82.9 ± 15.3	82.4 ± 15	85 ± 12.7	84.1 ± 11.9	.36	.22	.55
BMI ^b (kg/m ²)	26.6 ± 2.5	26.4 ± 2.5	27.8 ± 4	27.6 ± 4.1	28 ± 3.3	27.6 ± 2.6	.28	.21	.53
Body fat %	26.8 ± 5.7	26.5 ± 6.1	29.5 ± 5.5	28.4 ± 6.4	29.5 ± 5.1	28.8 ± 4.2	.16	.12	.60
Waist Circumference (cm)	96.8 ± 8.8	95.2 ± 8.2	98.7 ± 11.2	99 ± 11.4	99.5 ± 9.8	99.6 ± 9.6	.81	.29	.11
Hip circumference (cm)	101.1 ± 5.9	101 ± 5.4	102.6 ± 7.4	102.7 ± 7.6	102.5 ± 4.1	102.1 ± 5.1	.31	.42	.82
SBP ^d (mmHg)	125.3±15.6	124.1± 13.9	127.4 ± 15	124.1 ± 13.8	123.6 ± 13	122.9 ± 14	.29	.75	.73
DBP ^e (mmHg)	75.4 ± 9.5	75.8 ± 9	76 ± 8.3	74.7 ± 8.2	75.5 ± 8.9	76.9 ± 7.9	.81	.91	.37
HR ^c (bpm)	56.8 ± 9.1	56.4 ± 7.4	57.1 ± 8.2	57.7 ± 10.1	56 ± 8.1	56.7 ± 14	.90	.68	.84

Data are presented as mean ± SD. b: Body mass index, d: Systolic blood pressure, e: Diastolic blood pressure, c: Heart rate in rest, m: Interaction.

Table 7. Changes in Health related quality of life.

	HB n = 28		CB n = 30		CG n = 26		P-Value		
	Baseline	3Month	Baseline	3Month	Baseline	3Month	Time	Group	Interact. ^m
<u>HRQoL^b</u>									
PF ^c	90±10.7	91.9±7.6	85.3±15.6	87.4±13.6	81.4±15.7	84.3±16.1	.19	.04	.49
RP ^d	83.6±27.3	87.5±28.4	74.2±36.6	83.9±31.3	58 ± 41.4	61.4±38.9	.15	.00	.43
BP ^e	84.2±13.7	80.9±17.7	82.5±19.2	83.8±23.3	72.7±23.3	77.6±23.2	.83	.11	.70
GH ^f	74.2±13.1	75.2±18.7	75.7±13.6	72.4±22.9	64.2±16.6	71.5±19.1	.41	.17	.17
VT ^g	72.8±13.9	71 ± 13.4	69.3±15.6	74.6±15.4	65.3±14.6	63.9 ± 20	.70	.06	.10
SF ^h	87.6±16.7	90.6±16.5	86.6±17.3	89.1±15.7	83.7±18.2	89.5±17.5	.20	.81	.90
RE ⁱ	84.6± 27	86.8±22.8	84.5±33.3	86.8±29.1	86.2±30.2	84.7 ± 31	.73	.99	.79
MH ^j	78.6±15.6	77.5±17.6	79.3±13.3	81.4 ± 15	78.2±15.6	76.6±21.1	.91	.72	.59
PCS ^k	80.9±12.3	81.3±13.1	77.2±15.2	80.8±16.3	67,9±17.1	71.8±18.3	.008	.07	.50
MCS ^l	79.8±13.7	80.2±13.5	77.5 ± 18	81.3±15.5	75.1±13.8	77.2±16.2	.06	.38	.85
SF-36	82.2±13.3	82.6 ± 13	79.8±16.1	82.6±15.8	73.3±15.1	76.4±16.4	.07	.06	.57

Data are presented as mean ± SD. b: Health related quality of life. Scores of the domains of the 36-Item Short-Form of SF-36: 0= worst and 100= best score. c: Physical function, d: Role-physical function, e: Bodily pain, f: General health, g: Vitality, h: Social function, i: Role-emotional function. j: Mental health, k: Physical composite score, l: Mental composite score, m: Interaction.

Training data

Patients in the HB group performed an average of 2.5 (range: 12-60 sessions during 12 weeks) sessions per week, while the CB group performed an average of 2.0 sessions per week during the 12 weeks (range: 4-36 sessions during 12 weeks). Patients in the HB group exercised on average 164 minutes per week at an average intensity of 46.8% of HRR (76.7 minutes within prescribed zone). The CB group exercised on average 90 minutes per week at an average intensity of 61.2% of HRR.

DISCUSSION

The significant finding of our randomized controlled study is that a 3 month HB training intervention with tele-monitoring guidance results in a further improvement of exercise capacity (VO_2P) in CHD patients who just completed a phase II ambulatory program and is as effective as a prolonged CB cardiac rehabilitation. The observed improvements of $1.30\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $1.10\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in VO_2P for CB and HB groups respectively, are likely to be clinically relevant as it has been shown earlier that $1\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ increase in exercise capacity is associated with a 10% reduction in cardiovascular mortality (20). As such, our results support the added value of a structured continued rehabilitation program.

There are only few studies in the literature that have investigated the effectiveness of a HB tele-monitored phase III CR program, starting immediately after completion of a phase II CB cardiac rehabilitation program. A small proof of concept study by Brubaker et al (5) randomly assigned 31 patients to HB, CB or standard care. In line with our results, they found that a HB program was as effective as the CB program at improving/maintaining oxygen consumption nine months after exiting a cardiac rehabilitation program. In the Telerehab III trial (21), 140 patients were randomized to a tele-rehabilitation program in addition to conventional cardiac rehabilitation or conventional cardiac rehabilitation alone. This study also reported that a 6-month patient-specific comprehensive tele-rehabilitation program initiated six weeks after the start of ambulatory rehabilitation leads to a bigger improvement in VO_2P and

confirmed our results of a lack of an additional weight loss, blood pressure reduction or lipid profile improvement and/or glycaemic control.

In the last decade, several meta-analyses have been published demonstrating the effectiveness of HB programs for CHD patients implemented as a phase II cardiac rehabilitation program (22-24). Although the increase in VO_2P of 4 to 5% in our phase III CB and HB groups is less than what is seen in previous phase II programs, this is still of clinical relevance as the purpose of phase III (maintenance phase) of cardiac rehabilitation is to preserve or if possible enhance the health benefits gained in phase II. Our results further show that even although patients in the HB group only exercised 75 minutes per week at the prescribed intensity and the average intensity was below the recommended thresholds, patients were still able to further increase their exercise capacity when compared to patients in the CG that received the advice to maintain a physically active lifestyle. This is in line with meta-analytic results of Swain and Franklin (25), demonstrating that in healthy individuals with a mean baseline $VO_2max < 40 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ there is no clear minimal intensity threshold to increase their aerobic capacity and patients can already show improvements when exercising at intensity of 40% of HRR. Yet, there is abundant evidence that larger effects on health and fitness are established when individuals/patients exercise at higher intensities and larger volumes (26).

With regard to PA, Ayabe et al (27), reported that 6500-8500 steps/day should be considered as the minimal and optimal goal of PA for secondary prevention of cardiovascular disease. With the number of steps ranging between 7612 steps (HB) and 7700 steps (CB our patients are within this target zone; whereas patients in the CG (5566) do not seem to reach this. However, we were not able to promote an additional increase in the number of daily steps. These results are in line with previous publications that showed how exercise interventions focused on physical fitness improvement in cardiac patients do not have effect on the improvement of PA (21, 28, 29).

We observed however a small but significant increase in sedentary time in the entre-based group. Evidence suggests that those participating in exercise-focused

interventions are not likely to reduce their sedentary time by a meaningful amount (30). King et al.,(31) explained this behaviour as a compensatory effect for exercise. That is, the simple fact of enrolling in a supervised exercise program might reduce PA levels throughout the rest of the day. This compensatory effect acts in different ways – by promoting adjustments in energy expenditure in order to save energy or recover from the exercise training, consequently increasing the sedentary time (32). Growing evidence suggest that prolonged sedentary behaviour can affect cardiovascular and all-cause mortality risk independent of PA (33). Probably, recommendations on sedentary behaviour might be included in cardiac rehabilitation programs, given the current state of the evidence (30).

Small improvements in weight reduction and body composition as well as in blood pressure were observed post-intervention, although this did not reach significance. This is consistent with the findings in the Telerehab III study (21). According to Frederix et al, digital health interventions seem to be able to improve cardiovascular risk factors in primary prevention, but not in secondary prevention programs (21). Furthermore, we might hypothesize that when the pharmacological management of the groups is close to optimal, like in our patients, then the incremental benefit of secondary prevention programs over usual care may be very small (34).

One of the main objectives of cardiac rehabilitation is to optimize patients' physical functionality as a means to improve quality of life. In our study, no effects of our interventions on different HRQoL domains could be found. Contrary to our results, Smith et al (35) found clinically and statistically significant improvements in HRQoL in their home group after a six month intervention compared to their hospital group. The author considered that six months of cardiac rehabilitation, regardless of location, was associated with improvements in physical HRQoL. Thus, it is possible that with a longer intervention for both groups some differences could have been obtained in our study.

One area that is not commonly considered in cardiac rehabilitation is the functional status or abilities of the patients. The typical patient in cardiac rehabilitation is over the age of 60, presents with multiple cardiovascular risk factors, such as inactivity

and obesity, and is recovering from a recent cardiac event. All these factors can lead to deficits in balance, mobility and function. Sumide et al., found that musculoskeletal fitness and flexibility, measured by the SRT, was a significant predictor of mortality in 51-80 year-old participants (36). In the present study no significant difference was present in the SRT between the groups ($P = .36$). Our results are in line with previous studies (Oerkild et al) (37). As for components of muscular fitness, Mroszczyk et al (38) and Thomaes et al (39) found increased HG strength in patients following three months of a (predominantly aerobic exercise training) cardiac rehabilitation program. In our study though, no changes were observed after 12 weeks of intervention. It is possible that the largest gains in HG strength appear during phase II of cardiac rehabilitation, while our intervention targeted Phase III patients. In addition, we found no significant difference in knee extension strength or resistance after 3 months of HB or CB training which could be explained by the focus on aerobic training during the intervention. These results are also consistent with previous studies (40, 41). Conraads et al, collected muscle strength data in 75 CAD patients before and after 12 weeks of an AIT or ACT cardiac rehabilitation program finding that muscle strength did not improve. The author considered as possible causes the use of statins that has been associated with negative side effects on the muscles. In our study 94% of the patients were treated with statins, although insufficient evidence exists to prove that statins really affect muscle strength (42). Currently, there is very limited evidence regarding the effects of tele-rehabilitation on muscle strength and more research is needed (43).

Finally, while short-term changes are of interest, it is important to establish whether the benefits are maintained in time, thus further research should focus on the long term effects of HB cardiac rehabilitation with tele-monitoring guidance.

Limitations

Our study should be interpreted within the context of its limitations. First of all, next to PA training, cardiac rehabilitation includes other important core components such as nutritional counselling, risk factor management and psychosocial management. Although, PA training comprises 30-50% (up to >70%) of all cardiac rehabilitation

activities. It should be acknowledged that this study evaluated the effect of PA tele-monitoring rather than tele-rehabilitation (3). Second, heart rate monitors were only used in the HB group as we opted to not change the traditional CB program where heart rate is measured by palpation by physiotherapists. As such, we were not able to precisely define the exact number of minutes patients spend within the prescribed training zone.

Another limitation in this study is the lack of blinding of test personnel. However, as the main outcome measure was $\dot{V}O_2P$, the effort of the participants can be objectively quantified by means of the respiratory exchange ratio (RER) and subjectively by means of the Borg scale (44). The study, as most randomized controlled trials, had missing outcome data. In muscle strength due to technical problems 19 values were missing completely at random and for PA, in 12 patients the data was incomplete and thus excluded.

CONCLUSION

The results of our study show that HB cardiac rehabilitation with tele-monitoring guidance can be an effective alternative to CB cardiac rehabilitation for further improving exercise capacity following phase II cardiac rehabilitation in CHD patients.

Acknowledgments

AA is supported by a doctoral research grant funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate programme (2011-0015). RB received a research grant from the Belgian Fund for Cardiac Surgery.

The authors thank the patients who participated in the TRiCH study as well as the staff of the cardiac rehabilitation center in UZ Leuven for their enthusiastic support of this project.

REFERENCES

1. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren WM AC, Benlian P, Boysen G, Cifkova R, Deaton C. European Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*. 2012;33(13):1635-701.
2. Piepoli M CU, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, Dendale P, Doherty P, Gaita D, Höfer S, McGee H, Mendes M, Niebauer J, Pogosova N, Garcia-Porrero E, Rauch B, Schmid J, Giannuzzi P. 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. *European Journal of Preventive Cardiology*. 2014;21(6):664-81.
3. 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. *European Journal of Preventive Cardiology*. 2015;22(2):150-8.
4. Janssen V, De Gucht V, Van Exel H, Maes S. Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients. *European journal of preventive cardiology*. 2013;20(3):431-41.
5. Brubaker PH, Rejeski WJ, Smith MJ, et al. A home-based maintenance exercise program after center-based cardiac rehabilitation: Effects on blood lipids, body composition, and functional capacity. *Journal of Cardiopulmonary Rehabilitation*. 2000;20(1):50-6.
6. Lear SA, Spinelli JJ, Linden W, Brozic A, Kiess M, Frohlich JJ, et al. The Extensive Lifestyle Management Intervention (ELMI) after cardiac rehabilitation: A 4-year randomized controlled trial. *American Heart Journal*. 2006;152(2):333-9.
7. Avila A, Goetschalckx K, Vanhees L, Cornelissen V. A Randomized Controlled Study Comparing Home-Based Training with Telemonitoring Guidance Versus Center-Based Training in Patients with Coronary Heart Disease: Rationale and Design of the Tele-Rehabilitation in Coronary Heart Disease (TRiCH) Study. *Journal of Clinical Trials*. 2014;4(4):1-5.
8. Rawstorn JC, Gant N, Direito A, Beckmann C, Maddison R. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. *Heart*. 2016;102(15):1183-92.
9. Ferrier S, Blanchard CM, Vallis M, Giacomantonio N. Behavioural interventions to increase the physical activity of cardiac patients: a review. *Eur J Cardiovasc Prev Rehabil*. 2011;18:15-32.
10. Buckingham SA, Taylor RS, Jolly K, et al. Home- based versus centre- based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart*. 2016;3(2):e000463.
11. *Cardiology Procedures: A Clinical Primer*. Hendel R, Carey K, editors: Springer; 2017.

12. Garmin International Inc garminconnect [Available from: <https://connect.garmin.com/nl-NL/> (Archived by WebCite® at <http://www.webcitation.org/6xRyfpipN>).
13. Kraal JJ, Peek N, Van Den Akker-Van Marle ME, Kemps HM. 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. *European Journal of Preventive Cardiology*. 2014;21(2_suppl):26-31.
14. Walker HKWHK, Hall WDHWD, Hurst JWHJW. *Clinical methods: the history, physical, and laboratory examinations*
edited by H. Kenneth Walker, W. Dallas Hall, J. Willis Hurst ; illustrations by Leon Schlossberg and Charles H. Boyter. 3rd ed. ed. Walker HK, Hall WD, Hurst JW, editors: Boston : Butterworths; 1990.
15. Pattyn N, L Vanhees L, Cornelissen V, et al. The long-term effects of a randomized trial comparing aerobic interval versus continuous training in coronary artery disease patients: 1-year data from the SAINTEX-CAD study. *European journal of preventive cardiology*. 2016;23(1154-1164).
16. Wallace TM, Matthews DR. The assessment of insulin resistance in man. *Diabetic medicine : a journal of the British Diabetic Association*. 2002;19(7):527-34.
17. Marques - Vidal P, Mazoyer E, Bongard V, et al. Prevalence of insulin resistance syndrome in Southwestern France and its relationship with inflammatory and hemostatic markers. (*Epidemiology/Health Services/Psychosocial Research*). *Diabetes Care*. 2002;25(8):1371-7.
18. Wasserman K HJ, Sietsema K, Sue D, Stringer W, MD , Whipp B, Sun X, MD. *Principles of exercise testing and interpretation; including pathophysiology and clinical applications*, 5th ed. Portland: Wolters Kluwer Health; 2015. 588 p.
19. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise*. 2011;43(7):1334.
20. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *Journal of the American College of Cardiology*. 2003;42(12):2139-43.
21. 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).
22. Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital Health Interventions for the Prevention of Cardiovascular Disease: A Systematic Review and Meta- analysis. *Mayo Clinic Proceedings*. 2015;90(4):469-80.
23. Huang K, Liu W, He D, Huang B, Xiao D, Peng Y, et al. Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: A systematic review and meta-analysis. *European Journal of Preventive Cardiology*. 2015;22(8):959-71.

24. Frederix I, L Vanhees L, Dendale P, Goetschalckx K. A review of telerehabilitation for cardiac patients. *Journal of Telemedicine and Telecare*. 2015;21(1):45-53.
25. Swain DP, Franklin BA. VO₂ reserve and the minimal intensity for improving cardiorespiratory fitness. *Medicine and science in sports and exercise*. 2002;34(1):152.
26. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *European journal of preventive cardiology*. 2013;20(3):442.
27. Ayabe M, Kiyonaga A, Shindo M, et al. Target step count for the secondary prevention of cardiovascular disease. *Circulation Journal*. 2008;72(2):299-303.
28. Kraal JJ, Van Den Akker-Van Marle ME, Abu-Hanna A, Stut W, Peek N, Kemps HM. Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study. *European Journal of Preventive Cardiology*. 2017;24(12):1260-73.
29. Ter Hoeve N, Huisstede BMA, Stam HJ, van Domburg RT, Sunamura M, van Den Berg-Emons RJG. Does cardiac rehabilitation after an acute cardiac syndrome lead to changes in physical activity habits? Systematic review.(Research Report)(Report). *Physical Therapy*. 2015;95(2):167.
30. Prince SA, Saunders TJ, Gresty K, Reid RD. A comparison of the effectiveness of physical activity and sedentary behaviour interventions in reducing sedentary time in adults: a systematic review and meta-analysis of controlled trials. 2014. p. 905-19.
31. King N, Caudwell P, Hopkins M, et al. Metabolic and Behavioral Compensatory Responses to Exercise Interventions: Barriers to Weight Loss*. *Obesity*. 2007;15(6):1373-83.
32. Moura BPD, Marins JCB, Franceschini SDCC, Reis JS, Amorim PRDS. Aerobic exercise did not have compensatory effects on physical activity levels in type 2 diabetes patients. *Journal of Sports Sciences*. 2015;33(6):545-51.
33. Biswas A, Faulkner GE, Oh PI, Alter DA. Patient and practitioner perspectives on reducing sedentary behavior at an exercise-based cardiac rehabilitation program. *Disability and rehabilitation*. 2017:1.
34. Clark AM, Haykowsky M, Kryworuchko J, Macclure T, Scott J, Desmeules M, et al. A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2010;17(3):261-70.
35. Smith KM, Arthur HM, McKelvie RS, Kodis J. Differences in sustainability of exercise and health- related quality of life outcomes following home or hospital-based cardiac rehabilitation. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2004;11(4):313-9.
36. Brito LBB, Ricardo DR, Araújo DSM, Ramos PS, Myers J, Araújo CGSD. Ability to sit and rise from the floor as a predictor of all-cause mortality. *European journal of preventive cardiology*. 2014;21(7):892-8.

37. Oerkild B, Frederiksen M, Hansen JF, Simonsen L, Skovgaard LT, Prescott E. Home- based cardiac rehabilitation is as effective as centre- based cardiac rehabilitation among elderly with coronary heart disease: results from a randomised clinical trial. *Age and Ageing*. 2010;40(1):78-85.
38. Mroszczyk-Mcdonald A, Savage PD, Ades PA. Handgrip strength in cardiac rehabilitation: normative values, interaction with physical function, and response to training. *Journal of cardiopulmonary rehabilitation and prevention*. 2007;27(5):298-302.
39. Thomaes T, Thomis M, Onkelinx S, et al. Muscular strength and diameter as determinants of aerobic power and aerobic power response to exercise training in CAD patients. *Acta Cardiologica*. 2012;67(4):399-406.
40. Sumide T, Shimada K, Ohmura H, et al. Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: Comparison of patients after cardiac surgery and patients with myocardial infarction. *Journal of Cardiology*. 2009;54(2):273-81.
41. Servantes DM, Pelcerman A, Salvetti XM, et al. Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes. *Clinical Rehabilitation*. 2012;26(1):45-57.
42. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: The SAINTEX-CAD study. *International Journal of Cardiology*. 2015;20(179):203-10.
43. Hwang R, Bruning J, Morris N, Mandrusiak A, Russell T. A Systematic Review of the Effects of Telerehabilitation in Patients With Cardiopulmonary Diseases. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2015;35(6):380-9.
44. Aamot I-L, Forbord SH, Gustad K, Aamot, I.L., Forbord, S.H., Gustad, K., Løckra, V., Stensen, A., Berg, A.T., Dalen, H., Karlsen, T. and Støylen, A., 2014. Home-based versus hospital-based high-intensity interval training in cardiac rehabilitation: a randomized study. *European journal of preventive cardiology* , 21 (9), pp.1070-1078. Home- based versus hospital- based high- intensity interval training in cardiac rehabilitation: a randomized study. *European Journal of Preventive Cardiology*. 2014;21(9):1070-8.

Chapter 4

Home-based exercise with tele-monitoring guidance in patients with coronary artery disease; Does it improve long-term physical fitness?

Andrea Avila*; Jomme Claes*; Roselien Buys; May Azzawi; Luc Vanhees; Veronique

Cornelissen

*Shared first authorship

Submitted

ABSTRACT

Background: Exercise and PA are an essential part of contemporary CAD management. However, evidence shows that patients experience clear difficulties in maintaining a physically active lifestyle following completion of a structured and supervised phase II exercise-based cardiac rehabilitation program. HB interventions have shown to enhance a patient's self-efficacy and might facilitate the lifelong uptake of a physically active lifestyle. Yet, data on the long-term effectiveness of HB exercise training on PA and exercise capacity are scarce.

Objective: The main purpose of the TeleRehabilitation in Coronary Heart disease (TRiCH) study was to compare the long-term effects of the implementation of a short HB phase III exercise program with tele-monitoring guidance to a prolonged CB phase III program in patients with CAD. Primary outcome measure was exercise capacity. Secondary outcome measures included PA behaviour, cardiovascular risk profile and health related quality of life.

Methods: Ninety CAD patients (80 male) were randomized to three months of HB (=30), CB (=30) or a control group (CG) (=30) on a 1:1:1 basis after completion of their phase II ambulatory cardiac rehabilitation program. Outcome measures were assessed at discharge of the phase II program and after one year.

Results: Eighty patients (72 (91%) men and mean age 62.6 years old) completed the one-year follow-up measurements. Exercise capacity (VO_2P), cardiovascular risk factors and HRQoL were preserved in all three groups (p -time >0.05 for all), irrespective of the intervention (p -interaction >0.05 for all). Eighty five percent of patients met the international guidelines for PA (p -time < 0.05). No interaction effect was found for PA (steps, amount of active time, and amount of sedentary time) over the one-year period after discharge of a phase II program.

Conclusion: Overall, exercise capacity remained stable during one year following phase II cardiac rehabilitation. Our HB exercise intervention was as effective as CB and did not result in higher levels of exercise capacity and PA compared to the other two interventions.

INTRODUCTION

Cardiac rehabilitation contributes significantly toward the care of cardiovascular disease patients (1), and is nowadays considered as a class IA recommendation by all international guidelines (2, 3). Cardiac rehabilitation is a complex multidisciplinary intervention that comprises different therapies: i.e. risk factor education and modification, health behaviour change, psychological support, vocational support and nutritional counselling. These interventions target risk factors for CAD(4), and have PA and exercise as their core accounting for 30-70% of the total programme. Among patients with established CAD, participation in an exercise-based cardiac rehabilitation programme provides major health benefits including reduced risk for cardiovascular mortality and hospitalization (and associated health care costs) and improvements in health related quality of life (HRQoL) (5).

Nevertheless, long-term adherence to a healthy active lifestyle remains the biggest challenge for these patients (6). Evidence shows that PA levels decline after cardiac rehabilitation completion with as few as 28% of patients maintaining the recommended levels at 12 months of usual care (7). Previously, Hansen et al (8), showed that only 27% of patients that participated in a CB phase II programme adhered to the minimal PA level (9) that is required for significant health benefits at 18 months of follow-up. This is especially worrisome since PA might underlie the maintenance of exercise capacity (VO_2P) which when compared with other known cardiovascular risk factors, is the strongest predictor of mortality among CAD patients (10).

