Cover page:

TITLE

Effects of comprehensive cardiac rehabilitation on functional capacity and cardiovascular risk factors in Brazilian patients assisted by public health care: protocol for a randomized controlled trial

Trial registration:

Clinical Trials, NCT02575976. Registered 14 October 2015.

Methods and statistical plan

Methods

Study design

The design is a single-blinded, single-site, pragmatic, superiority RCT with 3 parallel arms: comprehensive CR (education and exercise) *versus* exercise-based CR (no education, as delivered in Brazil) *versus* wait-list control (i.e., no CR). Patient assessments will be undertaken pre-randomization and again 6 months later (in accordance with the end of CR). Mortality will be ascertained at 6 months and 1 year post-recruitment. Research ethics approval has been secured from Federal University of Minas Gerais (898.235) and York University (e2015 - 172).

Setting

This RCT will be conducted in the Brazilian city of Belo Horizonte (capital of the Minas Gerais state). Brazil was chosen as the initial MIC setting for testing because of: (1) the great burden of CVD[2], (2) the availability of country-specific CR guidelines (the only CR guidelines developed in any MICs are in South America and China)[6], and (3) there has never been an RCT of CR (with any outcome) in South America to our knowledge[10].

The program where the trial will be conducted is called **"The Acute Myocardial Infarction (AMI) Management System"**, which was established in 2009. It was developed to reduce the high level of mortality from AMI in the region, around 16.2%[2]. The program provides a continuum of care for AMI patients from emergency care through to secondary prevention 6 months after the event. The program includes CR for interested patients, however this has never been evaluated.

Participants

Patients will be approached at the established AMI Sistema Único de Saúde unified healthcare system of the City of Belo Horizonte. Coronary artery disease or post-MI patients, or those who have undergone percutaneous coronary intervention or coronary artery bypass grafting and have been referred to CR will be eligible to participate in the study. The inclusion criteria are: patients older than 18 years old, living in the Belo Horizonte area. The exclusion criteria are: any comorbid physical or serious mental condition which would interfere with the ability to exercise according to CR clinical practice guidelines[14] (i.e., heart failure with ejection fraction less than 45%, complex ventricular dysrhythmia, advanced dementia, leg amputation, advanced cancer, disabling stroke, Parkinson's or substance dependence), and any visual or cognitive condition which would preclude the participant from completing the questionnaires.

Intervention Arms

The CR program was developed based on Canadian[4] and Brazilian[15] CR guidelines. It is delivered by a multidisciplinary team including physiotherapists, dietitians, nurses, and physical educators. The program is exercise-based, not comprehensive. It is offered at no charge to patients. Participants undergo an intake assessment, which includes a risk factor assessment, and are re-assessed at program end.

The main program is 6 months in duration, with 36 1-hour exercise sessions offered at the following frequencies:

1. participants come to CR for 12 sessions, 3 times a week (total of 4 weeks of intervention).

2. participants come to CR for 8 sessions, 2 times a week (total of 4 weeks of intervention).

3. participants come to CR for 16 sessions, 1 time a week (total of 16 weeks of intervention).

Each participant will receive an individualized exercise prescription based on a grade exercise stress test. Participants will be exercising between 50 and 80% of heart rate reserve. At all stages of the program, patients will be requested to exercise in their community other days of the week, to accumulate 30 or more minutes of physical activity at a moderate to vigorous-intensity five or more days per week, as recommended in the guidelines[4,14,15].

In the comprehensive CR arm, 24 education sessions will be offered, each of 30 minutes duration. More specifically, the education component consists of:

- weekly group education sessions, which are strategically mapped based on patients' information needs and sequenced to support the program learning outcomes[16]. Education sessions are delivered by a health educator team. See table 1 for the content of the educational curriculum.

- a comprehensive education workbook to accompany the sessions, containing 20 chapters. The empirically-validated English version[16,17] has been translated and culturally-adapted to Brazilian-Portuguese. Clinicians and patients have reviewed the material, and a plain language and clear design review was completed in preparation for this trial.

The standard of care for Brazilian adults with CVD does not include access to CR for all patients, given the gross lack of capacity[6]. All participants will have follow-up appointments with their physician as deemed medically-appropriate.

Consistent with CONSORT guidelines, usual care will be described in detail for each participant (e.g., number of health visits - both inpatient and outpatient, other treatments). Participants randomized to the wait-list control arm will receive CR after 6-months mortality is ascertained.

