Author’s response to reviews

Title: Randomized clinical trial to evaluate the effect of a supervised exercise training program on readmissions in patients with myocardial ischemia: a study protocol

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Author’s response to reviews: see over
Manresa, February 20 2013

Revision decided for MS:53345267282979877, "Randomized clinical trial to evaluate the effect of a supervised exercise training program on readmissions in patients with myocardial ischemia: a study protocol".

Dear Dr. Shipley,

Thank you for your review of our manuscript "Randomized clinical trial to evaluate the effect of a supervised exercise training program on readmissions in patients with myocardial ischemia: a study protocol". We are very pleased to hear that the reviewer considers the manuscript to be relevant to BMC Cardiovascular Disorders. His comments have been very helpful and have enabled us to make important improvements.

The changes we have made are listed below in our response to the reviewer’s comments.

We hope very much that you will now consider the paper suitable for publication.

Sincerely,

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The manuscript by Santauraria et al. describes the methods for a randomized, controlled trial. This study will enroll patients with a hospitalization associated with a primary diagnosis of a myocardial infarction (MI). The intervention is an exercise program. The primary outcome is admission for a recurrent MI. The authors sufficient identify how this study addresses a gap in our current knowledge on this topic. This continues to be an important area for clinical research.

- Thank you for your continued interest in the topic of the article. We very much appreciate the positive comments of reviewer, and have introduced the modifications suggested (see response to specific comments).

**Major revisions/considerations**

1. The power calculations appear to be for a chi-square analysis. If this is true, this study may not be adequately powered to show a 13% difference in event rates between groups based on a log-rank test. How will deaths and loss to follow-up be handled in this analysis? How many covariates might be included in the analysis based on the event rates?

- We thank the reviewer for the remark.

- Sample size will be calculated under the premise of a 13-point decline in the percentage of readmissions for cardiac causes. The main outcome variable is the percentage of readmissions for cardiac causes. We will also perform a survival analysis to test if the event rates in the two groups are different. To clarify this point we have changed the order in which the information appears in the paragraph related to primary outcome measures (page 15).

> **Primary outcome measures**

The primary outcome measures will be the percentage of patients readmitted, total number of readmissions and length of hospitalization for cardiac disease during the first year after hospital discharge and time to first hospital admission for cardiac disease. The primary outcome will be assessed by an expert committee blind to the patient’s treatment group.”

How will deaths and loss to follow-up be handled in this analysis?

- To clarify how deaths and loss to follow up will be handled in the survival analysis we have added the following text (page 17):
In readmissions analysis: “The deaths occurring without hospitalization will be introduced in the survival analysis as censored data. Event or censored times for all patients will be measured from the time of randomization (visit 0). All information available on the primary and secondary end points will be collected until the time of final contact with the patient, including patients lost to follow-up, at which point follow-up will be censored.”

How many covariates might be included in the analysis based on the event rates?

- Assuming that the percentage of readmissions in the control group will be 25% and the proportion in the intervention group will be 12%, with 139 patients included per study arm, 35 patients are expected to be readmitted in the control group and 17 in the intervention group. With 52 events, it would be possible to introduce 4-5 covariates in the multivariate analysis.

2. The primary outcome stated under “Assessment of outcomes” seems to conflict with the study purpose. Listed here is “hospital admission for cardiovascular disease”. It seems like should be specific to MI. Is the primary outcome time to first MI hospitalization?

- Thank you for this remark and we apologize for the lack of clarity.

- We have now added the term “cardiac” before “readmissions” to stress that our aim is to evaluate the efficacy of a supervised exercise training program for reducing cardiac readmissions in patients with MI in the first year after the hospital discharge.

- The primary outcome measures will be the percentage of patients readmitted, total number of readmissions and length of hospitalization for cardiac disease during the first year after hospital discharge and time to first hospital admission for cardiac disease. The primary outcome will be assessed by an expert committee blind to the patient’s treatment group.