In Belgium, 15-20% of patients participate in an ambulatory cardiac rehabilitation programme (phase II), whereas only 5% participates in a long-term phase III maintenance intervention (11). Since it is often easier to integrate an exercise routine into the home and community environment (12), the use of HB cardiac rehabilitation carries the potential to improve compliance to an active lifestyle compared to CB cardiac rehabilitation in the long-term post-hospitalization (12).

The technological advances of the last decade have allowed moving away from the hospital setting towards the use of exercise training in the patients' home. Amongst

others, tele-rehabilitation involves the guidance and monitoring of the patient from a distance and provision of personalized feedback on a regular base. Earlier meta-analytic data already showed that HB rehabilitation could be an alternative for supervised cardiac rehabilitation for promoting maintenance of exercise capacity in the short-term (13). However, the long-term effects of HB have not been widely studied. Recently Claes et al. (14) identified respectively, three and seven studies evaluating PA and exercise capacity at least one year following HB cardiac rehabilitation (14). Small, though clinically none significant, effect sizes for exercise capacity were found in favour of HB cardiac rehabilitation compared to CB cardiac rehabilitation in the longer-term with similar effects on PA behaviour. Moreover, none of these studies used objective tools to assess PA.

Given the limited data available, the objective of the current report was to compare the long-term effects (i.e. one year after completion of an ambulatory phase II cardiac rehabilitation programme) of a 12-week HB program or a 12-week prolonged CB program on exercise capacity by objectively measuring PA behaviour in CAD patients. We hypothesized that patients enrolled in the HB group would show less decrease in peak oxygen consumption (VO_{2P}) and higher levels in PA compared to patients in the CB and CG group.

METHODS

Study design and Population

The TRiCH study is a randomized controlled clinical trial designed to investigate the long-term effect of a HB exercise intervention with tele-monitoring guidance on exercise capacity, PA and other secondary outcomes in CAD patients after discharge from a phase II cardiac rehabilitation program. A detailed description of the experimental design (15), recruitment procedure and eligibility criteria as well as the short-term results (16) have been reported elsewhere. The study protocol was approved by the medical ethical committee of the UZ Leuven/ KU Leuven and all patients provided written informed consent. The TRiCH study was registered in ClinicalTrials.gov database: NCT02047942.

In summary, ninety CAD patients who successfully completed a supervised and structured phase II cardiac rehabilitation program were randomized on a 1:1:1 basis to HB, prolonged CB or CG for 12 weeks. As described previously (15), the HB group trained the first three sessions under supervision of the investigator after which they received an individualized aerobic endurance exercise prescription recommending them to exercise for at least 150 minutes a week at a target heart rate of 70-80% of HRR at home for 12 weeks. Patients were asked to log all exercise data by means of a Garmin Forerunner (Garmin Forerunner 210, Wichita USA) and to upload the data on the online web application (<https://connect.garmin.com/nl-NL/>) for review by the investigators (17). Once a week, patients received feedback by phone or e-mail. Patients randomized to CB continued their training on an ambulatory base at the outpatient clinic of UZ Leuven under direct supervision of physical therapists. This intervention included three weekly sessions, consisting of approximately 45 minutes of endurance training at 70-80% of HRR followed by relaxation. The CG was advised to maintain a physically active lifestyle and was invited for the follow-up visits at 12 weeks and one-year. Following completion of the 12-week intervention, all groups were encouraged to continue exercising but no contact or feedback was provided during the subsequent nine months.

Primary outcome measure

Cardiorespiratory fitness or exercise capacity. The primary outcome, *exercise capacity*, was determined as VO_2P assessed by a maximal graded test on a bicycle until volitional exhaustion with breath-by-breath respiratory gas analysis (Ergometrics 800S, Ergometrics, Bitz, Baden-Württemberg, Germany) and continuous 12-lead electrocardiogram. The test started at 10 or 20 W and was increased with 10 or 20 W/minute. We defined VO_2P as the 30 seconds average oxygen uptake at the highest workload (15). Individual VO_2P results were compared with predicted reference values of Wasserman (18). Additionally, we measured peak heart rate, calculated peak respiratory exchange ratio and determined both ventilatory thresholds (VT) (15).

Secondary outcome measures

Physical activity. PA was measured with a Sensewear® Mini Armband (BodyMedia, Inc., Pittsburgh, PA, USA) worn on the non-dominant arm for a minimum of five consecutive days. Steps, sedentary time (duration of sedentary activity at an intensity of ≤ 1.5 metabolic equivalents of task [METs]; minutes), duration of light intensity physical activity (≥ 1.5 and ≤ 3 METs; minutes) and duration of moderate and vigorous PA (≥ 3 METs; minutes) were used in the analyses (19). Patients meeting the international guidelines of minimum 150 minutes of moderate PA or 60 minutes of vigorous activity at the one year follow up were labeled as 'physically active' (9). A valid day was considered if at least 1368 minutes of data was obtained (95% of a 24 hour period) (20).

Muscle function. Sit and rising test (21), handgrip strength (JAMAR grip strength dynamometer) (22, 23) and quadriceps maximal isometric knee extension strength and endurance (Biodex Medical Systems Inc., 840-000 System 4, New York, USA) were also obtained (23).

Traditional cardiovascular risk factors. Further, we measured the following traditional cardiovascular risk factors including anthropometric characteristics (body mass index, waist and hip circumference), blood pressure and biochemical analysis of a fasting blood sample (glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides).

Health-related quality of life. Finally, the SF 36 was used to assess HRQoL (15).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS (version 20; SPSS for windows; SPSS Inc., Chicago, IL). The current report compares the data obtained at discharge of the phase II cardiac rehabilitation program (= baseline) and after one year follow-up between the different groups. The Shapiro-Wilk test was used to assess normality of distributions. Continuous variables are reported as means \pm standard deviation (SD) or median, categorical data as numbers and percentages. One-way analysis of variance (ANOVA) and chi-square tests were used to analyse differences in

demographic and clinical data between groups at baseline. For follow-up data, a linear mixed modelling method was used to evaluate time, group and time x group interaction effects. Spearman correlation coefficients (ρ) were calculated between VO_2P and PA characteristics. A two-tailed $P \leq 0.05$ was considered statistically significant.

RESULTS

Figure 6 shows the flow throughout the study. Ninety one percent or 80 patients completed the one year follow up measurements. Four patients (3 men) from the HB group, one patient from the CB group (1 men) and five patients (4 men) from the CG group dropped out. At baseline, groups were equal with regard to demographic and clinical characteristics, reason for referral and pharmacological treatment (Table 8). Demographic characteristics of patients that dropped out were not different from the other participants.

Figure 6. Flow of patients throughout the study.

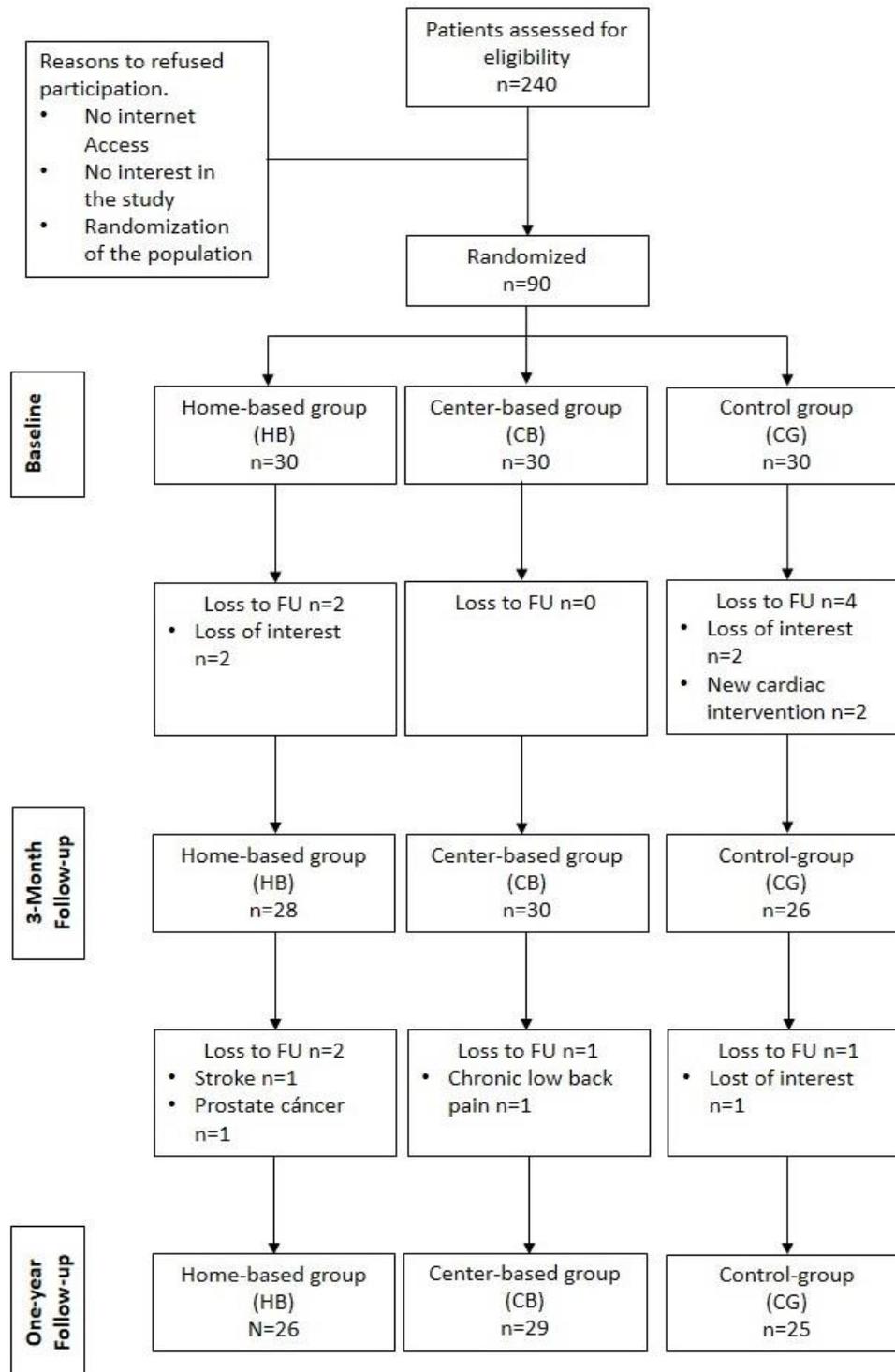


Table 8. Baseline characteristics of patients.

Characteristics	HB n = 26	CB n = 29	CG n = 25
Age (years) \pm SD ^g	62.2 \pm 7.1	62.0 \pm 7.4	63.7 \pm 7.4
Female (%) ^b	3 (12)	3 (10)	2 (8)
<u>Reason for referral</u>			
CABG ^c (%)	15 (58)	17 (59)	16 (64)
PCI ^d (%)	11 (42)	12 (41)	19 (36)
<u>Cardiovascular risk factors (%)</u>			
Familial predisposition	11 (42)	8 (27)	9 (36)
Hypertension	10 (38)	10 (34)	13 (52)
Diabetes	2 (8)	7 (24)	3 (12)
Dyslipidemia	13 (50)	16 (55)	14 (56)

(Continued on next page)

Table 8. Baseline characteristics of patients. (Continued)

Characteristics	HB n = 26	CB n = 29	CG n = 25
Smoking			
Never-smoker	11 (42)	14 (48)	13 (52)
Ex-smoker	12 (12)	14 (48)	12 (48)
Current-smoker	3 (46)	1 (4)	0
Medication			
Anti-hypertensive ^f	19 (73)	26 (90)	19 (76)
Beta Blockers	17 (65)	22 (76)	20 (80)
Statins	24 (92)	28 (97)	23 (92)
Aspirin	24 (92)	27 (93)	24 (96)
Anti-thrombotic	18 (69)	17 (59)	19 (76)
Anti-arrhythmic	1 (4)	1 (3)	0
Hypoglycaemic	3 (12)	8 (28)	4 (16)
Vasodilators	0	1 (3)	2 (8)

g: Continuous variables are expressed as means \pm SD, b: Dichotomous variables are expressed as numbers and percentages. c: coronary artery bypass graft, d: percutaneous coronary intervention, f: warfarine and clopidogrel.

Primary outcome measure

As can be appreciated from the respiratory exchange ratios (RER) and the BORG score, participants in all three groups performed a comparable maximal effort at the end of phase II and at one year follow-up (Table 9). Overall VO_2P ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and the maximal test duration remained stable over time whatever the group, with subtle though non-significant decreases in the CB and CG group. In line, VT_1 insignificantly decreased in the CB and CG group, whereas it remained stable in the HB. Difference in responses between groups did however not reach statistical significance (P -interaction = $>.05$ for all). After one year, 12 patients (46%) from the HB group decreased their VO_2P in more than $1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, as well as 12 patients (41%) in the CB group and 14 (56%) of the CG group.

Table 9. Changes on primary outcome and other respiratory parameters during the study.

	HB n = 26		CB n = 29		CG n = 25		P-Value		
	<u>Baseline</u>	<u>1 Year</u>	<u>Baseline</u>	<u>1 Year</u>	<u>Baseline</u>	<u>1 Year</u>	Time	Group	Interact. ^m
VO ₂ Peak (mL•kg ⁻¹ •min ⁻¹)	26.7 ± 6.55	27.1 ± 6.5	25.4 ± 7.3	24.5 ± 6.4	26.6 ± 4.97	26.2 ± 7.6	.53	.54	.72
VO ₂ Peak (ml/min)	2140 ± 599	2227 ± 670	2090 ± 601	2004 ± 508	2300 ± 449	2251 ± 641	.73	.32	.36
VT ₁ ^d (mL•kg ⁻¹ •mi n ⁻¹)	19.5 ± 4.9	20.7 ± 6	19.5 ± 6.4	18.7 ± 5.8	20 ± 4.9	19.8 ± 6.3	.99	.80	.13
VT ₂ ^e (mL•kg ⁻¹ •min ⁻¹)	24.9 ± 5.2	24.8 ± 6.2	22.7 ± 6.9	22.3 ± 6.1	23.8 ± 5.8	24.3 ± 5.4	.41	.37	.62
Peak HR (bpm) ^c	140 ± 18	142 ± 15	141 ± 21	141 ± 20	140 ± 18	146 ± 20	.12	.87	.47
Peak RER ^b	1.24 ± 0.8	1.20 ± 0.9	1.23 ± 0.8	1.22 ± 0.8	1.18 ± 0.1	1.21 ± 0.1	.22	.48	.07
Borg	16 ± 1	15.8 ± 1.2	16.2 ± 1.1	16.1 ± 1.1	15.9 ± 1	16.1 ± 0.9	.91	.56	.42

Data are presented as mean ± SD. b: Respiratory exchange ratios, c: Heart rate, d: First ventilatory threshold, e: Second ventilatory threshold, m: Interaction. ^a=P-interaction <0.05.

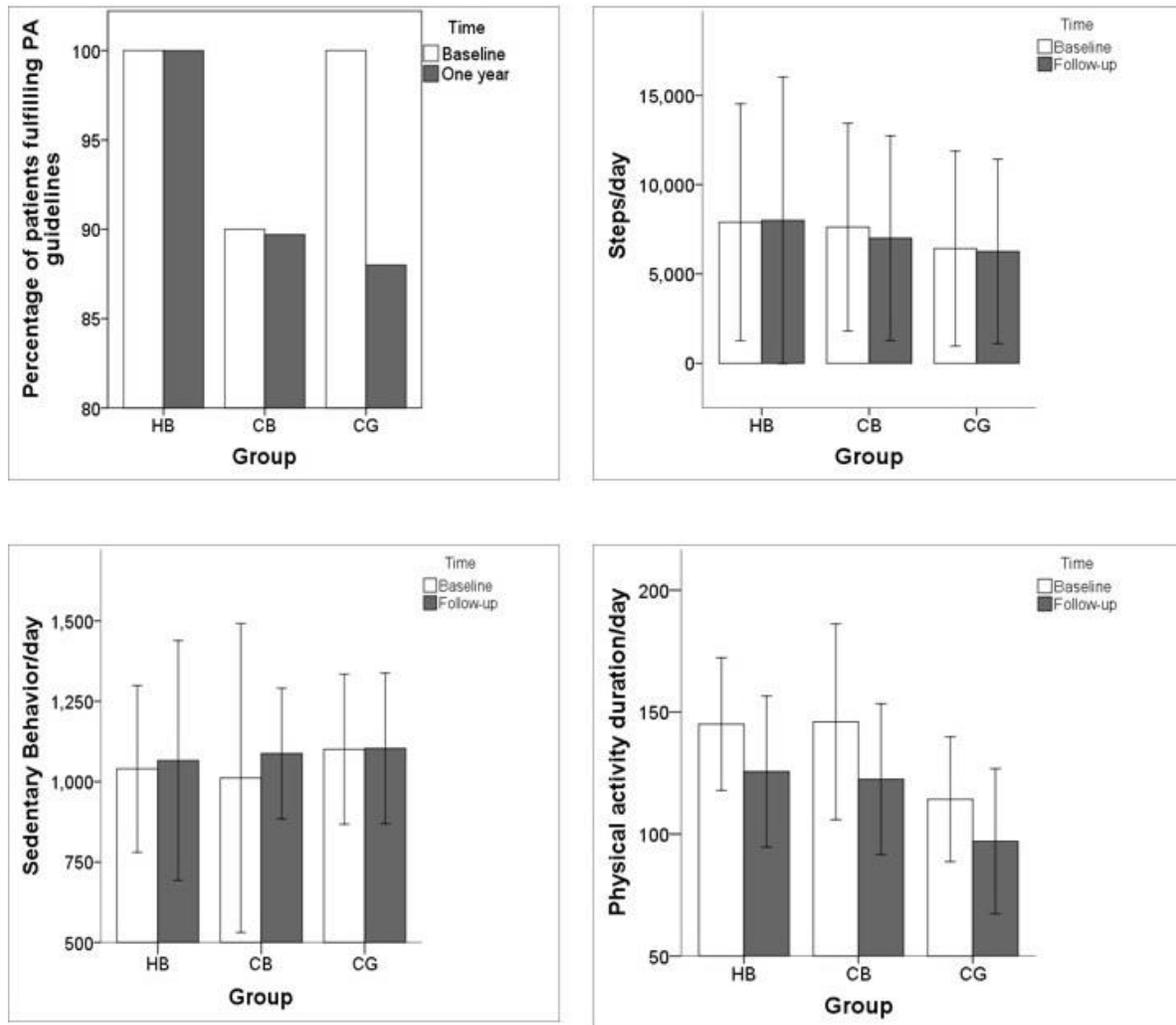
Secondary outcome measures

Figure 7 shows PA data of the three groups at the end of cardiac rehabilitation and at one year of follow-up. Overall, 96.6% of the population met the international guidelines of 150 minutes or more of moderate PA per week at discharge from phase II cardiac rehabilitation. At one-year of follow-up, the number of patients fulfilling these guidelines had decreased to 85% ($p = .1$). There were no differences across groups (P -group = .12). PA, by measurement of average steps per day, trended up in HB group from a median of 7896 (2018 - 12554) at baseline to 8002 (1612 - 17237) at follow-up, and down in the other groups although showing no significant interaction (P -interaction = .75). Although the time spent in light physical activity trended up in the three groups, it showed no significant interaction (P -interaction = .72). The time spent in moderate to vigorous physical activity, defined as PA with an intensity of > 3 METS, was lower at 12 months of follow-up compared to baseline (P -time = .01). However, the decrease was similar in the three groups (P -interaction = .95). As shown in Table 10, the improvement in isometric quadriceps extension, isokinetic total work and handgrip strength reached statistical significance (P -time = $<.001$) without significant differences among groups (P -interaction = $>.05$).

On the other hand, body weight (P -time = .14) increased over time with no change in other measures of body composition (Table 11). Systolic blood pressure remained stable (P -time = .36), whereas a small though significant increase was observed for diastolic blood pressure from baseline to follow-up (P -time = .05). A tendency towards higher total cholesterol and LDL values was observed among all three groups (p -time = 0.09 and .16 respectively). Other cardiovascular risk factors did not change significantly over the one-year period. Further, there were no interactions with the group for any of these parameters (P -interaction = $>.05$ for all).

Finally, all groups maintained high scores for all HRQoL parameters at one year of follow-up, the interaction in the overall score as well as the sub scores were not significant between the groups (P -interaction = .70) as can be seen in Figure 8.

Figure 8. Daily physical activity at baseline and follow-up.



Data are presented as percentage, mean \pm SE. Panel A: PA guidelines (>150 min/week), B: The intervention had no effect in steps/day in any group, C: Sedentary behaviour = ≤ 1.5 METs; min/day, D: Physical activity duration = >3 METs; min/day, HB: Home-based group, CB: Centre-based group, CG: Control group. White column: Baseline, Dark gray column: one year follow-up.

Table 10. Changes in strength during the study.

	HB n = 16		CB n = 27		CG n = 18		P-Value		
	<u>Baseline</u>	<u>1 Year</u>	<u>Baseline</u>	<u>1 Year</u>	<u>Baseline</u>	<u>1 Year</u>	<u>Time</u>	<u>Group</u>	<u>Interact^m</u>
<u>Muscle strength</u>									
Handgrip strength (kg)	43.1 ± 10	45.7 ± 13	40.2 ± 8.6	42.6 ± 8.9	41.6 ± 8.3	47.2 ± 9.7	.00	.43	.49
Isometric quadriceps extension (Nm)	151.8 ± 28	168.9 ± 31	150.2 ± 45	157.7 ± 40	148.7 ± 30	163.7 ± 37	.00	.72	.33
Extension total work (180°/s (J))	1614 ± 680	1155 ± 272	1758 ± 756	1117 ± 293	1695 ± 796	1142 ± 254	.00	.86	.77
Sit and Rising Test	7.56 ± 1.8	7.93 ± 1.3	7.44 ± 1.5	7.42 ± 1.3	7.47 ± 1.1	7.30 ± 1.3	.39	.53	.22

Data are presented as mean ± SD. m: Interaction.

Table 11. Cardiovascular risk factors and anthropometrics characteristics during the study.

