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

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Abstract

Aerobic exercise capacity (peak VO2) 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 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 telemonitoring 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 telemonitoring guidance (Home-CR) with a supervised center-based cardiac rehabilitation program (Center-CR) 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-CR, Center-CR or a control group on a 1:1:1 basis. The exercise programs (frequency, intensity and time of exercise) of patients randomized to Home-CR or Center-CR 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 peak oxygen uptake at 3 and 12 months of follow-up. Secondary outcomes include determinants of exercise capacity, i.e. physical activity, endothelial function and muscle function, as well as traditional cardiovascular risk factors and quality of life. It is hypothesized that home-based training with telemonitoring guidance will result in higher levels of peak VO2 at one year of follow-up. Enrollment started in February 2014; last enrollment is expected in November 2015.

Keywords: Physical activity; Exercise capacity; Rehabilitation; Endothelial function; Muscle function; Cardiovascular risk factors; Training

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 (CR) 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 [3,4]. Given the strong association between higher exercise capacity and favorable 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 EuroAspide 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 center-based rehabilitation sessions and cost. Even if patients gain knowledge about the importance of physical activity and improve their exercise capacity during the structured CR 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 in-hospital program adhered to the minimal physical activity 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 physical activity 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 physical activity 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

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Received July 17, 2014; Accepted July 31, 2014; Published August 02, 2014

Citation: Avila A, Goetschalckx K, Vanhees L, Cornelissen VA (2014) 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. J Clin Trials 4: 175. doi:10.4172/2167-0870.1000175

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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 training in combination with telemonitoring guidance. It has been demonstrated that self-regulatory techniques create empowerment and perceived control and might have longer lasting effects on physical activity improvements. That is, individuals who develop their own physical activity 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 home-based CR in low-to moderate-risk cardiac patients is safe, and has at least equal short-term clinical effects as center-based CR [12,13]. Therefore, home-based CR 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 center-based programs remain inconclusive [13].

To our knowledge, our study is the first to investigate clinical effects of home-based CR with telemonitoring guidance compared to center-based CR in a randomized controlled design in patients with coronary artery disease 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 home-based CR program with telemonitoring guidance in coronary artery disease patients (phase III) with a supervised center-based CR program. The primary outcome measure is exercise capacity, measured as peak oxygen uptake (peak VO₂) at 12 months. Peak VO₂ was chosen as the primary endpoint because it is the most important predictor of cardiovascular morbidity and mortality in patients with coronary artery disease [15,16]. We hypothesize that patients randomized to a home-based training program with telemonitoring guidance will demonstrate higher levels of physical activity at one year of follow-up, resulting in higher levels of physical fitness, compared to patients who have been enrolled to the center-based cardiac rehabilitation program or control group.

Secondary outcome measures include determinants of exercise capacity [17,18], i.e. physical activity, muscle function and endothelial function, quality of life and traditional cardiovascular risk factors.

The second objective of this study is to determine whether home-based CR versus center-based CR has a differential effect in improving physical fitness, and the secondary endpoints specified above, in the short-term (3 months) in coronary artery disease patients (phase III). It is hypothesized that the effect of home-based CR will have a larger effect compared to advice only (= control group), but that the effect will be similar to a center-based CR.

**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 CR, center-based CR 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 coronary artery disease 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, peak VO₂ 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.

**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 (VAC) 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 analyzing the data will be blinded to group allocation.

**Intervention**

| 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 cardiac rehabilitation in hospital 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 | |

Table 1: Inclusion and exclusion criteria.
Patients randomized to "center-based CR" 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 "Home-based CR" group will train the first three sessions under the supervision of the research group for acquaintance with the telemonitoring 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 home-based CR 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 cardiac rehabilitation 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 (peak VO₂ and submaximal measures of exercise), determinants of exercise capacity (physical activity, endothelial function, and muscle function), health-related quality of life 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, Baden-Württemberg, 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 (VO₂) and carbon dioxide production (VCO₂) 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. After reaching maximal volitional fatigue, participants recuperate by cycling for another six minutes at 25 Watt. Peak VO₂ will be defined as the highest 30-s average of VO₂ 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), VeVCO₂ slope, VO₂/Load as well as the VO₂-off time [21].

**Secondary outcomes**

**Physical activity:** Physical activity 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 [22]. 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 physical activity 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 (VO₂) kinetics quantifies the rate of increase in VO₂ during the early phase of exercise providing information on muscle energetics, metabolic control and the determinants of the efficiency of skeletal muscle contraction. Slowed VO₂ kinetics is associated with poor exercise performance [23]. This measurement will start with a 3 minutes seated rest on the bike to obtain resting VO₂ 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 [24]. Subsequently, exercise-onset VO₂ kinetics will be calculated according to previously published formula [24,25]. 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 [26]. 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 (6 s) 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 [27].

**Endothelial Function:** Brachial flow mediated dilation will be measured as previously described in our laboratory [28] and in agreement with international guidelines [29]. 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 arterial 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 analyzed 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 [30]. 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 [31,32]. 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 [32]. 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 (weight/height²) 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, health related quality of life will be assessed by means of the SF-36 health survey. This questionnaire will be used as a generic health status measure [33] 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 Analysis**

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). Telerehabilitation 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 [34]. Moreover, the use of activity monitoring makes patients aware of their activity, which is likely needed for successful treatment effects [35]. 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 behavior. 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 behavior 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 telerehabilitation program with a 3-month prolonged supervised in hospital program and regular practice (control group).

**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.

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