3. Absent in the study design is how the investigators will address issues of cross-over. Will this be an intent-to-treat analysis? Cross-over will affect the study’s internal validity. In a randomized trial of exercise training in patients with chronic heart failure (N = 2331), ~30% of the patients in the exercise group achieved the protocol target of 90 min of exercise per week and 22-28% of the non-exercise control group reported exercise during the first 3 mo (O’Connor et al., Efficacy and safety of exercise training in patients with chronic heart failure. HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1439-1450).

- Thank you for this remark and we apologize for the lack of clarity.

- To control for the strong possibility that patients assigned to the control group take unsupervised physical exercise, all patients will be asked to complete a physical activity questionnaire (Capersen and Powell classification) at 1, 3, 6 and 12 months. This test categorizes physical activity in four levels: sedentary, irregular activity, non-intensive regular activity, intensive regular activity. If no differences are observed between the two study groups, for the principal study variable and the secondary variables, one of the confounding variables that may be introduced in the multivariate model will be the
performance of unsupervised physical exercise recorded in this self-reported questionnaire. In the last paragraph of the statistical analysis section we specify that the outcomes will be analysed on an intention-to-treat basis.

- To clarify this point we have expanded the information on the recording of the unsupervised exercise during the follow-up period (page 13):

“To address a possible cross-over effect, all patients will be asked to complete a physical activity questionnaire (Capernsen and Powell classification) at baseline and in each follow-up visit. This test categorizes physical activity in four levels: sedentary, irregular activity, non-intensive regular activity, and intensive regular activity.

Minor revisions/considerations

1. Although a purpose statement is provided, the paper would be improved by providing a clearly defined hypothesis near the end of the introduction.

   - Thank you for this remark. We agree, and we now state our hypothesis in the introduction (page 8): “Our primary hypothesis is that a supervised exercise training program will significantly reduce the incidence of cardiac readmissions in patients with MI in the first year after hospital discharge. The secondary hypothesis is that patients in the intervention group will present significantly better functional capacity, better quality of life, and lower mortality rate”.

2. A randomized controlled trial is appropriate to address the study’s purpose (e.g., does exercise training reduce the recurrence of MI in patients who are post-MI). It is interesting that the randomization occurs before visit 1. Is it possible that some patients will drop out before visit 1 due to dissatisfaction with their group assignment?

   - Thank you for this remark. We have clarified the point in the text. We have added (page 12): “The cardiac nurse or the physiotherapist will give verbal and written information related to the study to eligible patients and will resolve all the patients’ doubts. These professionals will stress to the patient that the randomization process will decide the group inclusion”.

   - Therefore, in accordance with the CONSORT guidelines, we will record the number of patients in the intervention group who have not received the intervention assigned (i.e., have not attended any sessions) and the reason for the withdrawals.

3. Follow-up visits are shown out to 12 mo post-discharge. This will be just 10.5 mo after completion of the 10 wk exercise program. The time interval over which the primary outcome will be assessed is not clear. Is the maximum duration of follow-up 12 mo after discharge?

   - Thank you for this comment. We apologize for the lack of clarity.

   - Our aim is to evaluate the efficacy of a supervised exercise training program for reducing cardiac readmissions in patients with MI in the first year after the hospital
discharge. So, our follow-up will finish 12 months after the hospital discharge for both groups.

4. The authors suggest that cardiac rehabilitation is an international standard of practice for secondary prevention in patients with heart disease. With this in mind, it is interesting that a study that withholds cardiac rehabilitation was approved by their institutional review board. There may be regional issues that make this study acceptable. It would benefit the reader if the authors briefly discussed this.

- We thank the reviewer for this comment. We apologize for the lack of clarity.