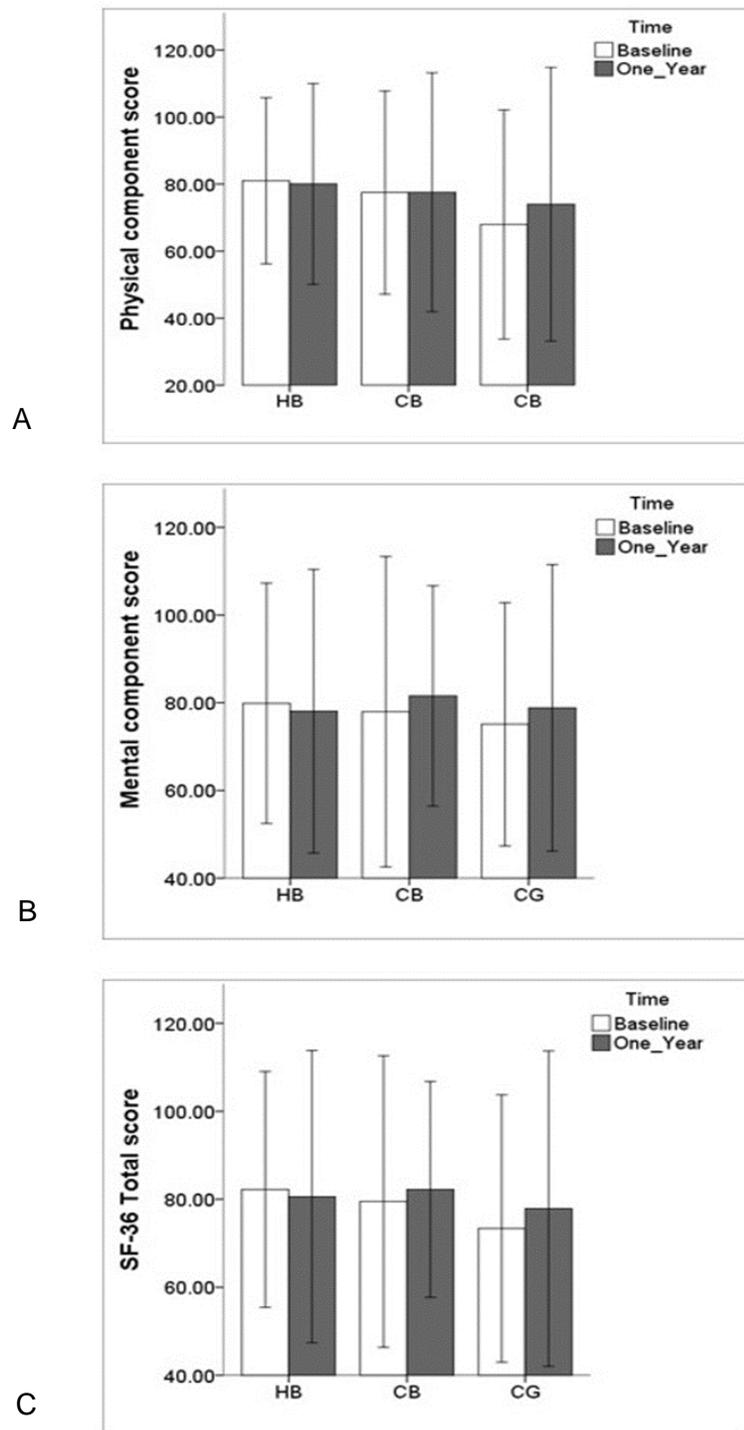
	HB n = 28		CB n = 30		Control n = 26		P-Value		
	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Time</u>	<u>Group</u>	<u>Interact^m</u>
<u>Anthropometrics</u>									
Weight(kg)	80.4 ± 10	81.5 ± 10	82.9 ± 15	82.9 ± 10	85 ± 12	85.6 ± 12	.14	.45	.51
BMI ^b (kg/m ²)	26.6 ± 2.5	26.9 ± 2.6	27.8 ± 4	27.8 ± 4.3	28 ± 3.3	28.2 ± 2.9	.12	.31	.62
Waist Circumference (cm)	96.8 ± 8.8	97.1 ± 9.1	98.7 ± 11	99.7 ± 11	99.5 ± 9.8	100.3 ± 10	.36	.51	.91
Hip circumference (cm)	101.1 ± 5	101.3 ± 5	103 ± 7.4	102.5 ± 7.8	102.9 ± 4	102 ± 4	.20	.60	.43
Body fat (Kg)	22.4 ± 4.7	23.5 ± 4.3	24.1 ± 7	24.4 ± 7.6	25.7 ± 6	25.6 ± 5	.14	.31	.25
Body fat %	26.8 ± 5.7	28.2 ± 4.1	29.5 ± 5	29.1 ± 6.3	29.5 ± 5	29.4 ± 4.7	.32	.29	.06

Data are presented as mean ± SD. B: Body mass index, m: Interaction. (Continued on next page)

Table 11. Cardiovascular risk factors and anthropometrics characteristics during the study (Continued).

	HB n = 28		CB n = 30		Control n = 26		P-Value		
	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Baseline</u>	<u>3Month</u>	<u>Time</u>	<u>Group</u>	<u>Interact^m</u>
<u>Cardiovascular risk factors</u>									
SBP ^d (mmHg)	124.6 ± 15	125.3 ± 15	127.3 ± 15	122.8 ± 15	124.2 ± 13	123.8 ± 17	.36	.95	.32
DBP ^e (mmHg)	75.4 ± 9.7	77.6 ± 11	75.6 ± 8	74.9 ± 8	76.1 ± 8	80.3 ± 11	.05	.44	.11
Total - C ^f (mg/dL)	3.62 ± 0.8	3.75 ± 0.7	3.42 ± 0.6	3.57 ± 0.8	3.35 ± 0.7	3.46 ± 0.5	.09	.34	.97
HDL - C ^f (mg/dL)	1.38 ± 0.2	1.39 ± 0.3	1.37 ± 0.5	1.38 ± 0.4	1.25 ± 0.3	1.31 ± 0.3	.47	.47	.69
LDL- C ^f (mg/dL)	1.82 ± 0.7	1.89 ± 0.6	1.57 ± 0.5	1.68 ± 0.6	1.67 ± 0.5	1.73 ± 0.3	.16	.23	.95
Triglycerides (mg/dL)	0.92 ± 0.4	1.04 ± 0.4	1.11 ± 0.9	1.06 ± 0.5	0.94 ± 0.3	0.94 ± 0.3	.63	.62	.51
Fasting glucose	5.62 ± 0.5	5.36 ± 0.4	5.96 ± 1.0	5.94 ± 1.1	5.56 ± 0.6	5.54 ± 1.0	.33	.08	.33
HOMA index	1.72 ± 0.7	1.93 ± 1.1	2.32 ± 1.4	2.81 ± 2.4	2.53 ± 1.5	3.18 ± 2.2	.00	.05	.49

Data are presented as mean ± SD. d: Systolic blood pressure, e: Diastolic blood pressure, f: Cholesterol, m: Interaction.

Figure 8. Changes in HRQoL during the study.

Data are presented as percentage, mean \pm SE. HB: Home-based group, CB: Centre-based group, CG: Control group. White column: Baseline, Dark gray column: one year follow-up.

DISCUSSION

The aim of our study was to compare the longer-term effects of a 12-week HB exercise programme with tele-monitoring guidance to a prolonged 12-week CB cardiac rehabilitation programme following completion of a phase II cardiac rehabilitation in patients with CAD. Overall, we showed that HB cardiac rehabilitation is as effective as a prolonged CB cardiac rehabilitation program to maintain physical fitness and PA levels. We also found maintenance of physical fitness and PA at one year follow-up; in fact, 85% of our patients met the international guidelines of 150 minutes of moderate PA per week (9).

Contrary to our hypothesis, we could not demonstrate higher levels of physical activity at one year of follow-up, in patients randomized to a HB training program with tele-monitoring guidance, therefore we could not document higher levels of physical fitness compared to the patients enrolled to the CB cardiac rehabilitation program or CG.

Yet, our results are in line with the findings of the FIT@Home study (24) in which 90 low-to-moderate cardiac risk patients initiating a phase II cardiac rehabilitation program were randomized to three months of either HB training with tele-monitoring guidance or CB cardiac rehabilitation. At one year of follow-up, they reported an improved exercise capacity in both group, without between-group differences. Our study complements their results since our intervention started in phase III cardiac rehabilitation showing no differences between HB training with tele-monitoring guidance and CB training in the long-term (one year). Our results also confirm those published in a recent report by Claes et al (14). By using meta-analytic techniques, they showed no influence on exercise capacity in HB cardiac rehabilitation compared to usual care when both were offered after completion of a phase II CB cardiac rehabilitation programme.

The results of these studies would suggest that although exercise-based cardiac rehabilitation is often aimed at short-term improvement of exercise capacity, it might also prepare the patients for independent lifestyle changes that favour the long-term

maintenance of the benefits obtained at completion of a phase II cardiac rehabilitation programme.

Frederix et al., published the Telerehab III trial (25, 26), a randomized controlled trial (n=140) comparing the efficacy and cost-efficiency of a 24-week tele-rehabilitation programme in addition to conventional cardiac rehabilitation versus conventional cardiac rehabilitation alone; patients in their intervention were provided with an internet-based tele-rehabilitation program in addition to conventional CB cardiac rehabilitation. The tele-rehabilitation program was composed of PA tele-monitoring in addition to dietary, smoking cessation and activity telecoaching; contrary to our intervention, they showed an improvement in exercise capacity in favour of the patients receiving tele-rehabilitation. The different outcomes of the studies might be explained by the lack of a clear definition for 'HB cardiac rehabilitation'. As such, the contents of HB cardiac rehabilitation interventions that have been investigated varied widely and ranged from the use of manuals for a healthier lifestyle to personalized exercise prescriptions (14). One such example is the study published by Park et al (27), who described a positive adherence study using an intervention of daily text messages in combination with a supporting website. The majority of participants (85%) in this study reported reading their text messages while the median number of visits to the website was only three visits in a six month period, thus they suggested that tele-monitoring interventions such as text messaging may have a higher likelihood of patient participation and adherence than internet-based programs (27). Complementary to the above, Coorey et al hypothesized that integrating gamification principles into tele-monitoring technologies may increase motivation for sustaining essential, but repetitive, routine lifestyle tasks over the longer-term (28).

During the past years, cardiac tele-rehabilitation was introduced as an adjunct or alternative to conventional cardiac rehabilitation to increase uptake rates, enable more prolonged care, and improve long-term success (25). Adherence to PA in both lifestyle choices and rehabilitation programmes remains to be low. Although we observed a small decrease in the proportion of patients meeting the international

guidelines for PA, still 85% of patients was doing more than 150 minutes of moderate PA one year following completion of the phase II cardiac rehabilitation program, which is much more than the 39 to 46% reported in earlier studies (29). We speculate that possibly patients underwent a real lifestyle change due to acquired self-motivation during the cardiac rehabilitation, though behavioural modifications were not measured in our study (19). However, we cannot rule out the impact of a selection bias whereby we potentially have recruited the more motivated patients. Furthermore, the awareness of follow-up testing could have motivated patients to maintain their PA level (30).

Cowie et al (31), randomized 60 patients with heart failure to home training, hospital training or control. There were no significant differences in mean upright duration, steps/day, or walking pattern at long-term assessment. They attributed this lack of improvement to the nature of the intervention, which was based on PA alone without behavioral counselling as is also the case in our study. Reid et al (32), found a significant decrease in habitual PA during long-term follow-up after hospital discharge in patients with CAD. In the same line, Hansen et al (8), found that only 27% of patients participating in cardiac rehabilitation adhered to the minimal PA level required to obtain significant health benefits 18 months after completion of a CB cardiac rehabilitation program. In the present TRiCH study, at completion of the phase II cardiac rehabilitation program, the Sensewear® Mini Armband data showed that 85% of our patients did achieve the PA levels recommended for chronic non-communicable conditions. Furthermore, the PA levels were regular and maintained in the long term for all groups. This finding is clinically important since the long-term success of cardiac rehabilitation rests in part on the patient's ability to maintain healthy behaviours, including participation in regular PA. Giannuzzi et al (32), indicated that continued patient interaction and monitoring, as well as continuation of a lifestyle intervention (phase III rehabilitation), is required to obtain long-term clinical benefits. However, we considered that prolonging the supervised exercise intervention for HB or CB groups in our study would not have resulted in differences between groups.

Although numerous studies have illustrated the effects of tele-monitoring interventions on the incidence of CVD, controversy still remains; a meta-analysis of Neubeck et al, has shown significantly favourable changes in total cholesterol, its lipoprotein fractions, and smoking habits with telehealth participation compared to usual care at medium to long-term follow-up (34). However Gu et al (35), noted that several telehealth interventions trials reported non-significant reduction of CVD risk factors in patients with prior CAD. Reasons for these different findings could be due to different sample sizes, different follow-up duration, and most of all, different design of studies centred on cardiovascular risk factors as primary end point which cannot detect differences between tele-monitoring and usual care in CVD. We considered that the patients included in our TRiCH study were at low risk over the first year after enrolment thus the likelihood of detecting a beneficial effect was small. Furthermore, the incremental benefit of secondary prevention programs over usual care may be very small if the medical management of the patients is probably close to optimal (36).

In relation to HRQoL, Frederix et al (26) evaluated the generic health status through the 5Q-5D questionnaire at baseline and at 24 weeks of follow-up. They described an improvement of QoL in their intervention group derived as result of a reduced cardiovascular rehospitalization rate while a deterioration in the control group was observed during the study period. Kraal et al (24), on the other hand found that HRQoL improved on the social and physical subscales at discharge and follow-up in HB and CB groups of their FIT@home study. We were unable to detect changes in HRQoL for either group after one year of follow-up, however, it remained stable during the time of the study, which is important as HRQoL seems to have a bi-directional relationship with increased PA (19).

Although the presence of CAD can have a profound impact on physical function, little data are available examining the value of HG strength, quadriceps strength and SRT in CAD patients after a tele-monitoring intervention in the long term. However, a reduction of 15% to 20% in strength has been reported in every decade after 50 years of age, leading to deleterious effects on the performance of basic activities of

daily living (37). Seco et al, described that 26% of adults over the age of 70 could not easily climb stairs, 31% had problems carrying a bag weighting 35 kg and 36% had walking difficulties. They also described a significant improvement of HG strength in 180 independent older adults who completed a simple nine month training program (consisting of two sessions per week lasting 55 minutes per session including mobility, strength, balance, coordination and walking exercises) and three month detraining follow-up. Although no strength differences between the interventions were found in our study, there was a significant improvement in muscular strength during the follow-up that was not accompanied by improvement in muscular strength. We considered the long-term maintenance of HG and quadriceps strength in all participants of our groups as a positive result since in older individuals, increased muscular strength and endurance tend to reduce disability and to improve functional independence and HRQoL, regardless of whether they have cardiovascular disease (38). Further research regarding muscle strength and tele-rehabilitation interventions are needed in order to confirm our results.

Strengths and limitations

The present TRiCH study has several strengths. First, we were able to obtain objective measures of PA using an accelerometer while previous studies of internet-based interventions have relied solely on self-reported PA data (39). Second, many patients expressed their preference for CB training and were subsequently disappointed when allocated to the HB or CG group. However, the randomization allowed us to have a proper representation of the cardiac rehabilitation population in all groups and their behaviour in the long-term. Third, as described by Claes et al (14), although long-term adaptations are the ultimate goal of cardiac rehabilitation, the number of that evaluated the longer-term effects of cardiac rehabilitation interventions are disappointingly low. Thus the TRiCH study with a follow-up period of one year is one of the few studies that allowed a reasonable time frame to assess long-term effects of a tele-monitoring program during phase III of cardiac rehabilitation.

A limitation in this study is the lack of blinding of test personnel. However, as the main outcome measure was exercise capacity, the effort of the participants can be compared through the respiratory exchange ratio (RER) and the Borg scale (40). The study, as do most of randomized controlled trials, had missing outcome data due mainly to technical problems or missing numbers in specific tests but these were missing completely at random. Cardiac rehabilitation includes important core components such as nutritional counselling, risk factor management and psychosocial management; but PA training comprises 30-50% (up to >70%) of all cardiac rehabilitation activities. Therefore, in this study PA tele-monitoring rather than tele-rehabilitation was assessed (41).

CONCLUSION

The results of this TRiCH study show that HB cardiac rehabilitation and usual care or prolonged CB cardiac rehabilitation are of similar value for maintaining exercise capacity, PA anthropometric measures, muscle strength and HRQoL in the long term in CAD patients who participated in phase II cardiac rehabilitation.

Acknowledgments

AA is supported by a doctoral research grant funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate programme (2011-0015).

The authors thank the patients who participated in the TRiCH study as well as the staff of the cardiac rehabilitation center in UZ Leuven hospital for their enthusiastic support of this project.

REFERENCES

1. Ting P, Saner H, Dafoe W. The lexicon of 'Cardiac Rehabilitation': is it time for an evolutionary new term? *European Journal of Cardiovascular Prevention and Rehabilitation*. 2010;17(3):1.
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, 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): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol*. 23. England 2016. p. NP1-NP96.
3. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation.(AHA/AACVPR Scientific Statement). *Circulation*. 2007;115(20):2675.
4. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Chchran Database Syst Rev*. 2011;7(4).
5. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*. 2016;67(1):1-12.
6. Arrigo I, Brunner-Larocca H, Lefkovits M, Pfisterer M, Hoffmann A. Comparative outcome one year after formal cardiac rehabilitation: the effects of a randomized intervention to improve exercise adherence. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2008;15(3):306-11.
7. Moore S, Charvat J, Gordon N, Roberts B, Pashkow F, Ribisl P, et al. Effects of a CHANGE intervention to increase exercise maintenance following cardiac events. *Annals of Behavioral Medicine*. 2006;31(1):53-62.
8. Hansen D, Dendale P, Raskin A, Schoonis A, Berger J, Vlassak I, et al. Long-term effect of rehabilitation in coronary artery disease patients: randomized clinical trial of the impact of exercise volume. *Clin Rehabil*. 2010;24(4):319-27.
9. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise*. 2011;43(7):1334.
10. Petter M, Blanchard C, Kemp K, Mazoff A, Ferrier S. Correlates of exercise among coronary heart disease patients: review, implications and future directions. *Eur J Cardiovasc Prev Rehabil* 2009. p. 515-26.

11. De Vos C, Li X, Van Vlaenderen I, Saka O, Dendale P, Eyssen M, et al. Participating or not in a cardiac rehabilitation programme: factors influencing a patient's decision. *European Journal of Preventive Cardiology*. 2013;20(2):341-8.
12. Shanmugasagaram DS, Oh LP, Reid LR, McCumber LT, Grace LS. A Comparison of Barriers to Use of Home- Versus Site-Based Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2013;33(5):297-302.
13. Piotrowicz E, Piotrowicz R. Cardiac telerehabilitation: current situation and future challenges. *European Journal of Preventive Cardiology*. 2013;20(2_suppl):12-6.
14. Claes J, Buys R, Budts W, Smart N, Cornelissen VA. 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. *European Journal of Preventive Cardiology*. 2017;24(3):244-56.
15. Avila A, Goetschalckx K, Vanhees L, Cornelissen V. A Randomized Controlled Study Comparing Home-Based Training with Telemonitoring Guidance Versus Center-Based Training in Patients with Coronary Heart Disease: Rationale and Design of the Tele-Rehabilitation in Coronary Heart Disease (TRiCH) Study. *Journal of Clinical Trials*. 2014;4(4):1-5.
16. Avila A, Claes J, Goetschalckx K, Buys R, Azzawi M, Vanhees L, et al. A randomized study of home-based training intervention with telemonitoring guidance in coronary artery disease patients - (TRiCH) Study. *Journal of Medical Internet Research*. 2018.
17. Kraal JJ, Peek N, Van Den Akker-Van Marle ME, Kemps HM. 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. *European Journal of Preventive Cardiology*. 2014;21(2_suppl):26-31.
18. Wasserman K HJ, Sietsema K, Sue D, Stringer W, MD, Whipp B, Sun X, MD. Principles of exercise testing and interpretation; including pathophysiology and clinical applications, 5th ed. Portland: Wolters Kluwer Health; 2015. 588 p.
19. Pattyn N, L Vanhees L, Cornelissen V, et al. The long-term effects of a randomized trial comparing aerobic interval versus continuous training in coronary artery disease patients: 1-year data from the SAINTEX-CAD study. *European journal of preventive cardiology*. 2016;23(1154-1164).
20. Scheers T, Philippaerts R, Lefevre J. SenseWear-determined physical activity and sedentary behavior and metabolic syndrome. *Med Sci Sports Exerc*. 2013;45(3):481-9.
21. Brito LBB, Ricardo DR, Araújo DSM, Ramos PS, Myers J, Araújo CGSD. Ability to sit and rise from the floor as a predictor of all-cause mortality. *European journal of preventive cardiology*. 2014;21(7):892-8.
22. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and Ageing*. 2011;40(4):423-9.
23. Ghroubi S, Chaari M, Elleuch H, Massmoudi K, Abdenadher M, Trabelssi I, et al. The isokinetic assessment of peripheral muscle function in patients with coronary artery disease: correlations with cardiorespiratory capacity. *Annales de réadaptation et de médecine physique*. 2007;50(5):295-301.

24. Kraal JJ, Van Den Akker-Van Marle ME, Abu-Hanna A, Stut W, Peek N, Kemps HM. Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study. *European Journal of Preventive Cardiology*. 2017;24(12):1260-73.
25. 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).
26. Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, et al. Effect of comprehensive cardiac telerehabilitation on one- year cardiovascular rehospitalization rate, medical costs and quality of life: A cost- effectiveness analysis. *European journal of preventive cardiology*. 2016;23(7):674-82.
27. Park LG, Beatty A, Stafford Z, Whooley MA. Mobile Phone Interventions for the Secondary Prevention of Cardiovascular Disease. *Progress in Cardiovascular Diseases*. 2016;58(6):639-50.
28. Coorey GM, Neubeck L, Mulley J, Redfern J. Effectiveness, acceptability and usefulness of mobile applications for cardiovascular disease self-management: Systematic review with meta-synthesis of quantitative and qualitative data. *European Journal of Preventive Cardiology*. 2018;25(5):505-21.
29. Livitckaia K, Koutkias V, Maglaveras N, Kouidi E, van Gils M, Chouvarda I. Adherence to physical activity in patients with heart disease: Types, settings and evaluation instruments. 2018. p. 255-9.
30. Brubaker PH, Rejeski WJ, Smith MJ, et al. A home-based maintenance exercise program after center-based cardiac rehabilitation: Effects on blood lipids, body composition, and functional capacity. *Journal of Cardiopulmonary Rehabilitation*. 2000;20(1):50-6.
31. Cowie A, Thow MK, Granat MH, Mitchell SL. A comparison of home and hospital-based exercise training in heart failure: immediate and long-term effects upon physical activity level. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2011;18(2):158.
32. Reid RD ML, Pipe AL, Dafoe WA, Higginson LA, Wielgosz AT, McDonald PW, Plotnikoff RC, Courneya KS, Oldridge NB, Beaton LJ. Determinants of physical activity after hospitalization for coronary artery disease: the Tracking Exercise After Cardiac Hospitalization (TEACH) Study. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2006;13(4):529-37.
33. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V, 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. *Archives of internal medicine*. 2008;168(20):2194.
34. Neubeck L, Redfern J, Fernandez R, Briffa T, Bauman A, SB F. Telehealth interventions for the secondary prevention of coronary heart disease: a systematic review. *European journal of cardiovascular prevention and rehabilitation*. 2009;16(3):281-9.

35. Gu X, Zhu Y, Zhang Y, Sun L, Bao Z, Shen J, et al. Effect of telehealth interventions on major cardiovascular outcomes: a meta-analysis of randomized controlled trials. *J Geriatr Cardiol.* 2017;14(8):501-8.
36. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease.(effects cardiac secondary prevention programs)(Author abstract). *Annals of Internal Medicine.* 2005;143(9):659.
37. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Medicine and science in sports and exercise.* 2009;41(7):1510.
38. Williams MA, Stewart KJ. Impact of Strength and Resistance Training on Cardiovascular Disease Risk Factors and Outcomes in Older Adults. *Clinics in Geriatric Medicine.* 2009;25(4):703-14.
39. Reid RD, Morrin LI, Beaton LJ, et al. Randomized trial of an internet-based computer-tailored expert system for physical activity in patients with heart disease. *European Journal of Preventive Cardiology.* 2012;19(6):1357-64.
40. Aamot I-L, Forbord SH, Gustad K, Aamot, I.L., Forbord, S.H., Gustad, K., Løckra, V., Stensen, A., Berg, A.T., Dalen, H., Karlsen, T. and Støylen, A., 2014. Home-based versus hospital-based high-intensity interval training in cardiac rehabilitation: a randomized study. *European journal of preventive cardiology* , 21 (9), pp.1070-1078. Home- based versus hospital- based high- intensity interval training in cardiac rehabilitation: a randomized study. *European Journal of Preventive Cardiology.* 2014;21(9):1070-8.
41. 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. *European Journal of Preventive Cardiology.* 2015;22(2):150-8.

Chapter 5

Validation of four physical activity trackers in a phase III cardiac rehabilitation population

Andrea Avila*; Jomme Claes*; Roselien Buys; May Azzawi; Luc Vanhees; Veronique
Cornelissen

*Shared first authorship

ABSTRACT

Introduction: Recently, the consumer marketplace has been flooded with an array of physical activity monitors. However, little research exists about the reliability and validity of these devices. Hence, the purpose of this study was to evaluate the reliability and validity of three consumer-based physical activity trackers (Fitbit Charge HR, MIO fuse and Sensewear Armband Mini) and one research monitor (Actiheart) for estimating energy expenditure (EE) and step count in a phase III cardiac rehabilitation (CR) population.

Methods: Fifteen patients with cardiovascular disease (CVD) in phase III of CR (n=2 females) aged 56 to 72 years (mean 65.4 ± 6.6) and BMI $26.8 \pm 4.8\text{kg/m}^2$ completed two sessions of 44-minutes of standardized structured activity within a period of 14 days. Each session consisted of 10 minutes of rest followed by walking on a treadmill at 2.5km/h (slow walk), 4km/h (moderate walk) and 5km/h with 5% incline (brisk walk) for 8 minutes each, interspersed with set times for rest. The participants wore a MIO Fuse device on their right wrist, Fitbit Charge HR on their left wrist, an Actiheart monitor on their chest, a SenseWear armband on the upper left arm and a gas analysis system (CPX Ultima; MedGraphics) as criterion for EE. Steps were registered through video-recording. Values for EE and steps were obtained for the entire protocol as well as per each bout. Reliability was assessed by Intraclass Correlation Coefficients (ICC). Validity was determined by ICC, Bland-Altman plots and Pearson correlation coefficients.