Procedure

See Figure 1 for the trial flow diagram. Consecutive patients will be approached during the first physician consult after hospital discharge by a doctoral student, if the patient is interested in learning about the study. The number of patients approached and date will be recorded, as well as the reasons for inclusion/exclusion. With informed written consent from the patient and CR clearance from the physician, potentially-eligible participants will be scheduled to come on-site to complete pre-test assessments. Participants will be asked to complete a sociodemographic questionnaire, to establish the generalizability of the sample, among other surveys. Clinical information will be extracted from participants' charts.

Eligible participants will be randomized to one of the 3 groups. The randomization sequence was generated using the randomization.com website in random blocks of 4, with a 1:1:1 allocation ratio. To ensure allocation concealment, the local principal investigator (RB) has the allocation sequence in a password-protected file, and will only provide randomization information to the student once it is confirmed the participant is eligible. Due to the nature of the intervention, participants and the doctoral student cannot be blind to treatment allocation.

The primary outcome of functional capacity and all other outcomes will be assessed again at 6 months post-randomization. Mortality will be

ascertained from hospital charts and family phone call at 6 months and 1-year. With regard to the 6 month assessment, participants will be invited to come to the study center to: (1) undertake the shuttle walk test as the indicator of functional capacity, (2) undertake assessments of secondary outcomes including a blood draw for lipids, and (3) complete surveys related to tertiary outcomes.

A master's student blinded to random allocation will undertake post-test assessments, outcome ascertainment and data entry. To minimize loss to follow-up, we will telephone reminders for patients to come on-site for these assessments.

Measures

Participants will be asked to complete a sociodemographic questionnaire. Clinical characteristics will be extracted from the medical charts, including sex, age, risk factors, cardiac history, cardiac test results, comorbidities and medications. CR session attendance will be extracted from program charts at post-test for participants randomized to the CR arms.

Primary Outcome: Functional Capacity

The primary outcome of this trial was carefully chosen. Functional capacity is not only important to an individual in terms of independent living and quality of life, it is also strongly related to health outcomes, including a graded inverse relationship with mortality[18].

At pre-test and 6-months later, the Incremental Shuttle walk test (ISWT)[19] will be performed. The ISWT consists of an incremental, walking test where participants are required to walk up and down a 10-meter course. The speed of walking, which is increased by a small increment every minute (0.17

ms-l), is externally-paced and controlled by audio signals played from a tape recorder[19]. There are 12 levels in total, beginning with 0.5 ms^{-1}, and each level lasts for one minute. At the end of each minute, exercise heart rate (HR) and rating of perceived exertion (RPE) scores will be recorded. The test is terminated if participants feel too breathless or fatigued to maintain the required speed to complete a 10-meter shuttle interval in the time allowed. After the test, the number of completed shuttles will be recorded and the total distance ambulated will be computed. Peak RPE, peak HR, time to exhaustion and the reason(s) for test termination will be also recorded.

Secondary outcomes: Risk Factors

Blood pressure will be assessed using the validated 7670-06 mobile stand (Welch Allyn, NY USA). Mean systolic and diastolic blood pressure values will be recorded, and hypertension will be considered where values exceed 140/90 mmHg[14]. A weight scale and measuring tape are available at the center and will be used to assess anthropometrics. Those with body mass index above 30 kg/m^2 will be considered obese[14]. Waist circumference will be assessed at the superior border of the iliac crest, in accordance with standardized guideline[14]. Values greater than 102 cm in men and 88 cm in women will be considered indicative of central obesity[20]. Glycaemia and lipid values will be extracted from center charts. Diabetes will be considered present where fasting blood glucose exceeds 126 mg/dl and dyslipidemia will be considered present where total cholesterol values exceed 240 mg/dl[14].

Tertiary outcomes:

Heart-health Behaviors

Smoking will be assessed via self-report (current, never, former). Other behaviors will be assessed using psychometrically-validated scales, as outlined below.

Exercise: Participants will be asked to wear a pedometer for 7 days at pre and post-test and to record their daily steps on a log. Exercise will also be assessed using the Brazilian-Portuguese version of The Godin-Shepherd Leisure-Time Physical Activity Questionnaire[21], which is a self-administered questionnaire that assesses the frequency and intensity of physical activity performed in a week. The respondents report the number of times they engaged for at least 15 minutes in vigorous, moderate and light intensity physical activity, considering a usual period of seven days. The frequency indicated by the individual is multiplied by a specific coefficient, which corresponds to the energy expenditure in metabolic equivalents of task (MET). Higher scores indicate higher levels of physical activity during leisure[21].