Results. For reliability, the ICCs for total EE varied between 0.80 (MIO Fuse) and 0.95 (SenseWear) with Actiheart having the highest reliability in every stage of the session ($\text{ICC} > 0.75$) and Fitbit Charge HR the lowest. The ICCs for total number of steps varied between 0.38 (MIO Fuse) and 0.91 (SenseWear). As for validity, SenseWear, Fitbit Charge HR and MIO Fuse overestimate the EE (0.55%, 11.2% and 51.1% respectively) while Actiheart underestimated EE (-4.6%) during the whole test. The devices also underestimated the number of steps for every stage, with SenseWear showing the highest percentage error (-2.73% to -51.04%) and Fitbit Charge HR the lowest percentage error with -0.57%.

Conclusion: Overall, the inability to accurately estimate EE was notable across all devices. Fitbit Charge HR had the lowest reliability concerning EE. For step count, results were slightly better with Fitbit Charge HR and SenseWear showing fair to good reliability and Fitbit Charge HR and MIO Fuse showing fair to good validity.

Introduction

Despite major improvements in diagnostics and interventional therapies; cardiovascular diseases (CVD) remain a major healthcare and socio-economic burden both in western and developing countries (1). In fact, CVD remain the leading contributor to global mortality and morbidity (2). Currently, it is publicly recognized that the fight against these diseases can only be won if their burden is faced by increasing the investment in interventions targeting lifestyle changes and prevention (1).

According to the European Society of Cardiology (ESC), secondary prevention by means of cardiac rehabilitation (CR) is a Class I recommendation following a cardiac event (3). CR is a multidisciplinary intervention of which exercise training is a core component and one of the key aims is to encourage patients to achieve the recommended levels of physical activity after termination of the phase II CR program (4, 5). During the last two decades, great epidemiologic evidence has supported the benefits of regular physical activity (PA), and it is widely accepted that higher levels of cardiorespiratory fitness and PA are beneficial for the prevention of CVD and the reduction in all-cause mortality (6). The ESC guidelines therefore recommend that patients with CVD engage in 30 minutes of moderate intensity physical activity on most days of the week (7). However, Hansen et al. have shown that only 27% of patients with coronary artery disease adhere to these guidelines 18 months after the event(8).

To increase uptake and adherence to PA recommendations we need new strategies and interventions that focus on supporting patients with cardiac disease to sustain a healthy and physically active lifestyle (8). Activity tracking devices have the potential to affect PA behavior (9). However, to monitor and evaluate the effectiveness of the interventions aiming to increase uptake and adherence to a PA lifestyle among CAD patients, an accurate assessment tool is mandatory. Physical activity trackers have evolved over time from simple mechanical pedometers, to more complex and complete accelerometers. The market currently focuses on user-friendly, nice-looking and wrist-worn activity trackers that link to cell phones and social media

applications for personalized monitoring. However, despite the widespread adoption and potential applications of these devices, there is relatively little information about their accuracy and reliability (5).

Although a wide number of devices are available, most have been validated in young, healthy subjects and their applicability to older populations, where movements tend to be slower, medication intake is higher and irregularities in heart rate are common, is not well established (10). To our knowledge, little research has evaluated the reliability and validity of physical activity devices to assess energy expenditure (EE) and step count in a phase III CR population under well-controlled laboratory conditions. Since living a physically active lifestyle has a profound and multiple benefits not only in healthy population but in older adults and specially populations living with chronic illness like CVD and that there is “strong evidence” that physically active older adults have higher levels of functional health, lower risks of falling, and improved cognitive health; the purpose of this study was to evaluate the reliability and validity of three consumer-based physical activity trackers (Fitbit Charge HR, MIO Fuse and Sensewear Armband Mini) to be used in daily life and a research monitor (Actiheart) to evaluate energy expenditure (EE) and step count in a phase III CR population.

Methods

Study population

Fifteen patients with CVD, who participated actively in a phase III CR program, were enrolled in this study. Participants were included by convenience sampling if they were between 60 and 75 years old, had a stable clinical condition in the last six months, underwent a negative maximal exercise test in the last six months and had absence of significant ventricular arrhythmia or major orthopedic limitations. Participants were informed that the test comprised a 44-minute standardized treadmill walking protocol and therefore being comfortable on a treadmill was desired. The study protocol was approved by the medical ethical committee of the University Hospitals Leuven/KU Leuven and participants signed an informed consent form before their enrollment.

Instruments

Criterion measures

To collect EE data, subjects were outfitted with a gas analysis system (CPX Ultima; MedGraphics, Minnesota, USA). The device was calibrated automatically for gas concentrations and manually for volume with a 3 liter cylinder prior to each measurement. The face-mask, attached to a turbine flow meter, allows for real-time collection of breath-by-breath VO_2 values. These data were used to calculate EE from minute averages of VO_2 . Step count data were collected through video recording. Step count data were independently analyzed by two observers, who manually counted the number of steps after the session.

Consumer activity trackers

The Fitbit Charge HR (Fitbit Inc., San Francisco, USA) is a heart rate and activity tracking wristband built to capture movements and health patterns continuously. It features Fitbit's proprietary PurePulse photoplethysmography (PPG) technology, which uses green-light infrared LED lights on the inside of the wristband to measure heart rate (HR) by detecting blood volume and capillary-size changes under pressure. The Fitbit measures general body movements and calculates basal metabolic rate (BMR) from participant characteristics: age, gender, height, and weight. Through a web-based interface, the Fitbit calculates total kcal/day based on each individual's BMR and his or her general body movements (Fitbit, 2010). Fitbit uses three-dimensional motion-sensing technology and converts this into activity information including the intensity (light, moderate, vigorous) and duration of activities (12). Approximately, the battery last 5 days without recharging. The MIO Fuse (Physical Enterprises Inc., Vancouver, Canada) is a commercially available PPG and activity tracking wristband developed in collaboration with Philips. The MIO Fuse is equipped with a Philips Optical Heart Rate Monitoring Module (OHRM) PPG sensor. It is waterproof and the battery capacity allows to measure R-R intervals of HR (13). Furthermore, MIO Fuse also carries a 3-axis accelerometer and provides estimations of step counts and EE based on proprietary algorithms. Battery life is 6

to 7 days for one hour of heart rate monitoring daily, or 24 hours in case of continuous heart rate monitoring.

The SenseWear Armband Mini (SWAM) (BodyMedia Inc., Pittsburgh, USA) is a small, non-invasive device that integrates demographic characteristics including gender, age, height and weight, a tri-axial accelerometer and heat-related sensors including a heat flux sensor to measure galvanic skin response, skin temperature and near-body temperature. Sensewear is expected to collect up to 14 days of continuous data (24/7), although the battery life is typically reduced under colder conditions (14).

Research activity monitor

The Actiheart monitor (CamNtech Ltd., Cambridge, United Kingdom) is a commercially available unit, which combines measurements of HR and uni-axial acceleration. The device collects both parameters with a high resolution. Depending on the selected length of the recording epoch, data can be recorded and stored continuously for up to 21 days. The monitor has been developed and validated during sedentary activities, low-intensity exercise and in children and adolescents (15).

Procedures

Subjects visited the laboratory twice within 14 days. During visit one, anthropometric measures including age, gender; height and weight were taken with the patient barefoot and wearing light sportswear. Standing height was measured to the closest 0.1cm using a stadiometer and the weight was measured to the nearest 0.1kg using a digital scale (SECA). As per manufacturer instructions, the devices were individualized for age, gender and anthropometric data to allow EE calculation (16). Devices with compatible smartphone software were synchronized via Bluetooth to an appropriate smartphone to assist with data collection (ease of visualization) (17). The participants wore all four devices during a standardized treadmill walking protocol. A walking protocol was chosen given that this is the preferred mode of physical activity in this patient population. The MIO Fuse was worn on the right wrist

and the Fitbit Charge HR was worn on the left wrist. According to the manufacturer's instructions the Actiheart monitor was placed on the participant's chest using standard ECG electrode patches. The SenseWear armband was worn according to the manufacturer's instructions on the participant's upper left arm. Next, the participants were equipped with the indirect calorimetry system. Participants then completed a 44-minute standardized treadmill protocol consisting of a 10 minute resting condition followed by three walking bouts at distinct speeds and elevations (Table 12). During the second visit, participants were fitted with the same devices and the same 44-minute protocol was completed.

Since these consumer-based activity trackers do not provide direct access to the raw data, estimates of EE were obtained directly from the trackers or the associated application during the test (16).

Table 12. Standardized treadmill protocol.

Time	Activity
5 minutes	Sitting on a chair
5 minutes	Standing on the treadmill
8 minutes	Walking at 2.5km/h (Slow walk)
1 minute	Standing on the treadmill
3 minutes	Sitting on a chair
1 minute	Standing on the treadmill
8 minutes	Walking at 4km/h (Moderate walk)
1 minute	Standing on the treadmill
3 minutes	Sitting on a chair
1 minute	Standing on the treadmill
8 minutes	Walking at 5.5km/h and 5% inclination (Brisk Walk)

STATISTICAL ANALYSIS

All data are expressed as means \pm SD, median and range or percentages (for categorical variables). Statistical analyses were performed using SPSS v.20. The Shapiro-Wilk test was used to assess normality. The complete duration of each bout was used for the analysis. For EE and steps, test-retest reliability of the devices was assessed by calculating the Intraclass Correlation Coefficient (ICC) (two-way random, absolute agreement, 95% confidence interval) for the whole session and

for each activity, during both visits. An ICC below 0.4 was considered poor, between 0.4 and 0.75 fair to good and above 0.75 was excellent reliability (20) .

The validity analysis for EE and steps was performed on the data of the second session, unless unavailable, in which case the data from the first session was used (2 participants). The validity of the devices was determined by several statistical tests. First, the mean absolute percentage error (M.A.P.E) compared to the criterion method was calculated for the total session and for each walking speed with the following formula for EE: $(\text{Calories from device} - \text{calories from the criterion method}) / \text{calories from criterion method} * 100$ and for steps: $(\text{steps from device} - \text{steps from criterion method}) / \text{steps from criterion method} * 100$. Second, in order to examine the correlation between the devices and the criterion method, the ICC was calculated (absolute agreement, two-way random, 95% confidence interval). Third, to examine the level of agreement between the devices and the criterion method, Bland-Altman plots were constructed, providing calculations of bias along with their limits of agreement. Furthermore, we calculated the mean absolute difference (M.A.D.) between the mean from the criterion method and activity tracker. In addition, Pearson correlation coefficients were used to assess the strength of the relationship between the physical activity trackers and the criterion method in measuring EE and number of steps.

RESULTS

Sample characteristics

Participants comprised 93.8% males (n=13), and a mean age of 65.4 ± 6.6 years old (range 56-78 years) (Table 13). All participants were part of a phase III cardiac rehabilitation community program (HARPA). Due to technical problems, SenseWear information was not available for the first session in two participants and for one participant in the second session, while Actiheart information was missing for two participants in the first session.

Table 13. Basic characteristics of the population.

Characteristics	Mean \pm SD
Age (years)	65.4 \pm 6.6
Gender (%)	
Male	93.8
Female	6.2
Height (cm)	175 \pm 0.7
Weight (kg)	83.1 \pm 16.1
BMI ^b (kg/m ²)	26.8 \pm 4.8

b: Body mass index.

Test re-test reliability

The ICCs between the first session and the second session for total EE varied between 0.80 (MIO Fuse) and 0.95 (SenseWear) as can be seen in Table 14. Actiheart showed the highest reliability from all devices in every stage of the session (ICC>0.75) and Fitbit Charge HR had the lowest reliability in every stage. Reliability for MIO Fuse was excellent for the sit/stand period, moderate walking and brisk walking, but was fair to poor for slow walking. As for the SenseWear, the reliability was poor during the sit/stand period, fair during slow walking, and excellent for moderate and brisk walking.

The ICCs between the first session and the second session for number of steps were established for all devices with the exception of Actiheart as can be seen in Table 15. The ICC varied between 0.03 (MIO Fuse) and 0.96 (Fitbit Charge HR) over the different stages of the protocol. SenseWear showed the highest ICC for the complete session, as well as the slow and brisk walking (ICC >0.75). The lowest total correlation was observed for the MIO Fuse that showed a poor ICC for every stage of the protocol. Fitbit Charge HR showed only fair to good correlation for the whole session and the slow walking, but an excellent ICC for brisk walking.

Table 14. Summary of the reliability analysis for energy expenditure of Fitbit Charge HR, MIO Fuse, Actiheart, SenseWear at first and second visit.

Activity	Oxycon Mobile			Fitbit Charge HR				MIO Fuse			
	1S (SD)	2S (SD)	ICC ^d (95%CI)	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)
Total session	156 (39.7)	157 (35)	0.75 (0.2-0.9)	165.8 (17.7)	165.9 (10)	-0.34	-0.94 (-0.7-0.2)	211.1 (66.9)	237.4 (88.7)	- 0.73 *	0.80 (0.44-0.93)
Sit/Stand Period	14.5 (3.2)	14.7 (3.2)	0.62 (-0.1-0.8)	8.8 (0.41)	8.8 (1.08)	0.64	0.08 (-2.1-0.7)	30.6 (15.1)	34.06 (19.07)	0.65 *	0.78 (0.36-0.92)
Slow Walk ^f	26.8 (7.2)	27 (6.8)	0.73 (0.1-0.9)	38.8 (5.1)	39.6 (3)	0.31	0.43 (-0.7-0.8)	36 (15.4)	47.5 (25.1)	0.30	0.44 (-0.44-0.81)
Moderate ^g Walk	35.9 (9.3)	35.2 (8.4)	0.72 (0.1-0.9)	53.6 (13)	50.1 (2.4)	-0.11	-0.24 (-3-0.59)	49.8 (19.5)	51.1 (23)	0.83 *	0.91 (0.73-0.97)
Brisk Walk ^h	59.6 (15.8)	59.6 (13.7)	0.84 (0.5-0.9)	51.7 (6.2)	53.4 (2.2)	0.09	0.16 (-1.64-0.72)	66 (16.3)	74 (21.8)	0.83 *	0.85 (0.48-0.95)

Activity	Actiheart				SenseWear			
	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)
Total session	146.1 (46.4)	150.4 (67.2)	0.80*	0.87 (0.59-0.96)	162.6 (32.7)	157.6 (35.6)	0.91*	0.95 (0.83-0.98)
Sit/Stand Period	14.5 (3.07)	14.6 (3.22)	0.90*	0.96 (0.89-0.99)	12 (1.74)	12.2 (2.28)	0.94*	0.18 (-0.01-0.59)
Slow Walk ^f	28 (13.2)	26.4 (8.8)	0.81*	0.87 (0.59-0.96)	39.5 (9.2)	36.6 (9.6)	0.57*	0.68 (-0.02-0.90)
Moderate ^g Walk	39.9 (13.7)	40.3 (21.7)	0.70*	0.77 (0.25-0.93)	45.1 (11.1)	44.5 (11.5)	0.89*	0.94 (0.79-0.98)
Brisk Walk ^h	46.6 (18.5)	51.3 (29.3)	0.75*	0.80 (0.35-0.93)	48 (9.9)	47.1 (9.3)	0.95*	0.97 (0.88-0.99)

b: Calories, e= Pearson's Correlation, d: Intraclass correlation, (95%CI): 95% Confidence Interval, SD: Standard Deviation, f: 2.5km/h, g: 4km/h, h: 5.5km/h with 5% incline. *= Correlation is significant at the 0.05 level (two-tailed).

Table 15. Summary of the reliability analysis for number of steps with Fitbit Charge HR, MIO Fuse and SenseWear at first and second visit.

Activity	Fitbit Charge HR				MIO Fuse				SenseWear			
	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)	1S (SD)	2S (SD)	R ^e	ICC ^d (95%CI)
Total session	2550.6 (91.2)	2593 (142.1)	0.54*	0.64 (0.16-0.87)	2444.6 (212.2)	2518 (184.4)	0.24	0.38 (-0.73-0.79)	2165 (238.7)	2196 (237.2)	0.82*	0.91 (0.68-0.97)
Slow Walk^f	699.4 (63.7)	718 (75.4)	0.33	0.49 (-0.48-0.83)	665.1 (177)	745.8 (97.7)	0.23	0.30 (-0.74-0.75)	417.7 (189.1)	394.9 (232.7)	0.87*	0.92 (0.72-0.97)
Moderate Walk^g	874.8 (48.1)	889.2 (56)	0.15	0.27 (-1.21-0.75)	886.9 (141.6)	871.7 (60.9)	0.02	0.03 (-2.26-0.68)	854.5 (50.1)	863.1 (70.4)	0.44	0.60 (-0.45-0.88)
Brisk Walk^h	924 (59.2)	931 (61.7)	0.94*	0.96 (0.90-0.98)	893 (120.4)	901.8 (122.8)	0.09	0.18 (-1.73-0.73)	892.8 (50)	912 (61)	0.82*	0.87 (0.54-0.96)

e= Pearson's Correlation, d: Intraclass correlation, (95%CI): 95% Confidence Interval, SD: Standard Deviation, f: 2.5km/h, g: 4km/h, h: 5.5km/h with 5% incline. *= Correlation is significant at the 0.05 level (two-tailed).

Validity

The M.A.P.E for total session EE between the devices and the criterion method showed that SenseWear slightly overestimated the EE (0.55%), as well as Fitbit Charge HR (11.2%) and a consistently higher overestimation with MIO Fuse (51.1%). Actiheart estimates for total EE were consistently lower (-4.6%) compared to the criterion method. During the sit/stand condition, an overestimation of EE was detected with the MIO Fuse. As for the different walking speeds, an overestimation of EE was observed with all devices during slow walking ranging from 0.7% (Actiheart) to 86.8% (MIO Fuse) and moderate walking ranging from 13.9% (Actiheart) to 50.1% (Fitbit Charge HR). During the brisk walk however, only MIO Fuse overestimate EE by 25.7% while Actiheart (-13.7%), Fitbit Charge HR (-3.7%) and SenseWear (-20.2%) underestimated the EE. The M.A.P.E for EE is shown in Figure 9A. Figure 9B illustrates the M.A.P.E for number of steps for Fitbit Charge HR, MIO Fuse and SenseWear compared to the criterion method. On average, the devices underestimated the number of steps for every stage, with SenseWear showing the biggest percentage ranging from -2.73% (brisk walk) to -51.04% (slow walk). For the whole session, Fitbit Charge HR had the smallest percentage error with -0.57%.

Figure 9. Mean absolute percentage error for EE and steps between devices and criterion methods.

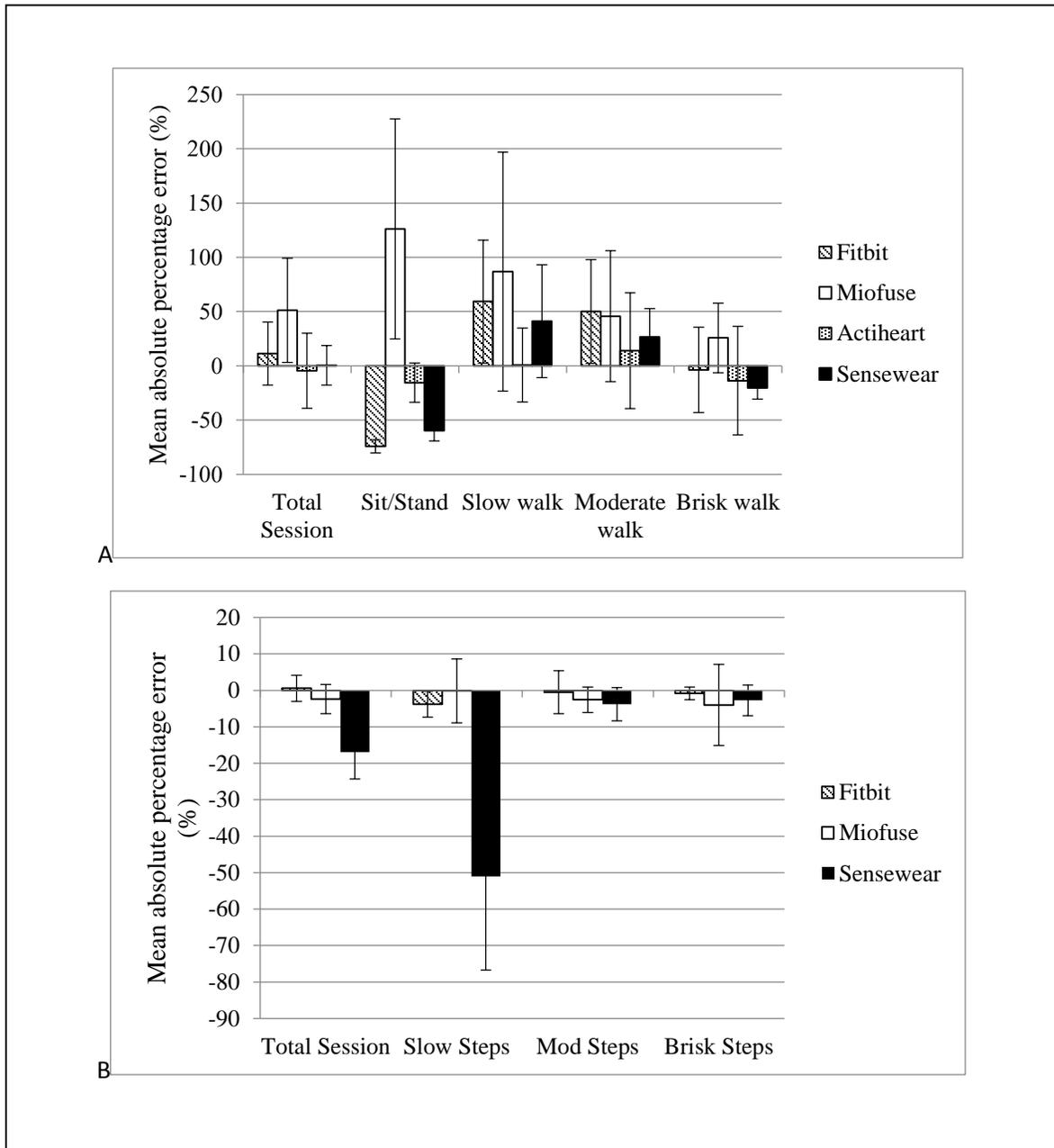


Figure 9A shows the mean absolute percentage error (M.A.P.E) for EE when devices are compared to the criterion method during the whole session, sit and stand and different walking speeds (slow, moderate and brisk). 9B. M.A.P.E for step count when devices are compared to criterion method during the whole session and the different walking speeds.

Table 16 illustrates the ICC between the activity trackers and the criterion method related to EE. The mean EE measured by the criterion method was 157 ± 35.2 calories for the whole session, while the mean calories measured by the devices ranged from 150 ± 62.7 (Actiheart) to 237.5 ± 88.7 (MIO Fuse). On average, correlations were fair to poor for all devices except for Actiheart during sit/stand period, where the correlation was excellent.

The mean number of steps for the whole session was 2579 ± 125.33 according to the criterion method and the devices reported values ranging from 2142.93 ± 222.45 (SenseWear) to 2593.06 ± 142.12 (Fitbit Charge HR). In general, Fitbit Charge HR and MIO Fuse showed an excellent correlation with the criterion method. However, this was not the case in every stage of the session. Fitbit Charge HR had a poor to fair correlation for moderate walking while MIO Fuse showed a poor to fair correlation during brisk walking. On the other hand, SenseWear had the worst correlations for step counts compared with the criterion method with poor values for total session and slow walking, but excellent correlation for moderate and brisk walking. Table 17 provides detailed information on every stage of the test for each device concerning the step count.

Finally, Figure 10 shows the Bland-Altman plots for EE and Figure 11 shows the Bland-Altman plots for number of steps. Graphically, there is a low agreement between the devices and the criterion method, demonstrating also that MIO Fuse has the greatest variability for estimated EE (-223.41, 62.61,). Fitbit Charge HR showed a better level of agreement compared to the criterion methods for both EE and step count.

Table 16. Validity of physical activity devices for energy expenditure.

Calories	Parameters	Calories Mean \pm SD	M.A.D ^b	LoA (U) ^c	LoA (L) ⁱ	R ^e	ICC ^d (95% CI)
Total session	Criterion method	157.06 \pm 35.16					
	Fitbit	165.93 \pm 10.08	-8.86 \pm 36.61	62.89	-80.61	-0.00	-0.00 (-2.03,0.66)
	MioFuse	237.46 \pm 88.71	-80.40 \pm 72.96	62.61	-223.41	0.60	0.39 (-0.28,0.77)
	Actiheart	150 \pm 62.69	7.06 \pm 55.94	116.70	-102.58	0.46	0.57 (-0.30,0.86)
	Sensewear	154.80 \pm 33.25	2.26 \pm 32.59	66.14	-61.61	0.54	0.72 (0.13,0.90)
Sit/Stand	Criterion method	14.72 \pm 3.25					
	Fitbit	8.80 \pm 1.08	5.92 \pm 2.79	0.45	11.38	0.56*	0.15 (-0.14,0.53)
	MioFuse	34.06 \pm 19.07	-19.34 \pm 17.11	14.20	-52.89	0.65*	0.20 (-0.21,0.63)
	Actiheart	14.68 \pm 3.02	0.40 \pm 2.68	5.65	-4.85	0.63	0.78 (0.35,0.93)
	Sensewear	12.04 \pm 2.17	2.67 \pm 2.99	8.54	-3.18	0.39	0.44 (-0.26,0.79)
Slow walk ^f	Criterion method	27.06 \pm 6.86					
	Fitbit	39.6 \pm 3	-12.60 \pm 8.16	3.39	-28.59	-0.24	-0.10 (-0.37,0.32)
	MioFuse	36 \pm 15.4	-9.19 \pm 12.04	14.40	-32.79	0.20	0.57 (-0.13,0.85)
	Actiheart	26.46 \pm 8.88	0.60 \pm 8.25	16.78	-15.58	0.47	0.64 (-0.10,0.88)
	Sensewear	36.06 \pm 9.63	-8.99 \pm 10.52	11.63	-29.62	0.22	0.24 (-0.42,0.68)
Moderate walk ^g	Criterion method	35.28 \pm 8.41					
	Fitbit	50.13 \pm 9.56	-14.85 \pm 11.33	7.35	-37.05	0.21	0.16 (-0.26,0.58)
	MioFuse	51.1 \pm 23	-15.85 \pm 20.21	23.77	-55.47	0.49	0.37 (-0.34,0.76)
	Actiheart	40.37 \pm 21.78	-5.09 \pm 20.10	34.30	-44.49	0.38	0.41 (-0.72,0.80)
	Sensewear	43.83 \pm 11.42	-8.54 \pm 9.9	10.85	-27.95	0.53	0.55 (-0.17,0.84)
Brisk walk ^h	Criterion method	59.65 \pm 13.72					
	Fitbit	53.46 \pm 8.83	6.18 \pm 17.74	40.95	-28.59	-0.35	-0.86 (-4.42,0.37)
	MioFuse	74 \pm 21.8	-14.41 \pm 18.84	22.52	-51.34	0.52	0.53 (-0.17,0.83)
	Actiheart	51.3 \pm 29.38	8.35 \pm 28.74	64.69	-47.99	0.28	0.34 (-0.85,0.77)
	Sensewear	46.81 \pm 9.07	12.84 \pm 9.16	30.80	-5.11	0.75	0.60 (-0.25,0.88)

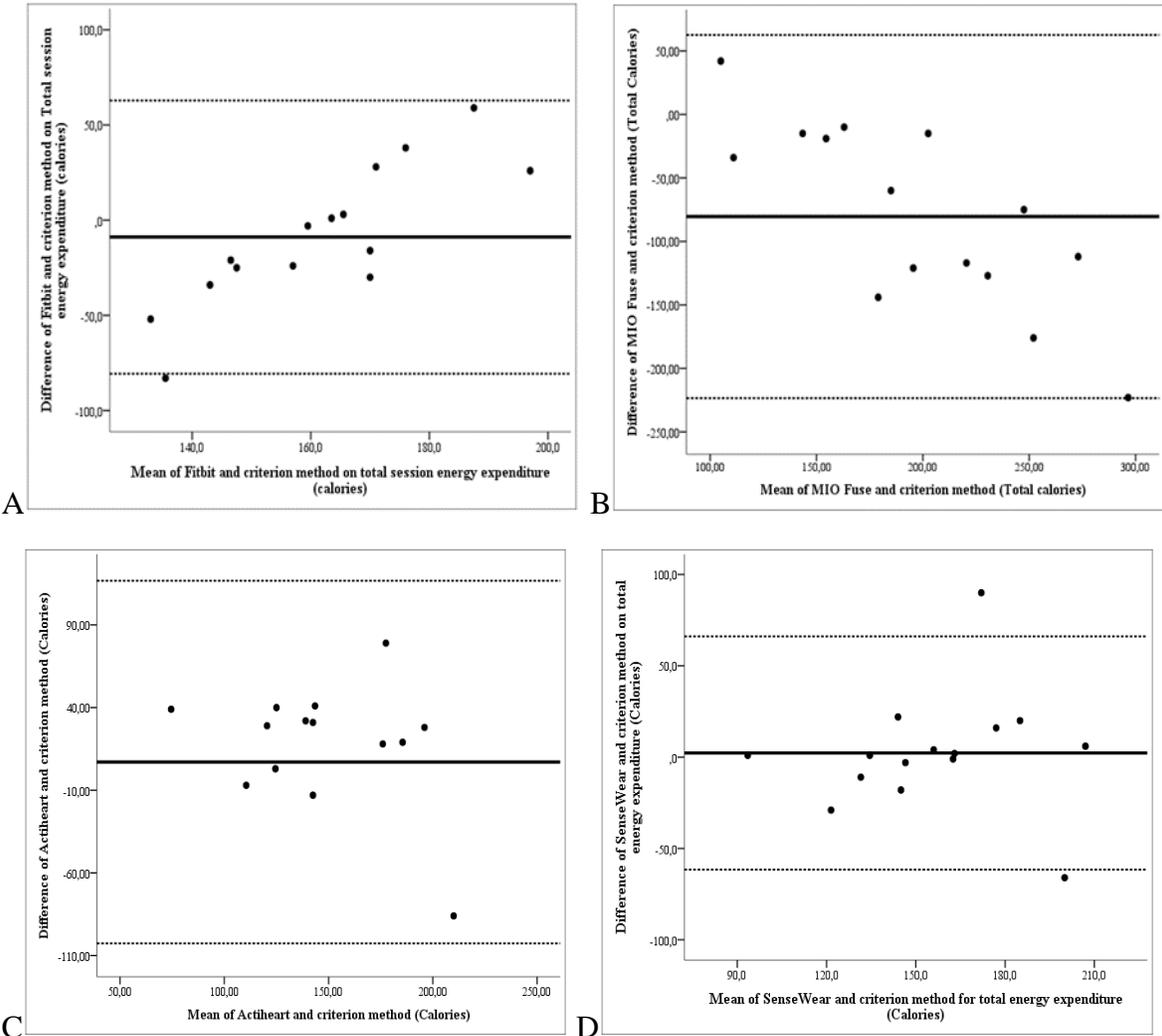
Table 16 illustrates the correlations between the activity trackers and the criterion method related to EE. b=Mean absolute difference, c: Level of agreement upper, i= Level of agreement lower, e= Pearson's Correlation, d= Intraclass correlation. (95%CI)= 95% Confidence Interval. f: 2.5km/h, g: 4km/h, h: 5.5km/h with 5% incline. *= Correlation is significant at the 0.05 level (two-tailed).

Table 17. Validity of physical activity devices for number of steps.

	Parameters	Steps Mean \pm SD	M.A.D ^b	LoA (U) ^c	LoA (L) ⁱ	R ^e	ICC ^d (95% CI)
Total session	Video	2579 \pm 125.33					
	Fitbit	2593.06 \pm 142.12	-14.06 \pm 91.47	165.22	-193.35	0.77*	0.87 (0.62,0.95)
	MioFuse	2518.80 \pm 184.48	60.20 \pm 101.68	259.50	-139.10	0.85*	0.85 (0.52,0.95)
	Sensewear	2142.93 \pm 222.45	436.06 \pm 198.9	825.91	46.20	0.46	0.18 (-0.14,0.57)
Slow walk ^f	Video	745.8 \pm 65.72					
	Fitbit	718.06 \pm 75.49	27.73 \pm 24.80	76.34	-20.87	0.94*	0.93 (0.38,0.98)
	MioFuse	745.86 \pm 97.74	-0.06 \pm 60.59	118.69	-118.83	0.79*	0.85 (0.56,0.95)
	Sensewear	370.46 \pm 213.59	375.33 \pm 191.81	751.28	-0.61	0.46	0.13 (-0.15,0.50)
Moderate walk ^g	Video	894.46 \pm 45.38					
	Fitbit	889.26 \pm 56.05	5.20 \pm 50.26	103.71	-93.31	0.52*	0.69 (0.05,0.89)
	MioFuse	871.73 \pm 60.99	22.73 \pm 29.68	80.92	-35.45	0.88*	0.88 (0.48,0.96)
	Sensewear	860.66 \pm 64.54	33.80 \pm 38.61	109.49	-41.89	0.80	0.78 (0.14,0.93)
Brisk walk ^h	Video	938.73 \pm 56.52					
	Fitbit	931.0 \pm 61.75	7.73 \pm 15.70	38.52	-23.05	0.96*	0.97 (0.93,0.99)
	MioFuse	901.86 \pm 122.87	36.86 \pm 101.67	236.14	-162.40	0.57*	0.59 (-0.13,0.85)
	Sensewear	912.46 \pm 59.04	26.26 \pm 41.97	108.54	-56.00	0.73*	0.80 (0.38,0.93)

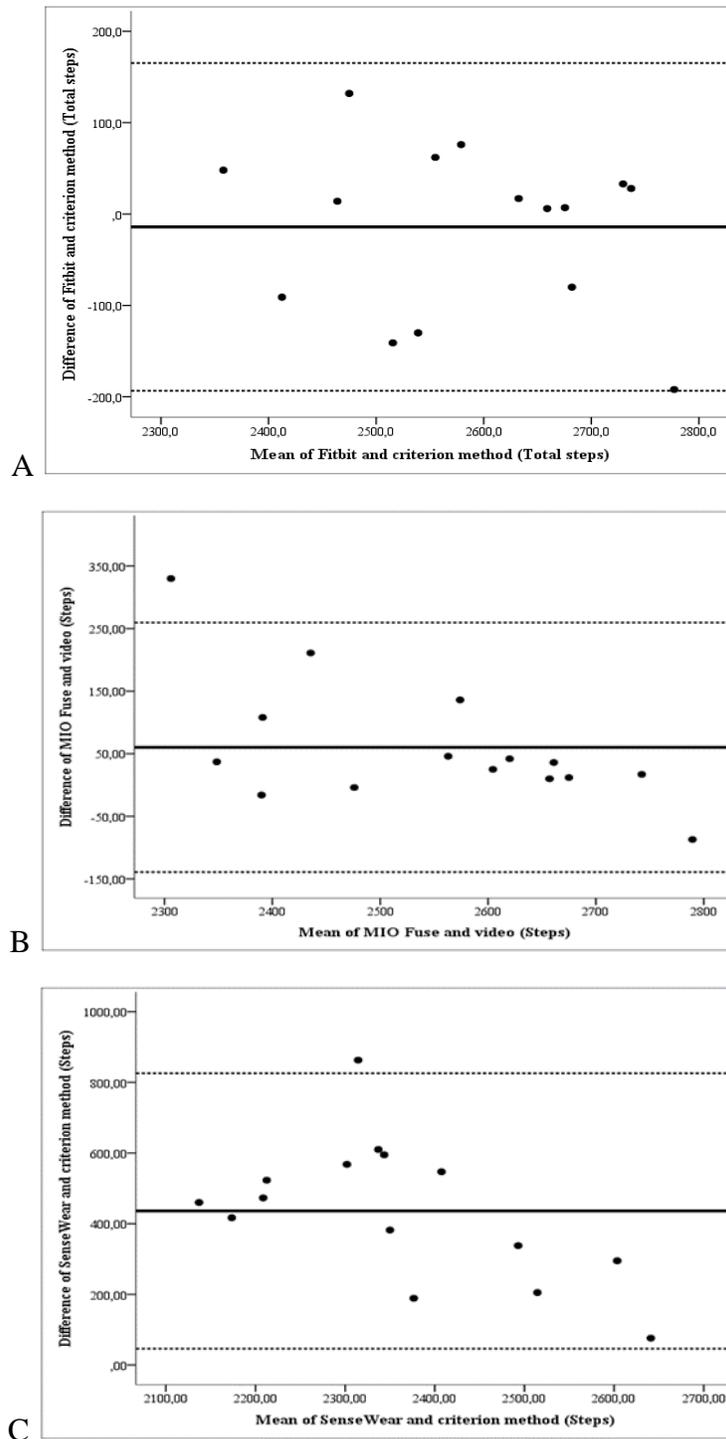
Table 17 illustrates the correlations between the activity trackers and the criterion method related to number of steps. b=Mean absolute difference, c: Level of agreement upper, i= Level of agreement lower, e= Pearson's Correlation, d= Intraclass correlation. (95%CI)= 95% Confidence Interval. f: 2.5km/h, g: 4km/h, h: 5.5km/h with 5% incline. *= Correlation is significant at the 0.05 level (two-tailed).

Figure 10. Bland-Altman plots for energy expenditure



Difference of total calories measured between the device and criterion method 10A: Fitbit Charge HR, 10B: MIO Fuse, 10C: Actiheart, 10D: SenseWear. The solid line corresponds to the mean difference, while the dashed lines correspond to the limits of agreement.

Figure 11. Bland-Altman plot for Fitbit Charge HR, MIO Fuse and SenseWear



Difference of total steps between the device and the criterion method. 11A Fitbit Charge HR, 11B: MIO Fuse and 11C: SenseWear. The solid line corresponds to the mean difference, while the dashed lines correspond to the limits of agreement.

DISCUSSION

This study highlighted the difficulties around the accurate estimation of EE by most PA devices in an older cardiac patient population during a common daily activity like walking. Yet, with the exception of the Fitbit Charge HR, all devices did show an excellent reliability for EE but with a low level of validity. Reliability for step count was fair to good for SenseWear and Fitbit Charge HR; MIO Fuse and Fitbit Charge HR showed fair to good validity for number of steps.

Reliability and validity of EE

Physical activity is a major component in a CR program and is integral to recovery from coronary heart disease (CHD) (5). It is also a multi-dimensional complex human behavior that can be described by the following parameters: i.e. type, pattern, duration and intensity of physical tasks and can be quantified by determining EE (21). In order to evaluate the effects of physical activities such as walking or jogging on the progression of the existing chronic disease, an accurate measurement of the volume of physical activity is needed (22). New physical activity trackers regularly enter the market, with advances in technology contributing to dramatic improvements, like inbuilt accelerometers for smartphone-based devices and wearable physical activity devices (5). From the four devices we investigated, Fitbit Charge HR showed the worst reliability and validity for determination of EE. Contrary to our results, Noah et al (23) found the Fitbit and Fitbit Ultra as reliable and valid devices for determining EE while walking and jogging without an incline in twenty-three subjects that participated in 6-min bouts of treadmill walking, jogging and stair stepping. Our results might be explained by the placement of the devices, while Fitbit and Fitbit Ultra are placed on the waistline, Fitbit Charge HR is a wrist worn accelerometer. The placement of the devices is important as recent research indicates that wrist worn accelerometers might not be as accurate as waist worn devices (24). The SenseWear and Actiheart had an excellent reliability (except for the Sit and Stand period for SenseWear) and a fair to good validity during the whole test and most of the phases except for brisk walk (Actiheart) and slow walk (SenseWear) in this cardiac population. These results are in line with previous

studies involving the Actiheart, which was the first commercially available device that combined a heart rate monitor and accelerometer into a single unit (25). In general, the Actiheart has been shown to provide accurate EE estimates of low-to-moderate intensity activities performed in a laboratory setting as well as during treadmill walking and running in healthy adults (25, 26). The poor correlation during brisk walk might be explained by the poor relative performance of the accelerometer component of the Actiheart. Spierer et al. estimated EE from the device during low intensity activities, walking and jogging describing mixed results depending on which activities were examined. They found that the Actiheart performs better during activities in which EE is not directly related to pelvic acceleration (card playing, weight lifting, and sweeping). They hypothesized that the location of the accelerometer component on the chest may be problematic due to the significant damping of acceleration forces which occurs in the torso during walking, compared to acceleration that occurs at the pelvis (27).

Several studies have been published on the validity of different models of SenseWear armband (28, 29). Early research has shown that the SenseWear Pro 2 armband can accurately estimate resting EE in healthy young (30) and obese subjects (31). The validity of SenseWear has also been tested with clinical populations including individuals with chronic obstructive pulmonary disease (COPD), cystic fibrosis, and arthritis (32-34). Van Remoortel et al. found that for estimating EE, SenseWear is a valid monitor during standardized physical activities in COPD patients (34). Cole et al (35) however, concluded that the accuracy of the SenseWear (version 2.2) appears to be exercise modality dependent in patients with heart disease when using software developed for general population. Fruin and Rankin (36) found that the SenseWear was valid and reliable for measuring resting EE, but it overestimated the EE of treadmill walking without inclination and underestimated the EE of treadmill walking up an incline. In our study however, the validity of SenseWear was fair for slow walk with a poor reliability for sit and stand. A possible reason for these results might reside in the software version used to analyze the data (Version 7.0). In a doubly labelled water validation study, the SenseWear Pro 2 with software version 5.1, but not version 6.1, was found to be

valid in overweight and obese children (37). The SenseWear accuracy seems to be improving over time, but researchers should follow the results of validation studies and be aware of which software version they are using (37).

As for MIO Fuse, only a few studies have been published previously (38, 39) validating devices from the same company (MIO Global) for heart rate monitoring, but information related to EE is scarce. It is difficult to speculate what contributed to errors of this device. It is assumed that each device has a specific algorithm for the determination of EE, however this information is not disclosed by the companies (17).

Reliability and validity on number of steps

Step counts are a simple way to quantify the amount of physical activity and are being used extensively in health promotion campaigns by governments and international organizations (22).

According to Tudor-Locke et al. (40) activity monitors should not exceed a 1% error deviation (M.A.P.E) from the gold standard during walking on a treadmill at a speed of 3mph (4.8 km/h) in order to be considered accurate. Only Fitbit Charge HR fitted this criterion. SenseWear had an error deviation slightly higher than the 1% threshold (-2.7%) while MIO Fuse exhibited the greatest deviation errors during the brisk walk (-4%). Similar to our results, Takacs et al.(22) found a percent relative error of Fitbit One less than 1.3% for number of steps in thirty volunteers during five pre-determined speeds on a treadmill, while Manns et al.(41), reported a constant underestimation of steps by the SenseWear in persons with stroke.

In our study, Fitbit Charge HR and MIO Fuse demonstrated a good to excellent agreement with the gold standard for the whole session and almost every separate stage (Fitbit Charge HR was fair to good during moderate walking and MIO Fuse had the same result for brisk walking). SenseWear showed the lowest ICC for the whole session. Takacs et al (22) found correlations between 0.97 and 1.0 for five different speeds on a treadmill for the Fitbit One. Although in our study, the correlation for the Fitbit Charge HR was somewhat lower (ICC 0.87), it is still

considered excellent. As for SenseWear, Manns et al. (41) found a poor agreement between the device and their criterion method (ICC = 0.352) which can be compared to the poor agreement in our study (ICC = 0.18) for the whole session, however, in our study results were excellent for moderate walking (ICC = 0.88) and brisk walking (ICC = 0.80).

The majority of activities in daily life are intermittent in nature, intensity and duration. Thus, research on activity devices in laboratory settings (such as treadmill walking) may not be generalizable to overall activities in free-living conditions (42). To date, only one study measured the accuracy of MioFuse and Fitbit Charge HR in laboratory and free living conditions. Their population consisted of forty healthy young adults (21.6 ± 2 years) that performed four five-minute stages at different speeds on a treadmill and wore the devices during walking hours of the ensuing day to obtain free-living data (42). The authors concluded that MIO Fuse substantially underestimated steps compared to Fitbit in free-living observation probably due to its difficulty in detecting sporadic movements. Further research is needed under free-living conditions to support these findings.

It seems that the investigated devices should not be recommended for tracking of exercise progress in a phase III cardiac rehabilitation population, even though they could be of use as a motivational tool.

Strength and limitations

Our results are based on laboratory settings involving only treadmill walking at different speeds and inclination. It is not known how well the results apply to free-living conditions or other physical activities since under free-living conditions there could be an increased variety of intensities, directions and walking speeds (43). However, validating physical activity tracking devices under free-living conditions presents the inability to use a gold standard criterion method for EE or number of steps.

The information provided by this study however, may be useful to researchers and medical personnel attempting to make practical decisions regarding the selection of

devices to measure physical activity in cardiac patients. The complete walking bouts were used for the analysis of each device including the first and last minute of every stage, although a difference in acceleration could be present during these moments, their influence on our results cannot be established since the filtering and processing of acceleration signals for the trackers is not publicly available.

CONCLUSION

This study documented a noteworthy inability of the Fitbit Charge HR, MIO Fuse, SenseWear Armband Mini and Actiheart to accurately estimate EE. It is difficult to speculate what contributed to errors of this magnitude for EE (17). However it is assumed that the devices have errors related to shortcomings of the used algorithms for the determination of EE and unfortunately, this information is not disclosed by the manufacturing companies. However, validity and reliability were higher for step counts. Fitbit Charge HR had an excellent validity for number of steps with fair to good test re-tests reliability, MIO Fuse showed good validity, but with a poor reliability.

REFERENCES

1. Piepoli MF, Corrà U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery. *European Journal of Preventive Cardiology*. 21(6):664-81.
2. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *European Journal of Preventive Cardiology*. 2016;23:1715-33.
3. Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, et al. Effect of comprehensive cardiac telerehabilitation on one- year cardiovascular rehospitalization rate, medical costs and quality of life: A cost- effectiveness analysis. *European journal of preventive cardiology*. 2016;23(7):674-82.
4. 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. *European Journal of Preventive Cardiology*. 2015;22(2):150-8.
5. Alharbi M, Bauman A, Neubeck L, Gallagher R. Validation of Fitbit-Flex as a measure of free-living physical activity in a community-based phase III cardiac rehabilitation population. *European Journal of Preventive Cardiology*. 2016;23(14):1476-85.
6. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57(4):306-14.
7. Stewart R, Held C, Brown R, Vedin O, Hagstrom E, Lonn E, et al. Physical activity in patients with stable coronary heart disease: an international perspective. *European Heart Journal*. 2013;34(42):3286-93.
8. Frederix I, L Vanhees L, Dendale P, Goetschalckx K. A review of telerehabilitation for cardiac patients. *Journal of Telemedicine and Telecare*. 2015;21(1):45-53.
9. Ferguson T, Rowlands AV, Olds T, Maher C. The validity of consumer- level, activity monitors in healthy adults worn in free-living conditions: a cross-sectional study. *The international journal of behavioral nutrition and physical activity*. 2015;12(1):42.
10. Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, et al. Validity of activity monitors in health and chronic disease: a systematic review. *Int J Behav Nutr Phys Act*. 2012;9:84.
11. Paul SS, Tiedemann A, Hassett LM, Ramsay E, Kirkham C, Chagpar S, et al. Validity of the Fitbit activity tracker for measuring steps in community-dwelling older adults. *BMJ open sport & exercise medicine*. 2015;1(1):e000013.
12. Stahl ST, Insana SP. Caloric expenditure assessment among older adults: Criterion validity of a novel accelerometry device. *Journal of Health Psychology*. 2014;19(11):1382-7.