Medication adherence: Cardiac medication adherence will be assessed using the Brazilian-Portuguese version of the Morisky Medication Adherence Scale (MMAS-8)[22]. The scale contains seven questions with closed dichotomous (yes/no) response options and the last question is scored on a 5-point Likert from "never" to "always". Scores are totaled, with higher scores indicating greater adherence, and scores above the cut-off of 6 considered "adherence".

Diet: Diet will be assessed using the 14-item Food Frequency Questionnaire (FFQ) Cardiovascular Prevention[23], which was designed to assess the consumption of foods associated with an increase or decrease in

coronary risk. A score is attributed to each food group, weighed according to their influence on coronary risk ranging from -36 to +47[23].

Depressive symptoms:

Depressive symptoms will be measured using the Patient Health Questionnaire-9 (PHQ-9), which is a brief screening instrument. Frequencies of symptoms of major depression are solicited from patients, yielding scores ranging from 0 to 27, with higher scores indicating more severe symptoms. Severity categorizations are specified, with scores above 10 generally accepted as "elevated". The PHQ-9 has been shown to have reasonable sensitivity and specificity for patients with CHD[24]. This instrument has been translated and validated to Portuguese[25].

Knowledge:

Patients' knowledge about their condition will be assessed using the Coronary Artery Disease Education Questionnaire II (CADE-Q II)[26]. The CADE-Q II is a 31-item test that assesses cardiac patients' level of knowledge about their medical condition, risk factors, exercise, nutrition, and psychosocial risk. Each item has 4 response options, and responses are scored from 0 to 3 (i.e., 3- fully correct answer; 1- partially correct answer; 0- wrong answer and 'I do not know' response). The maximum total CADE-Q II score is 93. For the purposes of this trial, the CADE-Q II is being psychometrically-validated in Brazilian-Portuguese prior to administration.

Mortality

According to Heran et al.'s 2011 Cochrane review[27], a trend towards a reduction in total mortality is observed in CR trials with 6-12 months follow-up.

For this reason, we will ascertain mortality at 6 months and 1 year. Given the lower rates of screening and treatment of CV risk factors in the middle-income setting, we expect mortality rates and treatment effects to be higher than in high-income countries where the RCTs summarized in the Cochrane review stemmed.

This data will be obtained from the center's health system records, and will be supplemented by family report via phone to capture deaths which may have occurred outside the hospital. Reason for death will be recorded where available.

Sample size calculation

Based on previous studies, we considered a clinically-important difference of 70 meters[28] and assumed a standard deviation of 139 meters[29]. Using these values, we would require 62 participants per group, to ensure 80% power at the 5% significance level to detect a statistically significant difference in our primary outcome of functional capacity (i.e., distance walked in the Shuttle Test)[30]. Conservatively assuming a 60% recruitment rate and a 70% retention rate (taking into consideration attrition due to death and loss to follow-up), we would need to approach 443 patients to achieve a sample of 267 at pretest and 186 at post-test (i.e., 62 per group).

Statistical Analyses

First, session attendance of participants in the 2 CR arms will be explored as a manipulation check. Second, differences in participants' sociodemographic and clinical characteristics will be compared between groups to identify any chance difference that may have occurred despite random assignment, using chi-square and analysis of variance as appropriate. Third,

retention rate will be computed, and differences in the sociodemographic and clinical characteristics of participants retained versus lost to follow-up will be compared using chi-square and t-tests as appropriate.

All statistical analyses will be performed on a per protocol basis to mitigate bias. For the primary outcome of functional capacity, an analysis of covariance (ANCOVA) will be performed, with group (i.e., comprehensive CR *versus* exercise-based CR *versus* wait-list control) and pre-test distance as the independent variables and the distance on the shuttle walk test at post-test as the dependent variable, adjusting for any clinical and sociodemographic biases based on retention. For risk factors, ANCOVAs will also be computed with post-test scores as the dependent variable, experimental group as the independent variable, and pre-test scores as covariates. Post-hoc tests will be performed where significant group differences are observed. A Bonferroni correction will be applied as there are multiple secondary outcomes.

A similar approach will be used to assess group differences in health behaviors, depressive symptoms and knowledge (except for smoking where a logistic regression model will be run). Finally, a chi-square test will be performed to evaluate mortality by group.