13. Parak J, Korhonen I. Evaluation of wearable consumer heart rate monitors based on photoplethysmography. *Engineering in Medicine and Biology Society (EMBC). 2014;36th Annual International Conference of the IEEE.(IEEE):3670.*
14. Erdogan A, Cetin C, Karatosun H, Baydar ML. Accuracy of the polar S810i[TM] heart rate monitor and the SenseWear Pro Armband[TM] to estimate energy expenditure of indoor rowing exercise in overweight and obese individuals. *Journal of Sports Science & Medicine. 2010;9(3):508.*
15. Koehler K, De Marees M, Braun H, Schaenzer W. Evaluation of two portable sensors for energy expenditure assessment during high- intensity running. *European Journal of Sport Science. 2013;13(1):31-41.*
16. Lee J-M, Kim Y, Welk GJ. Validity of consumer- based physical activity monitors. *Medicine and Science in Sports and Exercise. 2014;46(9):1840-8.*
17. Wallen MP, Gomersall SR, Keating SE, Wisloff U, Coombes JS. Accuracy of Heart Rate Watches: Implications for Weight Management.(Report). *PLoS ONE. 2016;11(5):e0154420.*
18. Nelson BM, Kaminsky AL, Dickin CD, Montoye KAH. Validity of Consumer-Based Physical Activity Monitors for Specific Activity Types. *Medicine & Science in Sports & Exercise. 2016;48(8):1619-28.*
19. Welk G. *Physical activity assessments for health-related research . kinetics.* H, editor2002.
20. Rosner B. *Fundamentals of biostatistics: study guide. 5th ed. ed. Pacific Grove: Pacific Grove : Duxbury; 2000.*
21. Kraal JJ, Sartor F, Papini G, Stut W, Peek N, Kemps HM, et al. Energy expenditure estimation in beta- blocker- medicated cardiac patients by combining heart rate and body movement data. *European Journal of Preventive Cardiology. 2016;23(16):1734-42.*
22. Takacs J, Pollock CL, Guenther JR, Bahar M, Napier C, Hunt MA. Validation of the Fitbit One activity monitor device during treadmill walking. *Journal of Science and Medicine in Sport. 2014;17(5):496-500.*
23. Adam Noah J, Spierer DK, Gu J, Bronner S. Comparison of steps and energy expenditure assessment in adults of Fitbit Tracker and Ultra to the Actical and indirect calorimetry. *Journal of medical engineering & technology. 2013;37(7):456-62.*
24. Sushames A, Edwards A, Thompson F, McDermott R, Gebel K. Validity and Reliability of Fitbit Flex for Step Count, Moderate to Vigorous Physical Activity and Activity Energy Expenditure. *PLoS ONE. 2016;11(9):e0161224.*
25. Crouter SE, Churilla JR, Bassett Jr DR. Accuracy of the Actiheart for the assessment of energy expenditure in adults. *European journal of clinical nutrition. 2008;62(6):704.*
26. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. *European journal of clinical nutrition. 2005;59(4):561.*
27. Spierer D, Hagins M, Rundle A, Pappas E. A comparison of energy expenditure estimates from the Actiheart and Actical physical activity monitors during low intensity activities, walking, and jogging. *European journal of applied physiology. 2011;111(4):659-67.*

28. Yang C, Hsu Y. A Review of Accelerometry-Based Wearable Motion Detectors for Physical Activity Monitoring. *Sensors*. 2010;10(8):7772-88.
29. Bassett DR, John D. Use of pedometers and accelerometers in clinical populations: validity and reliability issues. *Physical Therapy Reviews*. 2010;15(3):135-42.
30. Malavolti M, Pietrobelli A, Dugoni M, Poli M, Romagnoli E, De Cristofaro P, et al. A new device for measuring resting energy expenditure (REE) in healthy subjects. *Nutrition, metabolism and cardiovascular diseases*. 2007;17(5):338-43.
31. Papazoglou D, Augello G, Tagliaferri M, Savia G, Marzullo P, Maltezos E, et al. Evaluation of a Multisensor Armband in Estimating Energy Expenditure in Obese Individuals. *Obesity*. 2006;14(12):2217-23.
32. Dwyer TJ, Alison JA, McKeough ZJ, Elkins MR, Bye PTP. Evaluation of the SenseWear activity monitor during exercise in cystic fibrosis and in health. *Respiratory Medicine*. 2009;103(10):1511-7.
33. Hill K, Dolmage TE, Woon L, Goldstein R, Brooks D. Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease. *Thorax*. 65(6):486.
34. Van Remoortel H, Raste Y, Louvaris Z, Giavedoni S, Burtin C, Langer D, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One*. 2012;7(6).
35. Cole P. J. LLM, Klinger T. A., Strohecker K., McKonnell T. R.,. Measuring energy expenditure in cardiac patients using the Body Media (TM) Armband versus indirect calorimetry: A validation study. *Journal of sports medicine and physical fitness*. 2004;44(3):262.
36. Fruin LM, Rankin WJ. Validity of a Multi- Sensor Armband in Estimating Rest and Exercise Energy Expenditure. *Medicine and science in sports and exercise*. 2004;36(6):1063-9.
37. Bäcklund C, Sundelin G, Larsson C. Validity of Armband Measuring Energy Expenditure in Overweight and Obese Children. *Medicine & Science in Sports & Exercise*. 2010;42(6):1154-61.
38. Stahl SE, An H-S, Dinkel DM, Noble JM, Lee J-M. How accurate are the wrist-based heart rate monitors during walking and running activities? Are they accurate enough? *BMJ open sport & exercise medicine*. 2016;2(1):e000106.
39. Spierer DK, Rosen Z, Litman LL, Fujii K. Validation of photoplethysmography as a method to detect heart rate during rest and exercise. *Journal of Medical Engineering & Technology*. 2015;39(5):264-71.
40. Tudor-Locke C, Sisson SB, Lee SM, Craig CL, Plotnikoff RC, Bauman A. Evaluation of Quality of Commercial Pedometers. *Canadian Journal of Public Health/Revue Canadienne de Sante'e Publique*. 2006;97:S10-S5.
41. Manns PJ, Haennel RG. SenseWear Armband and Stroke: Validity of Energy Expenditure and Step Count Measurement during Walking. *Stroke Research and Treatment*. 2012;2012.
42. Deyarmin NK, Snyder MK, Mihalik GA, Hargens AT. Accuracy of Wrist and Hip-worn Commercial Physical Activity Monitors In Free Living Conditions: 2775 Board #298 June 3, 9: 30 AM - 11: 00 AM. *Medicine & Science in Sports & Exercise*. 2016;48(5S Suppl 1):781-.

43. Fokkema T, Kooiman TJ, Krijnen WP, CP VDS, M DEG. Reliability and Validity of Ten Consumer Activity Trackers Depend on Walking Speed. *Med Sci Sports Exerc.* 2017;49(4):793-800.

Chapter 6

General discussion

Cardiac rehabilitation has evolved considerably since the 1930s and is now viewed as a comprehensive multidisciplinary approach to complex medical conditions requiring behavioural, physical, emotional, and social care management in the secondary prevention of CAD (1). Exercise-based cardiac rehabilitation has been shown to reduce mortality, prevent hospital readmission and improve quality of life (2). Nonetheless, despite the clinical effectiveness of centre-based cardiac rehabilitation, the long-term clinical effectiveness of this intervention is often poor, due to the lack of attendance at rehabilitation sessions and non-adherence in the longer-term to lifestyle recommendations (3). Recent advances in information and communication technologies, such as smartphones and the internet, have shown potential to address some of the barriers through home-based cardiac rehabilitation programmes (4).

Therefore, the main scope of this doctoral project was to compare the short and long-term effects of a 12 week home-based cardiac rehabilitation program with tele-monitoring guidance in CAD patients. This final chapter summarizes and discusses the main findings of the TRiCH study complemented with findings on the validity and reliability research on PA trackers to create an overall understanding of the effects of tele-monitoring in CAD patients. The strengths and limitations of this doctoral research will also be discussed, followed by future research recommendations closing with the general conclusions of our research.

Summary of main findings

Chapter 2: In this chapter, we described the rationale, design and methods of the Tele-Rehabilitation in Coronary Heart disease study (TRiCH). The main objective of the TRiCH study was to compare the long-term effects of a 3-month HB cardiac rehabilitation program with tele-monitoring guidance in CAD patients (phase III) with a supervised CB cardiac rehabilitation program and a CG. We used exercise capacity measured as peak oxygen uptake (VO_{2P}) at 12 months as the main outcome and hypothesized that patients randomized to a HB training cardiac rehabilitation program with tele-monitoring guidance will demonstrate higher levels of PA at one-year of follow-up, resulting in higher levels of exercise capacity,

compared to the other two groups. Secondary outcomes included PA, muscle function, HRQoL and traditional cardiovascular risk factors.

The second objective was to determine the differential effect of HB cardiac rehabilitation versus CB cardiac rehabilitation on exercise capacity in the short-term; hypothesizing that in CAD patients on phase III of cardiac rehabilitation, HB cardiac rehabilitation will have a larger effect compared to the CG, but similar to CB cardiac rehabilitation.

The study was planned initially as a randomized controlled trial including 105 CAD patients to one of three groups: HB, CB or usual-care group (CG). The enrolment started in February 2014 and was expected to finish in November 2015. However, recruitment of participants went slower than anticipated due to logistical issues in the hospital. As a result, the recruitment ended in August 2016 and we could only recruit 90 patients.

Chapter 3: Cardiac rehabilitation is an essential part of contemporary coronary heart disease management. Yet, many patients exiting a CB cardiac rehabilitation program have difficulty retaining its benefits. Thus, we aimed to evaluate the second objective of the TRiCH study (**Chapter 2**) by establish the short-term effect of a HB cardiac rehabilitation program with tele-monitoring guidance on exercise capacity and other secondary outcomes in CAD patients in phase III of cardiac rehabilitation. The result of this study showed that a 3-month HB training intervention with tele-monitoring guidance is as effective as a prolonged CB cardiac rehabilitation. The changes obtained with an average training intensity below the recommended thresholds in our population led us to believe, as described previously by Swain and Franklin (1), that in healthy individuals, with a mean baseline $\text{VO}_2\text{max} < 40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, intensities above 40% of heart rate reserve can still bring improvements in exercise capacity. As for secondary outcomes, a small but significant increase in sedentary time was found in the CB group. We considered this behaviour as a compensatory effect for exercise (2), meaning that the simple fact of enrolling in a supervised exercise program might reduce PA levels throughout the rest of the day. Based on these results it was concluded that a HB cardiac rehabilitation with tele-

monitoring guidance can be an effective alternative to CB cardiac rehabilitation for further maintain exercise capacity following phase II of cardiac rehabilitation and although short-term changes are of interest, it was important to establish whether the benefits were maintained in the long-term.

Chapter 4: HB interventions have been shown to enhance a patient's self-efficacy and might facilitate the lifelong uptake of a physically active lifestyle. However, data on the long-term effectiveness of HB exercise training on PA and exercise capacity are scarce. Hence, following the main purpose of the TRiCH study (Chapter 2), we compared the long-term effects of the implementation of a short HB phase III exercise program with tele-monitoring guidance to a prolonged CB cardiac rehabilitation program in CAD patients. Contrary to our hypothesis, we could not demonstrate higher levels of PA at one year of follow-up in patients randomized to a HB training program, however, we showed that HB cardiac rehabilitation was as effective as a prolonged CB cardiac rehabilitation program in the maintenance of PA and exercise capacity. Overall, 85% of patients in our study maintain their PA levels independently of the group of randomization which led us to believe that they were prepared for independent lifestyle changes, favouring the maintenance of long-term benefits after the completion of a phase II cardiac rehabilitation program.

Chapter 5: The ESC guidelines recommend that patients with CAD engage in 30 minutes of moderate intensity PA on most days of the week (3). Since activity tracking devices have the potential to affect PA behaviour and make a direct and real-time impact on self-management of PA (4), we evaluated the validity and reliability of Fitbit Charge HR, MIO fuse, SenseWear Armband Mini and Actiheart for estimating energy expenditure and step count in CAD patients on phase III of cardiac rehabilitation. Our results showed that overall, the inability to accurately estimate energy expenditure was notable across all devices. By consequence, we did not recommend the studied devices for tracking the energy expenditure in a population of CAD patients on phase III of cardiac rehabilitation.

Appendices: Resveratrol is a polyphenol with anti-oxidant, anti-inflammatory, and cardio protective properties, and has been shown to reduce oxidative damage in the

aorta of aged rats (5). Since patients with CAD commonly present endothelial dysfunction, we intended to investigate whether acute supplementation with high doses of Resveratrol would improve flow-mediated dilation and oxygen kinetics in ten CAD patients on phase III cardiac rehabilitation. We found that the supplementation improve flow-mediated dilation in patients after CABG. However, our study should be interpreted within the context of its limitations that include the limited number of patients and the used of indirect measures.

Effectiveness of a HB cardiac rehabilitation program with tele-monitoring guidance in improving exercise capacity in the short-term and long-term

In **Chapter 3** we demonstrated that adding a HB exercise program in the early stage of phase III cardiac rehabilitation results in a further improvement of exercise capacity and is equally effective as a prolonged CB cardiac rehabilitation in patients with CAD.

In the TRiCH study, the home-based intervention consisted of a 12-week program with weekly follow-up on exercise compliance and adherence. A commercially available heart rate monitor (Garmin Forerunner 210) was provided to patients randomized to the HB group. As described in **Chapters 2 and 3**, the patients trained the first three sessions under the supervision of the researchers for acquaintance with the tele-monitoring system (use of the heart rate monitor) and were instructed to use the device during the training sessions. Additionally, patients were instructed on how to upload the information to the Garmin web application (<http://connect.garmin.com>). The application provided graphical information on the type of activity, duration of the activity and heart rate during each of the training sessions (minimum, maximal and average) as shown in Figure 12. The application was accessed by both patients and the researchers. Patients were advised to follow the current physical activity recommendations as formulated by the European Society of Cardiology: i.e. to exercise for at least 150 minutes a week (at least 3 times/week, preferably 6 to 7 days/week) at an individually determined target heart rate corresponding to moderate intensity (70-80% HRR) (6). The time patients spent

within the recommended heart rate zone was assessed by means of the garmin training centre program.



Figure 12. Platform garmin connect. Patients were encourage to upload their information after each training or once a week according to their preferences.

Patients were asked about their preferred contact method: e-mail (40% of participants) or phone call (60% for weekly feedback). The purpose of the feedback was twofold. First, to discuss adherence and compliance with the exercise prescription in the home environment and to evaluate motivational issues and incidence of injuries or adverse effects related to exercise. Patients opting for e-mail as their preferred method of feedback were given two days to reply a message after which a reminder email was sent. Figure 13 shows an example of one of the messages. We used short texts to make it fast and clear for participants, however its content was adapted according to patient's needs. In cases of questions related to training or technical problems with the device, patients were stimulated to contact

the researchers for further help. After 12 weeks, the weekly contacts terminated but patients were advised to continue their training with or without the heart rate monitor.

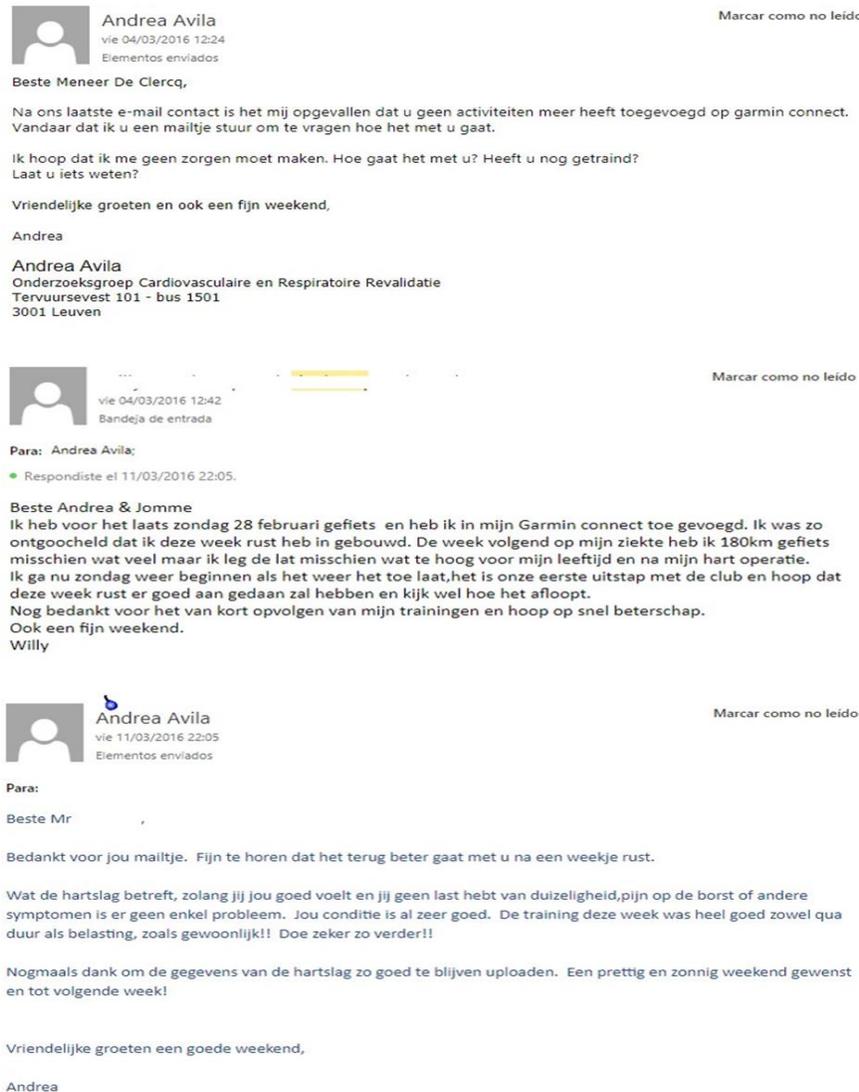


Figure 13. Patients were contacted according to their preference (phone call or email), the intensity, duration and frequency of the training was discuss weekly.

In line with our results, systematic reviews have shown the benefits of telehealth programmes when compared to usual care (7-9). Huang et al. reviewed the effectiveness of mainly phone-based telehealth interventions versus CB care in 1546 low to moderate risk CAD patients (8). They found no difference between the former and latter care delivery strategy for exercise capacity, cardiovascular risk factors,

mortality, quality of life (HRQoL) and psychosocial state. Hwang et al. compared remote rehabilitation with on-site care delivery in 908 CAD, chronic heart failure and/or respiratory disease patients (10). Tele-rehabilitation was shown to be as effective as CB cardiac rehabilitation in terms of exercise capacity and quality of life. Currently, the most common communication technology is smartphone, followed by email, and text messages (11).

When it comes to long-term, we found no further improvement in exercise capacity as discussed in **Chapter 4**. Contrary to our results, Smith et al (12) followed during 12 months a total of one hundred and ninety-eight patients after discharge from a randomized controlled trial of 6 months of monitor “home” versus supervised “hospital” cardiac rehabilitation after CABG. They found a declined in VO_2P in the “hospital” but not in the “home” group ($P = 0.002$). They suggested that if the exercise component of cardiac rehabilitation was initiated in the home environment and monitored for 6 months, the improvements will be maintained for at least an additional 12 months after the cessation of cardiac rehabilitation. Their study however was developed during phase II cardiac rehabilitation and patients only experienced “home” or “hospital” program. On the other hand, in the Telerehab III trial, Frederix et al (13, 14) observed a difference in favour of the patients receiving tele-rehabilitation. We considered that the changes could be attributed to the longer duration of the intervention in the Telerehab III study (24-weeks) compared to the TRiCH study (12-weeks). Another important aspect not fully disclosed in **Chapter 4** is related to the population included in the TRiCH study. Reasons for no-enrolment in cardiac rehabilitation usually include dislike of exercise, low exercise capacity or the perception that exercise is tiring or painful (15). Even though our population was randomized, we actively recruited patients who were already enrolled in phase II of cardiac rehabilitation potentially leading to a biased sample population; we assumed that our participants did like being physically active which is supported by the maintenance of their PA and exercise capacity after a year of inclusion. Traditionally, older age, female sex, a racial-ethnic minority group, low socioeconomic status, work-related factors, limited or lack of health insurance, multiple comorbidities, and

health care system factors have been associated with low referrals or enrolment rate (16, 17).

Thus, further research is needed to establish if a longer intervention with tele-monitoring guidance or a hybrid intervention (home-based additional to centre-based) for a specific CAD population could have a greater impact in the long-term.

Notwithstanding what has just been said, our results nicely complemented the previous publications on tele-monitoring and HB training showing that this novel care delivery strategy has the potential to become an alternative to CB cardiac rehabilitation. That is, HB programmes could be a beneficial option for patients who do not like or are not able to take part in a CB cardiac rehabilitation since it can be delivered in non-clinical settings, such as the home or community and consequently increase uptake of cardiac rehabilitation overall. In line with other studies we also illustrated that patients are able to independently execute a training programme in their home environment for 12-weeks when they receive weekly feedback (18).

Effectiveness of a HB cardiac rehabilitation program with tele-monitoring guidance on PA, anthropometric measures, muscle strength, traditional cardiovascular risk factors and HRQoL in the short-term and long-term.

Overall, our intervention did not affect the PA levels of the participants and we were unable to increase the PA in our population. In the short-term an increased in sedentary behaviour was seen on the CB group as described in **Chapter 3**, nevertheless in **Chapter 4** we found no differences between groups in PA. Contrary to our results, Van den Berg et al in a systematic review (19), reported that online interventions are effective in improving PA levels. However, objective measures such as activity monitors or pedometers were rarely used. Thus, our study add to the limitations of previous publications by exploring the results with a defined control group as well as with an objective PA outcome measure. A recent systematic review by Veen et al (20) included 19 RCTs on the effectiveness of e-coaching as a cardiac rehabilitation programme. They report that complex e-coaching (including ≥ 4 components of cardiac rehabilitation) was effective at short-term for PA, when

comparing to usual care. However for basic e-coaching (≤ 3 components) limited or no evidence of effectiveness was found.

As stated previously, objective PA measures were rarely used in online interventions. Hence we expected to increase our knowledge on PA tracking, by studying different monitors as shown on **Chapter 5**. We concluded that the Fitbit Charge HR and Mio Fuse had a high reliability and validity for number of steps in cardiac patients on phase III of cardiac rehabilitation. In line with our results, Alharbi et al (21) found valid and reliable the use of Fitbit-Flex as an alternative device for PA monitoring in cardiac patients.

Most of the instruments for self-report PA measures in cardiac patients have great variability, poor validity and reliability and are more suited to epidemiologic studies rather than assessing intervention outcomes where responsiveness to intervention is vital (22). Hence, establishing the reliability and validity of some activity trackers added value to the present PhD project, since we intended to further increase the knowledge of their utility in CAD patients participating in telemedicine and tele-rehabilitation programs.

Participants in the TRiCH study had an average BMI of 27.4 kg/m² that was maintained throughout the intervention in the short-term (**Chapter 3**) and longer-term follow-up (**Chapter 4**). In line with our findings, Dale et al (23) observed no effect on dietary behaviours or smoking cessation of mHealth interventions in the CVD population. A separate meta-analysis of 36 weight loss studies found that 71% of the studies reported some form of weight loss, although participants and heterogeneity precluded a summary estimate of weight loss achieved through digital health interventions (24). It is possible that changing dietary behaviours may be more difficult via mHealth. However, more research is needed before conclusions can be drawn on this topic.

On **Chapter 3** we described that participants of the TRiCH study maintained their systolic blood pressure and diastolic blood pressure, the same result were found in the long-term (**Chapter 4**). Purcell et al (25) reported in a review of reviews that the

use of tele-monitoring for patients with hypertension and heart failure was associated with multiple benefits. They included four reviews which investigated hypertension and CVD management using blood pressure as an outcome measure. All reviews reported significant reductions in blood pressure with various interventions (telephone-based intervention/internet-based intervention). We agreed with their conclusion that given the concomitant changes in extraneous variables such as medication use and lifestyle risk factors that occurred around the interventions is difficult to ascertain which specific aspects of tele-monitoring interventions might explain improvements in the blood pressure values.

When reporting on the effects of tele-monitoring in **Chapters 3 and 4**, surprisingly, we discovered that little is known about skeletal muscle strength in cardiac patients suffering from other diseases than heart failure (26). Therefore, we hope our results could increase the interest in this research field.

Overall, our TRiCH study assessed the effects in both the short and long-term on exercise capacity, cardiovascular risk factors, PA and HRQoL by means of a randomized controlled study, improving the body of evidence in favour of a tele-monitoring intervention that will maintained the benefits of a traditional CB cardiac rehabilitation program after the completion of phase II cardiac rehabilitation.

Different components of tele-monitoring in cardiac rehabilitation programs

In simple terms telemedicine refers to the delivery of medical health services at a distance, there is no single or uniform telemedicine or telehealth service as such (27). As can be seen in Figure 14, Telemedicine includes telehealth and remote patient management, telecare and teledisciplines (including teleradiology, teledematology, telescreening, etc).

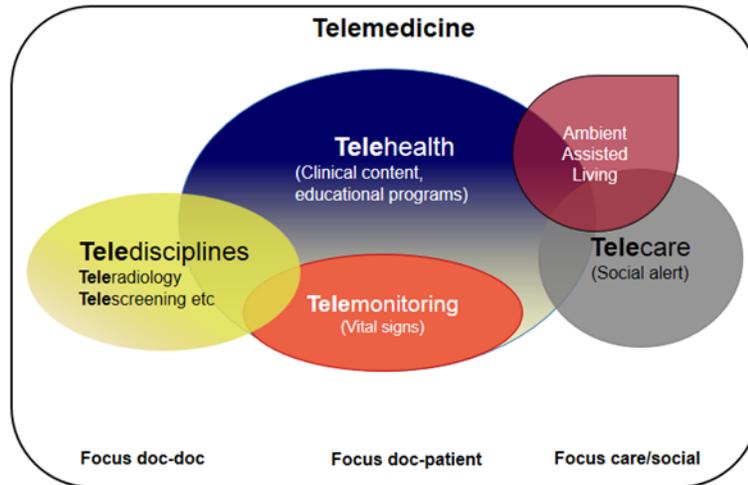


Figure 14. Different components of telemedicine. Adapted from COCIR (28)

Cardiac tele-rehabilitation is a care delivery strategy that is developing a role in secondary prevention after acute myocardial infarction according to the European Association of Preventive Cardiology in collaboration with the Acute Cardiovascular Care Association and the Council on Cardiovascular Nursing and Allied Professions (29). They identified cardiac tele-rehabilitation as a supplement and/or alternative to conventional CR services since it has shown potential to address some of traditional CR barriers through for example HB cardiac rehabilitation programs (30).

Tele-rehabilitation interventions however, as described by Frederix et al (31) employed only one or two core components of cardiac rehabilitation. According to the author, PA is the parameter most frequently evaluated. This tendency is explained by the benefits of a high cardiovascular fitness evidenced by reductions of 10% to 25% in mortality risk (in both men and women) per increase of 1 MET in exercise capacity (32, 33). Furthermore, a higher physical activity patterns and cardiovascular fitness have an important moderating role on the traditional cardiovascular risk factors (34). Studies suggest that even modest amount of exercise will be sufficient to achieve significant health benefits (jog slowly as little as 5-10 minutes per day) (35). In our TRiCH study, we employed the PA component, but the focus on phase III of cardiac rehabilitation increased the interest in our results since is a CR phase that has not been greatly investigated.

Further analysis will be developed in the *future research* section of this discussion in relation to the wide heterogeneity with respect to patient population, tele-rehabilitation intervention used, and primary and secondary outcome measures in tele-rehabilitation with CAD population.

Safety and cost-effectiveness of HB programmes with tele-monitoring guidance

Patients undertaking HB cardiac rehabilitation are not necessarily at greater risk of adverse events, but because emergency services are not immediately available, future research should give consideration to patient safety, especially in specific circumstances such as traffic hazards, unsafe walking surfaces or areas with inadequate public safety (36) as well as patients in medium to high CV risk. In **Chapters 3** and **4** we established that HB cardiac rehabilitation is a feasible, safe and comparable strategy to the conventional in-hospital rehabilitation approach in patients with low to medium risk, as have been shown by previous studies (37) (18).

Although cost-effectiveness of tele-rehabilitation has been rarely researched, Frederix et al, in the Telerehab III trial (13) showed that a supplemental programme of cardiac tele-rehabilitation lasting 6-months remained cost-efficient even 2 years after ending the tele-intervention. However, other publications do not support this findings. The BRUM study compared the costs of a home-based CR programme that used a heart rate manual compared to a CB cardiac rehabilitation in 525 CAD patients finding higher costs in the HB programme (€ 234 vs € 186) (38). Complementary, Teledialog study evaluated the cost-utility of cardiac tele-rehabilitation in 151 CAD, heart failure and valve surgery patients, concluding that tele-rehabilitation was not a cost-effective strategy (39).

It is not possible to establish the cost-effectiveness of the TRiCH study since it was never a purpose of our project; however, further research would clarify the costs of such interventions.

Strengths and limitations of the present doctoral thesis

The TRiCH study was strengthened by the design of a randomized controlled trial using a three arm, parallel group, being one of the few studies including a control

group and two intervention groups (HB and CB) which allow us to draw an accurate conclusion concerning treatment efficacy (40). Including patients in phase III cardiac rehabilitation is also a big strength of the study since most of the publication centred its interventions in phase II cardiac rehabilitation program. The longer-term follow-up can also be considered a strength since the number of studies are disappointingly low; thus, the TRiCH study with a follow-up period of one year is one of the few studies that allowed a reasonable time frame to assess long-term effects of a tele-monitoring program during phase III of cardiac rehabilitation.

Another strength of our research is the objective evaluation of PA through the use of accelerometer. The ability to assess energy expenditure and estimate PA in free-living individuals is extremely important in the global context of non-communicable diseases like CAD (41). While some studies contend that it is possible for self-report PA questionnaires to assess some aspects of EE, most agree that questionnaires are less accurate than objective methods such as SenseWear armband used in our research (42). Recording objectively free-living activity behaviour may be helpful in quantifying levels of activity and could provide insights into important symptoms in the future (42).

The main limitation of our study is related to the recruitment of participants that took longer than anticipated, then only 90 patients were included in the study, thus our results must be analysed carefully, another limitation is as with most randomized control trials, missing outcome data mostly in muscle strength and PA due to technical problems or incomplete data; this information was missing completely at random.

Future research

This document highlights the diversity that tele-monitoring and tele-rehabilitation brings to cardiac rehabilitation of CAD patients, however it also brings the attention to factors that could point the way for future research.

Currently, the main shortcomings might be related to four topics being: a) Heterogeneous data availability and variable quality of the publications that limits the

possibility to draw conclusions on the effectiveness of HB cardiac rehabilitation with tele-monitoring guidance. b) A wide definition of HB cardiac rehabilitation and its components c) Significant variance in the follow-up of the HB program interventions d) Wide technology available to monitor patients at distance.

Today, the need to design, evaluate, and implement evidence-based alternative approaches to traditional cardiac rehabilitation that help provide all appropriate patients affordable access to clinically effective secondary prevention intervention is clear (16). The usual model of care for people with CVD includes regular visits to the doctor and emergency services, involving high healthcare costs. However, new methods to deliver healthcare using mobile digital communication devices, mobile health (mHealth), may increase the number of patients treated while facilitating patient self-management and saving costs (43). A recent report found that 77% of adults aged 65 years old owned a mobile phone and over half (59%) used the Internet (23). Since 2011, there has been a 30% increase in ownership of smartphones with nearly 62% owners reporting using their cell phone to seek health information within the past year (44). Clearly, telehealth can combine the accessibility of HB cardiac rehabilitation with the specialist monitoring, interaction and support of centre-based programmes (45).

The meta-analysis of Huang et al. (8) that included nine randomized controlled trials compared a total of 781 participants in a CB cardiac rehabilitation with telehealth versus 765 participants in CB group; they found that exercise in telehealth intervention varied in total duration (six weeks to six months), frequency (1-6 sessions/week) and session length (25-60 min/session). They suggested however that telehealth intervention delivered CR does not have significantly inferior outcomes compared to a CB supervised program in low to moderate risk patients. Rawstorn et al (45) described 11 studies including 1189 patients that compared telehealth cardiac rehabilitation against usual care or CB cardiac rehabilitation. In their meta-analysis, telehealth technologies were mainly fixed-line telephone, biosensors (accelerometry, heart rate) and websites. Among studies that described exercise prescription parameters, telehealth interventions comprised ≥ 2 to ≥ 5

sessions per week, lasting 30-60 min per session with exercise intensity increasing from moderate (40-60% peak capacity) to vigorous (70-85% peak capacity) through telehealth cardiac rehabilitation programs with walking as the predominant exercise mode. The main finding also support the idea that telehealth cardiac rehabilitation is at least as effective, and in some cases more effective than CB cardiac rehabilitation..

Finally, Frederix et al (31) include in their meta-analysis 37 publications, they described wide heterogeneous studies regarding study population and implementation of tele-intervention that made the inter study comparison difficult. Furthermore, it was not always clear whether tele-rehabilitation intervention were compared with conventional cardiac rehabilitation or whether the impact of the addition of tele-rehabilitation intervention on top of conventional cardiac rehabilitation was assessed. They also concluded that tele-rehabilitation could be a feasible and effective additional and/or alternative form of rehabilitation, compared to conventional in-hospital cardiac rehabilitation. A review of reviews found the majority of SMS interventions delivered to healthy and clinical populations were effective when addressing PA, smoking cessation or medication adherence which remains understudied in the CVD population (23); it is unknown whether more complex tele-monitoring interventions are effective at changing behaviour as more studies are needed. On the other hand, exercise and PA has a “dose-response” relationship with CVD risk (46). Moreover, a higher exercise capacity (VO_2P) is associated with an improvement in mortality risk. It is a legitimate concern that if patients engaging in cardiac rehabilitation do not achieve the correct dose of exercise, a physiological benefit is unlikely.

Thus, future randomized controlled trials on diverse populations could include more components in the tele-monitoring intervention, and could reproduce the training parameters used in previous publications like the TRiCH study.

Currently, a clear definition for “HB cardiac rehabilitation” is lacking. As such, the contents of these interventions varied widely and ranged from the use of manuals for a healthier lifestyle to personalized exercise prescriptions (47). HB cardiac

rehabilitation programmes were first reported in the early 1980s and were defined by Jolly et al (38) as a structured programme with clear objectives for the participants that also included monitoring, follow-up, visits, letters or telephone calls from staff, or at least self-monitoring diaries. Clark et al (48) considered the HB secondary prevention interventions as formalized interventions for the secondary prevention of CVD with predominant or exclusive HB components. These interventions can be provided in a range of ways including paper, face-to-face, electronic, or telephone-based methods. In general, HB cardiac rehabilitation programmes can include supervised and unsupervised elements and increasingly use technology or “telehealth” interventions to support or encourage exercise or behaviour change or to overcome barriers of time and distance (49).

Using telehealth to deliver cardiac rehabilitation has been proposed as an innovative way of improving patient’s uptake, choice and access (50). Telehealth is part of the “telemedicine” group that has a wide definition and is considered to be medicine practice at a distance and corresponds to a wide range of telemedicine applications (50). Telemedicine interactions have been of two types, either taking place in real-time such as for video conferences, or asynchronously such as store and forward transmission of data from HB measurements or require the patient to do something (e.g. transmitting home-measurement values using conventional telephones or smartphones). A systematic review indicate that telehealth cardiac rehabilitation improves cardiovascular risk factors, health-related quality of life, adverse events and cost-effectiveness; however, few studies have used telehealth to deliver or monitor structured, individualised, prescriptive exercise training in a manner similar to CB cardiac rehabilitation (44). Furthermore, most studies explore PA tele-monitoring rather than tele-rehabilitation, since it includes other important core components (nutritional counselling, risk factor management, psychosocial management) (51). A review from Frederix et al (31) found that only 10% of their assessed tele-rehabilitation trials included multi core component approach; therefore the possible value of this innovative way of remote rehabilitation could be underestimated.

Thus, future trials including all components of traditional CB cardiac rehabilitation will be necessary to confirm the effectiveness of HB tele-rehabilitation for enhancing PA and exercise adherence, changes to a healthier lifestyle and medication use.

To be successful, follow-up strategies need to embrace overall risk reduction, and at the same time, interventions must be accessible and relevant to clinical practice (52). Duff et al (53) identified a follow-up duration of HB cardiac rehabilitation interventions ranging from 3 weeks to 16 months, which meant that was impossible to pool results in a meta-analysis. Supervía et al (43) described that the maximum follow-up reported in their review was six months, with a high participant drop-out rate in most of the studies. This is a troubling finding considering that secondary prevention is a lifelong intervention, underscoring the need for studies with longer follow-up (43).

Given the secondary prevention goal of cardiac rehabilitation, a follow-up period of 1 year is negligible, and there is an urgent need for studies evaluating the effect of cardiac rehabilitation over even longer periods of time (47). 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 cardiac rehabilitation; however, when it comes to HB with tele-monitoring guidance Claes et al described a disappointingly low number of studies available evaluating the longer-term effects of cardiac rehabilitation (47).

Since assessing the long-term effectiveness of mHealth interventions will prove the value of mHealth in clinical practice we stress the importance of further research in the longer-term focusing on exercise adherence. We considered that a one-year follow-up may be insufficient to detect real lifestyle changes.

Tele-monitoring is defined as the use of information technology to monitor patients at a distance, including “the use of audio, video, and other telecommunications and electronic information processing technologies to monitor patient status at a distance” (54). HB cardiac rehabilitation should ideally permit functional monitoring

and in order for telemedicine to have a significant impact on healthcare systems, mHealth should offer a sustainable, low-resource and cost-effective approach to a wide range of people, improving patient outcomes, such as reducing hospitalization rates and increasing medication adherence (43). The uptake of mHealth for CVD has been slow, but despite lower mobile phone usage among older adults, recent reviews have shown that CVD population are able to use and engage with technology (23). Furthermore, mobile phones are now omnipresent, with world-wide usage rates nearing 100% and recent estimates suggest 7.7 billion mobile broadband subscription in 2020, while the number of smartphone subscriptions is expected to equal about 70% of the world's population (55).

The most researched form of mHealth has been the use of text or short-message service (SMS), found to facilitate significant positive effects on health outcomes and/or behaviours (23). Previous reviews have reported that the effective mHealth behaviour change interventions were those that were theory-based and offered personalized, tailored and bi-directional messaging (56). However Pfaeffli et al (23) found that the degree of personalization or tailoring did not appear to influence outcomes. Furthermore, establishing reliable and clinically meaningful digital health data is still problematic, while some apps and devices are developed using evidence-based guidelines and are continuously evaluated, most remain unevaluated (55); this can lead to consumer confusion, reluctant promotion by healthcare providers and unnecessary consumption of health care resources.

The main factors associated with low attendance to cardiac rehabilitation programs have been reviewed previously, and include older age, lower income and a lower understanding of the severity of their illness (57). Smoker patients, unmarried, unemployment, and a lower socioeconomically status and living distant from the programme venue are also commonly named (58); thus, the use of home-based cardiac rehabilitation with tele-monitoring guidance carries the potential to increase participation of these specific groups in cardiac tele-rehabilitation programmes.

Thus, future studies should target populations known to have a lower participation on cardiac rehabilitation programs who might potentially benefit the most through the

use of mobile applications as well as the validity and reliability of the devices used for their mHealth interventions.

General conclusion

From the present PhD thesis we can conclude in the short term:

- Home-based cardiac rehabilitation with tele-monitoring guidance can be an effective alternative to centre-based cardiac rehabilitation for further improving exercise capacity following phase II cardiac rehabilitation in coronary heart disease patients.
- Home-based cardiac rehabilitation is safe in clinically stable coronary artery disease patients.
- To increase the body of evidence, targeted populations, individualized training programs and multicentre studies are needed.

In the long-term we can conclude:

- Three-month home-based exercise cardiac rehabilitation with tele-monitoring is insufficient to improve the exercise capacity of coronary artery disease patients in maintenance phase.
- Given the significant heterogeneity and scarcity of longer-term follow-up studies for tele-monitoring intervention in phase III of cardiac rehabilitation, further studies reproducing previous protocols in different coronary artery disease population might be needed to increase the evidence of its effectiveness.

REFERENCES

1. Swain DP, Franklin BA. VO₂ reserve and the minimal intensity for improving cardiorespiratory fitness. *Medicine and science in sports and exercise*. 2002;34(1):152.
2. King N, Caudwell P, Hopkins M, et al. Metabolic and Behavioral Compensatory Responses to Exercise Interventions: Barriers to Weight Loss*. *Obesity*. 2007;15(6):1373-83.
3. Stewart R, Held C, Brown R, Vedin O, Hagstrom E, Lonn E, et al. Physical activity in patients with stable coronary heart disease: an international perspective. *European Heart Journal*. 2013;34(42):3286-93.
4. Ferguson T, Rowlands AV, Olds T, Maher C. The validity of consumer- level, activity monitors in healthy adults worn in free-living conditions: a cross-sectional study. *The international journal of behavioral nutrition and physical activity*. 2015;12(1):42.
5. Tang Y, Xu J, Qu W, Peng X, Xin P, Yang X, et al. Resveratrol reduces vascular cell senescence through attenuation of oxidative stress by SIRT1/NADPH oxidase-dependent mechanisms. *J Nutr Biochem*. 23. United States: 2012 Elsevier Inc; 2012. p. 1410-6.
6. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, 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): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol*. 23. England 2016. p. NP1-NP96.
7. Clark RA, Conway A, Poulsen V, Keech W, Tirimacco R, Tideman P. Alternative models of cardiac rehabilitation: A systematic review. *European Journal of Preventive Cardiology*. 2015;22(1):35-74.
8. Huang K, Liu W, He D, Huang B, Xiao D, Peng Y, et al. Telehealth interventions versus center-based cardiac rehabilitation of coronary artery disease: A systematic review and meta-analysis. *European Journal of Preventive Cardiology*. 2015;22(8):959-71.
9. Neubeck L, Redfern J, Fernandez R, Briffa T, Bauman A, SB F. Telehealth interventions for the secondary prevention of coronary heart disease: a systematic review. *European journal of cardiovascular prevention and rehabilitation*. 2009;16(3):281-9.
10. Hwang R, Bruning J, Morris N, Mandrusiak A, Russell T. A Systematic Review of the Effects of Telerehabilitation in Patients With Cardiopulmonary Diseases. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2015;35(6):380-9.
11. Lima de Melo Ghisi G, Pesah E, Turk-Adawi K, Supervia M, Lopez Jimenez F, Grace SL. Cardiac Rehabilitation Models around the Globe. *J Clin Med*. 2018;7(9).
12. Smith KM, Arthur HM, McKelvie RS, Kodis J. Differences in sustainability of exercise and health- related quality of life outcomes following home or hospital-

based cardiac rehabilitation. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2004;11(4):313-9.

13. 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. *European Journal of Preventive Cardiology*. 2015;22(2):150-8.

14. Frederix I, Hansen D, Coninx K, Vandervoort P, Vandijck D, Hens N, et al. Effect of comprehensive cardiac telerehabilitation on one- year cardiovascular rehospitalization rate, medical costs and quality of life: A cost- effectiveness analysis. *European journal of preventive cardiology*. 2016;23(7):674-82.

15. Salmoirago-Blotcher E, Wayne PM, Dunsiger S, Krol J, Breault C, Bock BC, et al. Tai Chi Is a Promising Exercise Option for Patients With Coronary Heart Disease Declining Cardiac Rehabilitation. *J Am Heart Assoc*. 2017;6(10).

16. Balady JG, Ades AP, Bittner AV, Franklin AB, Gordon FN, Thomas JR, et al. Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond: A Presidential Advisory From the American Heart Association. *Circulation*. 2011;124(25):2951-60.

17. Zhang L, Sobolev M, Pina IL, Prince DZ, Taub CC. Predictors of Cardiac Rehabilitation Initiation and Adherence in a Multiracial Urban Population. *J Cardiopulm Rehabil Prev*. 2017;37(1):30-8.

18. Kraal JJ, Peek N, Van Den Akker-Van Marle ME, Kemps HM. 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. *European Journal of Preventive Cardiology*. 2014;21(2_suppl):26-31.

19. van Den Berg M, Schoones JW, Vlieland T. Internet-based physical activity interventions: A systematic review of the literature. *J Med Internet Res* 2007.

20. Veen Ev, Bovendeert JFM, Backx FJG, Huisstede BMA. E-coaching: New future for cardiac rehabilitation? A systematic review. *Patient Education and Counseling*. 2017;100(12):2218-30.

21. Alharbi M, Bauman A, Neubeck L, Gallagher R. Validation of Fitbit-Flex as a measure of free-living physical activity in a community-based phase III cardiac rehabilitation population. *Eur J Prev Cardiol*. 23. England: The European Society of Cardiology 2016.; 2016. p. 1476-85.

22. Le Grande MR, Elliott PC, Worcester MU, Murphy BM, Goble AJ. An evaluation of self-report physical activity instruments used in studies involving cardiac patients. *J Cardiopulm Rehabil Prev*. 28. United States 2008. p. 358-69.

23. Pfaeffli Dale L, Dobson R, Whittaker R, Maddison R. The effectiveness of mobile-health behaviour change interventions for cardiovascular disease self-management: A systematic review. *European Journal of Preventive Cardiology*. 2016;23(8):801-17.

24. Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital Health Interventions for the Prevention of Cardiovascular Disease: A Systematic Review and Meta- analysis. *Mayo Clinic Proceedings*. 2015;90(4):469-80.

25. Purcell R, McInnes S, Halcomb E. Telemonitoring can assist in managing cardiovascular disease in primary care: a systematic review of systematic reviews. *BMC Fam Pract* 2014.

26. Baum K, Hildebrandt U, Edel K, Bertram R, Hahmann H, Bremer F, et al. Comparison of skeletal muscle strength between cardiac patients and age-matched healthy controls. *Int J Med Sci*. 2009;6(4):184-91.
27. Grigsby J, Rigby M, Hiemstra A, House M, Olsson S, Whitten P. Chapter 7: The Diffusion of Telemedicine. *Telemedicine Journal and e-Health*. 2002;8(1):79-94.
28. COCIR. Telemedicine toolkit for a better deployment and use of Telehealth 2010 [Available from: http://cocir.org/fileadmin/Publications_2011/telemedicine_toolkit_link2.pdf.
29. Frederix I, Solmi F, Piepoli MF, Dendale P. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. *European Journal of Preventive Cardiology*. 2017;24(16):1708-17.
30. Varnfield M, Karunanithi M, Lee C-K, Honeyman E, Arnold D, Ding H, et al. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomised controlled trial. *Heart*. 2014;100(22):1770.
31. Frederix I, Vanhees L, Dendale P, Goetschalckx K. A review of telerehabilitation for cardiac patients. *Journal of Telemedicine and Telecare*. 2015;21(1):45-53.
32. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation*. 2010;122(16):1637-48.
33. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation*. 2010;122(7):743-52.
34. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57(4):306-14.
35. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol*. 2014;64(5):472-81.
36. Worringham C, Rojek A, Stewart I. Development and Feasibility of a Smartphone, ECG and GPS Based System for Remotely Monitoring Exercise in Cardiac Rehabilitation. *PLoS One*. 2011;6(2).
37. Scalvini S, Zanelli E, Comini L, Dalla Tomba M, Troise G, Febo O, et al. Home-based versus in-hospital cardiac rehabilitation after cardiac surgery: a nonrandomized controlled study. *Phys Ther*. 2013;93(8):1073-83.
38. Jolly K, Taylor RS, Lip GYH, Stevens A. Home-based cardiac rehabilitation compared with centre-based rehabilitation and usual care: A systematic review and meta-analysis. *International Journal of Cardiology*. 2006;111(3):343-51.
39. Kidholm K, Rasmussen MK, Andreasen JJ, Hansen J, Nielsen G, Spindler H, et al. Cost-Utility Analysis of a Cardiac Telerehabilitation Program: The Teledialog Project. *Telemed J E Health*. 2016;22(7):553-63.
40. Karlsson P, Bergmark A. Compared with what? An analysis of control-group types in Cochrane and Campbell reviews of psychosocial treatment efficacy with substance use disorders. *Addiction*. 2015;110(3):420-8.
41. Chiauzzi E, Rodarte C, Dasmahapatra P. Patient-centered activity monitoring in the self-management of chronic health conditions. *BMC Med*. 2015;13(1).

42. Andrew PH, Najat E, Nuala MB. Assessment of physical activity and energy expenditure: an overview of objective measures. *Frontiers in Nutrition*. 2014;1.
43. Supervia M, Lopez-Jimenez F. mHealth and cardiovascular diseases self-management: There is still a long way ahead of us. *Eur J Prev Cardiol*. 2018;25(9):974-5.
44. Brager Jenna, Melissa P, Adam K. Theory Driven Mobile-Based Interventions: A Scoping Review. *Journal of Mobile Technology in Medicine*. 2017;6(3):48-65.
45. Rawstorn JC, Gant N, Direito A, Beckmann C, Maddison R. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. *Heart*. 2016;102(15):1183-92.
46. Powell R, McGregor G, Ennis S, Kimani PK, Underwood M. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. *BMJ Open*. 2018;8(3).
47. Claes J, Buys R, Budts W, Smart N, Cornelissen VA. 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. *European Journal of Preventive Cardiology*. 2017;24(3):244-56.
48. Clark AM, Haykowsky M, Kryworuchko J, Macclure T, Scott J, Desmeules M, et al. A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2010;17(3):261-70.
49. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*. 2016;67(1):1-12.
50. Saner H, Van Der Velde E. eHealth in cardiovascular medicine: A clinical update. *European Journal of Preventive Cardiology*. 2016;23(2_suppl):5-12.
51. 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).
52. Blasco HA, Carmona GM, Fernández-Lozano MI, Salvador AC, Pascual AM, Sagredo LP, et al. Evaluation of a Telemedicine Service for the Secondary Prevention of Coronary Artery Disease. *Journal of Cardiopulmonary Rehabilitation and Prevention*. 2012;32(1):25-31.
53. Duff OM, Walsh D, Furlong BA, Connor N, Moran K, Woods C. Behavior Change Techniques in Physical Activity eHealth Interventions for People With Cardiovascular Disease: Systematic Review. *J Med Internet Res* 2017.
54. Meystre S. The current state of telemonitoring: a comment on the literature. *Telemedicine journal and e-health : the official journal of the American Telemedicine Association*. 2005;11(1):63.
55. Coppetti T, Brauchlin A, Müggler S, Attinger-Toller A, Templin C, Schönrrath F, et al. Accuracy of smartphone apps for heart rate measurement. *European Journal of Preventive Cardiology*. 2017;24(12):1287-93.
56. Hall AK, Cole-Lewis H, Bernhardt JM. Mobile Text Messaging for Health: A Systematic Review of Reviews. *Annu Rev Public Health*. 2015;36:393-415.

57. Daly J, Sindone AP, Thompson DR, Hancock K, Chang E, Davidson P. Barriers to participation in and adherence to cardiac rehabilitation programs: a critical literature review. *Prog Cardiovasc Nurs*. 2002;17(1):8-17.
58. Kotseva K, Wood D, De Backer G, De Bacquer D. Use and effects of cardiac rehabilitation in patients with coronary heart disease: results from the EUROASPIRE III survey. *Eur J Prev Cardiol*. 2013;20(5):817-26.

The effect of acute supplementation with resveratrol
on flow-mediated dilation and oxygen consumption
kinetics in older coronary artery disease patients:
intervention dependent effects.

Miguel Diaz, **Andrea Avila**, Hans Degens, Ellen Coeckelberghs, Luc Vanhees, May
Azzawi, Veronique Cornelissen

*Shared first authorship

Submitted

INTRODUCTION

Patients with coronary arterial disease commonly present endothelial dysfunction, characterized by a compromised capacity of vessels to dilate due to elevated levels of reactive oxygen species. Resveratrol (RV) is a polyphenol with anti-oxidant, anti-inflammatory and cardio-protective properties (1). In humans, RV has been shown to improve flow mediated dilation (FMD) in obese type 2 diabetic men (2); but blunts the positive effects of regular exercise in healthy young men (3). Considering that the effects of RV may occur in conditions with elevated systemic inflammation and oxidative stress, we reasoned that acute supplementation with high RV doses would improve FMD in older CAD patients after rehab following coronary intervention.

METHODS

CAD patients (45-75 yr) from a cardiac rehabilitation program participated in a placebo-controlled single-blind crossover study (according to guidelines of the Declaration of Helsinki; ethical approval ML9734). Patients with a history of CAD had either a percutaneous coronary intervention (PCI), or post-coronary artery bypass graft (CABG). Patients attended the laboratory on two occasions: once after RV supplementation and once after supplementation with placebo. During each visit, patients underwent measurements of endothelial function in the brachial artery. All tests were performed in a fasted state, one hour after ingestion of the last capsule (RV or placebo,) and a seven-day wash-out period in-between.

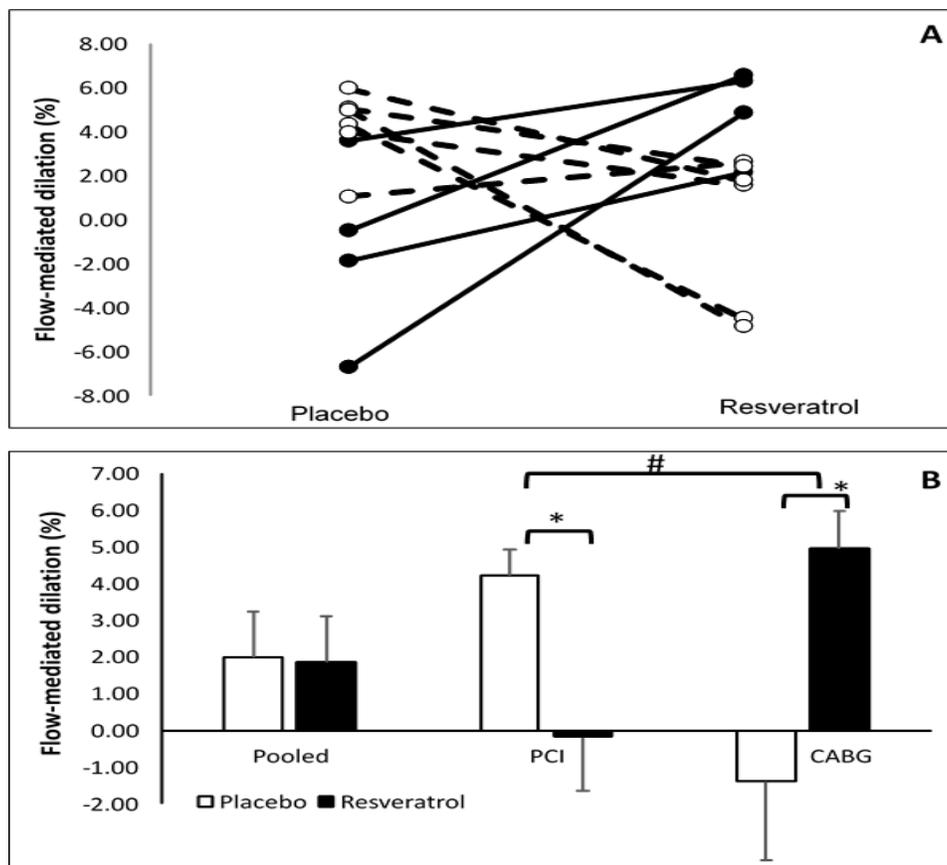
Both RV (98.57% pure, *polygonum cuspidatum* extract; microcrystalline cellulose, 21st Century Alternatives, GB) and placebo were given as 330 mg capsules, consumed every 8 hours (i.e. three times per day) for three days. The last capsule was ingested one hour before the experimental session on the fourth day. Brachial artery images were obtained with a 12-MHz linear-array vascular ultrasound scanning transducer (Vivid 7; GE Healthcare) and longitudinal images recorded (Flomedi, Brussels, Belgium) 30 seconds before occlusion and for 150 seconds following cuff deflation.

Statistical analyses were performed using SPSS (Chicago, USA). The Shapiro-Wilk test was used to check normality of the data. A repeated-measures ANOVA with as within factor RV (placebo vs. RV) and between factors condition (PCI vs. CABG) was used to assess effects of RV treatment, and PCI and CABG, respectively. Statistical significance was established at $P < 0.05$ (2-tailed).

RESULTS

There was a significant intervention * RV interaction ($p = .004$) reflected by an RV-induced reduction in FMD in patients who underwent PCI, and an RV-induced increase in FMD in patients who had a CABG (Figure 15).

Figure 15. Individual and average resveratrol-induced changes in FMD



A: Individual and B: average resveratrol-induced changes in flow-mediated dilation (FMD) in patients that had a percutaneous intervention (PCI: ---○) or post-coronary artery bypass graft (CABG: _____●).*: Significantly different from corresponding baseline; #: significantly different from other group. Data are mean \pm SEM. Interaction resveratrol x intervention $P = .004$.

DISCUSSION

The key finding of our study is that RV has differential effects on vascular function in older CAD patients, depending on the type of clinical intervention they have undergone. In the subset of patients who had undergone PCI, while their FMD values were within the normal expected range (2), acute RV supplementation, led to a significant reduction in FMD. On the contrary, for the CABG patients, supplementation led to a significant improvement in FMD.

Prior to RV supplementation, compromised endothelial function was evident in the patients with CABG, as reported previously (4). This is not surprising, given the fact that CABG patients usually present with more severe CAD, affecting multiple vessels and having co-morbidities (5). Treatment with RV reduced FMD in the subset of patients with PCI but significantly improved it in CABG. In a rabbit model of CABG, RV administration over 8 weeks protected against EC injury (6). In addition, in isolated normal murine femoral arteries, RV improved acetylcholine-induced dilation while inhibiting flow-mediated dilation, suggesting that RV might improve dilation via endothelial independent mechanisms, by acting directly on the smooth muscle cell layer (7). Whilst the mechanisms leading to improved dilation after CABG but not PCI intervention are unclear, our study suggests that RV might have differential effects on endothelial function depending on shear stress and/or inflammatory status (1)¹. Our findings have important implication for patient stratification towards therapeutic intervention.

Contributions: Funding: V.C., M.A., H.D. and L.V. All authors contributed substantially to the conception, design, data analysis and drafting of the manuscript.

Funding: This research was funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate program (2011-2015). VC is supported by Research Foundation Flanders (FWO) and by a Krediet aan Navorsers Grant (FWO).

Declarations of interest: None.

REFERENCES

1. Diaz M, Degens H, Vanhees L, Austin C, Azzawi M. The effects of resveratrol on aging vessels. *Experimental Gerontology*. 2016;85:41-7.
2. Wong RH, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, et al. Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. *J Hypertens*. 2013;31(9):1819-27.
3. Scribbans TD, Ma JK, Edgett BA, Vorobej KA, Mitchell AS, Zelt JG, et al. Resveratrol supplementation does not augment performance adaptations or fibre-type-specific responses to high-intensity interval training in humans. *Appl Physiol Nutr Metab*. 2014;39(11):1305-13.
4. Dedichen HH, Hisdal J, Skogvoll E, Aadahl P, Kirkeby-Garstad I. Reduced reactive hyperemia may explain impaired flow-mediated dilation after on-pump cardiac surgery. *Physiol Rep*. 2017;5(10).
5. Sangalli F, Guazzi M, Senni S, Sala W, Caruso R, Costa MC, et al. Assessing Endothelial Responsiveness After Cardiopulmonary Bypass: Insights on Different Perfusion Modalities. *J Cardiothorac Vasc Anesth*. 29. United States: 2015 Elsevier Inc; 2015. p. 912-6.
6. Zhu Y, Feng B, He S, Su Z, Zheng G. Resveratrol combined with total flavones of hawthorn alleviate the endothelial cells injury after coronary bypass graft surgery. *Phytomedicine*. 40. Germany: 2018 Elsevier GmbH; 2018. p. 20-6.
7. Diaz M, Degens H, Austin C, Azzawi M. 207 The Vascular Effects of Resveratrol on Aged Mouse Femoral Arteries. *Heart*. 2015;101(Suppl 4):A114.1-A.

APPOSITIONS

In individuals with a well-balanced diet, nutritional supplementation might not confer additional health benefits.

Excessive reliance upon telemedicine and digitalizing health could be detrimental of traditional health care personnel-patient relationships and against the risk and responsibilities of each part.

Physically active health care providers are more likely to provide physical activity advice to their patients.

ABOUT THE AUTHOR

Andrea Avila was born in Bogota, Colombia on december 30th 1980. She graduated from high school at Colegio El Carmen Teresiano in 1997; then continued her studies in Medicine at Universidad Colegio Mayor de Nuestra Señora del Rosario graduating in 2004. On 2006 she started her specialization in Sports Medicine at Universidad El Bosque in Bogota where she obtained an internship sponsored by the Gatorade Science and Sports Institute (GSSI) for postgraduate Latin American students having the opportunity to work with Prof. Dr. R. Mora-Rodriguez at Universidad Castilla-La Mancha (Toledo, Spain) in 2008; that same year she traveled to Leuven to continue her education in the EMMAPA program sponsored by a loan-scholarship from Colfuturo, a private grant institution in Colombia graduating “cum laude” in 2009. She then return to her country and worked as a sports medicine physician for the biggest fitness company in Colombia. With the financial support of the Erasmus Mundus Joint Doctorate Programme (EMJD) Fellowship in 2013 she traveled back to Leuven to start her Phd at the Research Group for Rehabilitation in Internal Disorders under the guidance of prof. Dr. L. Vanhees (promotor), prof. Dr. V. Cornelissen (co-promotor) and Prof. Dr. M. Azzawy (co-promotor) from MMU (UK). She worked in telemonitoring. She was an active member of Harpa during 2015-2016 and is a certified Xpert pole fitness instructor (UK) in basic and intermediate level of pole dancing as well as an air yoga certified instructor in basic an intermediate level by the Escuela Internacional de yoga, danza y pilates aéreo (Spain).

Articles in internationally reviewed academic journals

Avila A*, Claes J*, Buys R, Azzawi M, Vanhees L, Cornelissen V. Home-based exercise with telemonitoring guidance in patients with coronary artery disease; Does it improve long-term physical fitness? *Submitted*

Avila A, Claes J, Goetschalckx K, Buys R, Azzawi M, Vanhees L, Cornelissen V. A randomized study of home-based training intervention with telemonitoring guidance in coronary artery disease patients-(TRiCH) Study. *J Med Internet Res.* 2018 Jun; 20(6): e225.

Diaz M*, **Avila A***, Coeckelberghs E, Degens H, Vanhees L, Azzawi M, Cornelissen V. Acute Supplementation with Resveratrol does not Improve Flow-mediated Dilation or Oxygen Consumption Kinetics in Older Coronary Artery Disease Patient. *Revised version submitted.*

Buyts R, **Avila A**, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. *BMC pulmonary medicine.* 2015 Apr 22;15 (1):1.

Avila A, Goetschalckx K, Vanhees L, Cornelissen VA. A Randomized Controlled Study Comparing Home-Based Training with Telemonitoring Guidance Versus Center-Based Training in Patients with Coronary Heart Disease: Rationale and Design of the Tele-Rehabilitation in Coronary Heart Disease (TRiCH) Study. *Journal of Clinical Trials.* 2014 Sep 18; 2014.

Hamouti N, Del Coso J, **Avila A**, Mora-Rodriguez R. Effects of athletes' muscle mass on urinary markers of hydration status. *European journal of applied physiology.* 2010 May 1; 109(2):213-9.

**Authors contributed equally*

Abstracts presented at international conferences

Avila A, Claes J, Goetschalckx K, Vanhees L, Cornelissen V. A randomized controlled trial of telemonitoring in coronary heart disease: Short-term results of the tele-rehabilitation in coronary heart disease - (TRiCH) study. *ECS Congress.* August 26-30 2017.

Avila A, Goetschalckx K, Cornelissen V. Short term effects (3 Months) of a Home-based versus Center-Based cardiac rehabilitation program in coronary artery disease patients - TRiCH STUDY. *Europevent.* April 6-8 2017.

Avila A, Claes J, Buyts R, Gossler K, Cool H, Segers A, Cornelissen V. Validity of the Mio Fuse and Actiheart to measure steps and energy expenditure in healthy adults. *6th ISPAH Congress.* Bangkok. November 16-19. 2016.

Avila A, Claes J, Buys R, Gossler K, Cool H, Segers A, Cornelissen V. Validity of the MIO fuse and Actiheart to measure steps and energy expenditure in healthy adults. 21th Annual Congress of the European College of Sports Science. Vienna. July 6-9. 2016.

Claes J, **Avila A**, Buys R, Gossler K, Cool H, Segers A, Cornelissen V. Validity of the fitbit charge hr and garmin forerunner 225. 21th Annual Congress of the European College of Sports Science. Vienna. July 6-9. 2016.

Diaz M, **Avila A**, Coeckelberghs E, Vanhees L, Cornelissen V. Acute supplementation with resveratrol does not improve flow-mediated dilation in coronary arterial disease elderly patients. Malmö, 24th-27th June. 2015.

Avila A, Diaz M, Coeckelberghs E, Vanhees L, Cornelissen V. Supplementation with resveratrol does not affect muscle oxidative capacity in coronary artery disease patients in the short term. Europrevent. Lisbon, 14-16 May 2015.

Avila A, Flores M, Garzon F, Povea C. Changes in Urinary Specific Gravity during a Spinning Class on Recreational Athletes (Pilot Study). 60th Annual Meeting & 4th World Congress on Exercise is Medicine. Indianapolis. May 28-June 1, 2013.

Avila A, Daza F, Povea C. Use of Emails to improve medical controls for weight management on fitness facilities. 30th Obesity Annual Scientific Meeting. San Antonio. September 20-24. 2012.

Avila A. Daza F, Povea C. Physical Activity Program for Obese and Overweight Individuals on a Fitness Facility: Is it Working?. 29th Obesity Annual Scientific Meeting. Orlando. October 1-5. 2011.

Donado C, Duperly J, Lobelo F, Ramirez A, Montoya E, Cano N, **Avila A**, Sarmiento O, Pratt M. Prevalence of Risk Factors for Recreational Race-Associated Cardiovascular Events Among runners in Bogota City. 58th Annual Meeting & 2nd World Congress on Exercise is Medicine. Denver. May 31-June 4, 2011.

C Povea, Albarracin J, Mosquera J, Arias H, Mauri J, **Avila A**, Olarriaga A. Impact of Training on Autonomic Nervous System Profile in Professional Soccer Players

During a Competitive Season. 58th Annual Meeting & 2nd World Congress on Exercise is Medicine. Denver. May 31-June 4, 2011.

Van Remoortel H, Hornikx M, Saucedo C, **Avila A**, Burtin Chris, Langer D, Gosselink R, Decramer M, Janssens W, Troosters T. The Impact of Mild COPD on Daily Physical Activity in Patients with Overweight. American Thoracic Society International Conference. Denver. May 13-18. 2011

Hamouti N, Del Coso J, Estevez E, **Avila A**, Mora-Rodriguez R. Sensitivity of Urine Specific Gravity as a Hydration Index During And After Dehydrating Exercise. ACSM Annual Meeting. Seattle. May 27-30. 2009.

Pardo A, **Avila A**, Nino A, Povea C. Effect of One Session of Hydrotherapy in the Physical Qualities In soccer Players. ACSM Annual Meeting. Seattle. May 27-30. 2009.

Avila A, Melgarejo I, Povea C. Detection of cardiovascular abnormalities in female football players using the Italian Model of pre-participation screening. XXX FIMS World Congress of sports Medicine. Barcelona. November 18-23, 2008.

LIST OF ABBREVIATIONS

AEE	Active energy expenditure
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CB	Centre-based
CG	Control group
CHD	Coronary heart disease
CR	Cardiac rehabilitation
CVD	Cardiovascular disease
FMD	Flow mediated dilation
HB	Home-based
HDL - C	High-density lipoprotein cholesterol
HG	Hand grip
HOMA	Homeostasis assessment model
HR	Heart rate
HRR	Heart rate reserve
HRQoL	Health related quality of life
ICC	Intraclass correlation coefficient
LDL - C	Low-density lipoprotein cholesterol
MAD	Mean absolute difference
MAPE	Mean absolute percentage error
METs	Metabolic equivalent (of task)
MRT	Mean response time
NO	Nitric oxide
PA	Physical activity
PCI	Percutaneous coronary intervention
RER	Respiratory exchange ratio
RV	Resveratrol
SRT	Sitting-rising test
TRiCH	Telerehabilitation in coronary heart disease

VAT	Ventilatory anaerobic threshold
VO ₂ P	Peak oxygen uptake

SCIENTIFIC ACKNOWLEDGMENTS

This research was funded by the European Commission through MOVE-AGE, an Erasmus Mundus Joint Doctorate program (2011-2015).

The author of this document was responsible for the data collection, analysis, interpretation and writing of the chapters included in this PhD thesis. We have no conflicts of interest on this research. Furthermore, the funding was not involved in either study design, data analysis or results.

ACKNOWLEDGMENTS

Dear all,

If you are reading this is because...I DID IT!. However, it would have never been possible without several people.

First of all I would like to thank my promoter Prof. Luc Vanhees and co-promoters Prof. Veronique Cornelissen and Prof. May Azzawi. Dear Luc, your wise advice was always welcome and invaluable treasured during this process. Dear May, thank you for your patience, support and guidance during these years and sorry in advance for my broken English. Veronique, you were not only a great guide but an inspiration. I will always admire your braveness and commitment to every project you take. I am incredibly grateful for having you guiding my path in this personal and professional challenge.

This story started back in 2013 thanks to the Joint Doctorate Program “MOVE-AGE”, funded by the European Commission as part of the Erasmus Mundus program. This initiative allowed me and other researchers from all over the world to receive the best education under the best conditions. Special thanks to professors Jaap van Dieën (VU Amsterdam), Hans Degens (Manchester Metropolitan University) and Sabine Verschueren (KU Leuven) for their commitment to the program. It was definitely a learning experience not only professionally but personally. I learned to appreciate and embrace other cultures and countries different from mine but above all I understood as someone once said that *“The name of this one people is the world. The name of this one race is humanity”*.

To my colleagues, well...we were a nice group. Ellen, thank you for being a great hosts on my arrival. Nele thank you for your help during my data analysis but also during phone calls, patient recruitment and personal advice, your bread saved me from starvation at the ECS congress 2017 and that will never be forgotten girl!. Nils, flying is safe, the chance to be on a plane crash is 1 in 11 million. As for the feeling of control, follow the advice of the great Frozen movie “let it go”. Roselien, I have to see you dance one day. Thank you for your precise feedback on each and every

paper as well as every blood sampling for the TRiCH study. Dear Jomme, sir you suffered me and survived!. What a great guy you are. I will always miss a bright, wise and funny colleague as you and a friend with an open ear for every possible available topic on the planet.

I also thank the support and help from the personnel at UZ Gasthuisberg: Frederik, Herwig and Dirk, without your help I would still be in the recruiting phase. Miek, thanks for hosting us during the validation measurements. Kristel, you almighty women found always a solution for every practical problem that we find along the way. All patients that participated in the TRiCH study, thanks for your commitment and discipline during the training and measurement moments. Dear Jos Geleyns, TRiCH allow me to meet you, thank you for letting me practice my Spanish while in Belgium. Dear Celine, thanks for your kindness and warmth, I hope Emile was here with us today, but I know he is in a better place. Dear Harpa members, you cannot imagine how afraid I was at the beginning, but you made a great experience. Thanks Victor for trusting someone so different and short of Dutch words like me.

To my friends here and abroad. Andrea and Jorgito, your kindness and good heart is incomparable, thank you for sharing your space with me and your support during all this time. Karla, even though we were different, you were a great support and gave me great advices during your stay. Eva and Sergio, horrible friends, thank you for being around and travel to Colombia against all odds. Dra Alvarez, thanks for the lessons on pretty much everything, you were always the “who wants to be a millionaire” perfect contestant. Laura and Alex, I am missing beer evenings discussing the world. Gabriel, who would have thought after so many years we would ended up taking a parkour class together, the best of you is that I met Juliana, it was a pleasure to share time with you two. Diana las niñas y el patrón (e.g. Nohora los niños y yo), thanks for let my soul speak and be truthful in the best possible way, you are priceless. Pili, tonta ridícula, please do not change EVER. You are pure happiness and positivism, hard to find in this world. Cinthia and family, so long and yet we are still were it all started, I wish you the greatest future ever. Miss Bow, the best travel advisor and expert Thailand could have ever exported, thanks for your

listening ear and keep going, the end is near. Dr Povea, you have always been a professional inspiration, your advice will be forever needed and appreciated. Dr Sarmiento, your unselfishness and commitment to the sports medicine community in Colombia is admirable, thanks for your confidence in my work. Dr. Juan Fernando Ortega, you open the road for all of us and are still one of the best. Thanks for your support. Eliana, Andrea Torres, Lalis, Jessica, Lucesita, thanks for asking how I was doing and for listening to the same stories over and over again. My Move-age friends Aijse, Susana and Sreedra, I am happy to see you all happy. Dr. Daza and Ibeth (mi manita), it all started as a professional group and ended up being a great group of friends, thanks. Pacheco, Moquis no matter where the world put us, we will always be aware of each other. I am proud of you!. Alicia and Angela, Europe was a lot better where you were around. We made the most of our time together. Kike, you conquered Japan with your enthusiasm and happiness. I am a proud cousin of all your success.

This long road was also enlighten by the amazing pole dance community that embraced me since I started back in the day at (currently non-existent) BPDS in Bogota and grew here in Leuven and abroad. Girls from DC Pole Leuven, you are amazing, especially Diana, Tatiana, Katrien and Shelly. And of course now the girls and friends from elite body pole and fitness dance studio back in Bogota. Pole gave me perspective and taught me that I don't have to walk if I can fly because at the end, the floor will always be there to hold me.

Finally to my biggest supporters, examples, guides and nurturers: my beloved parents, Aunty Graciela and cousin Marlen. Thank you for travel with me, run with me, laugh with me and dream with me. This would have never been possible without your support and the end result is for you and you only.

That being said...

*¡Suerte es que les digo!
That's all folks!*