- Cardiac rehabilitation is an international standard of practice for secondary prevention in patients with heart disease. As we state on page 10, both groups “will receive verbal and written information on cardiovascular risk factors from the cardiac nurse or the physiotherapist. This educational information will be related to cardiac disease, cardiovascular risk factors (hypertension, diabetes, cholesterol, triglycerides, tobacco and other drugs, alcohol, stress, overweight, sedentary lifestyle), lifestyle (progressive rehabilitation activities, return to work, driving), diet, physical exercise (phases of readaptation, phases of normal activity, work activity, sexual activity), specific medication in case of cardiac angina (nitroglycerin), pharmacological regimen, complementary assessment (electrocardiogram, echocardiogram, chest X-ray, SPECT, cardiac catheterization, arteriography, electrophysiological study) and treatment of coronary artery disease (pharmacological, coronary angioplasty, surgical treatment). Hospitalized patients will be instructed to do exercises to regain mobility in order to maintain and improve muscular tone and peripheral circulation, and will be taught breathing exercises by the physiotherapist to improve their breathing patterns. Before discharge, the physiotherapist will instruct patients on how to return to physical activity”. Unsupervised physical activity is recommended to both groups in the study in accordance with international guidelines. Additionally, the intervention group will be provided with a supervised outpatient exercise training program to assess our aim.

5. What criteria will be used for MI diagnosis?

- Thank you for this remark. We have added the criteria for MI diagnosis.

- We have added (page 8): “diagnosis of MI (myocardial ischemia, pre-infarct angina, cardiac angina, other specific forms of chronic ischemic heart disease or unspecified ischemic heart disease) in the current admission”.

6. Myocardial “ischemia” appears to be used interchangeably with “infarction”. I believe the authors mean to use “myocardial infarction”.

- We thank the reviewer for this comment.

- We have changed the term “infarction” to “ischemia”.


7. Specific exclusions are limited or vague. Are there specific exclusions, such as ability to ambulate?

- We thank the reviewer for this comment.

- We have specified the exclusion criteria in more detail. We have added (page 9):
  “Patients will be excluded if they have symptoms of right heart failure producing pulmonary hypertension or dyspnea caused by severe pulmonary pathology, additional comorbidities affecting the prognosis of cardiac disease, major comorbidities or limitations that could interfere with the exercise training program, cognitive impairment or if they do not provide informed consent.”

8. Please provide more information relative to the exercise test. Is this a maximal exercise test? What instructions (e.g., medications) are provided to patients in preparation for this test?

- Thank you for this remark. We agree with the reviewer.

- We have added (page 13): “The Bruce protocol stress test will be used. Before starting, the staff will describe the test to the patient and give some recommendations such as taking a light meal three hours before the test, avoiding stimulating drinks, taking prescribed medication and wearing comfortable shoes and clothes. In this protocol, exercise is performed on a treadmill (QUINTON Q-STRESS TM 55). The leads of the ECG are placed on the chest wall. The treadmill is started at 2.74 km/hr (1.7 mph) and at a gradient (or incline) of 10%. At three minute intervals the incline of the treadmill increases by 2%, and the speed increases progressively. The exercise stress test will be limited by clinical signs such as arrhythmias and/or ECG changes and clinical symptoms such as general exhaustion, claudication of the legs, chest pain or dyspnea”.

9. How long after the exercise test do patients start the exercise program? Do patients continue in the exercise program until they complete 30 visits or does their participation end after 10 wks?

- Thank you for this remark. We have now clarified this point (page 11).

- “The program will be performed in the hospital and it will start within the three days after the exercise stress test. It will comprise three hours a week (spread over three alternate days) of supervised exercise training for 10 weeks. The intervention will end after 10 weeks, regardless of whether the patients have completed 30 sessions”.

10. Are there methods, such as heart rate monitors, to ensure that patients are exercising at their prescribed intensity?

- Thank you for the comment.
- We have added (page 11): “The physiotherapist will check that patients are exercising at their prescribed intensity with a pulse oximeter (Quirumed® Health & Care)”. 

11. Isometric exercise (muscle contractions with no change in muscle fiber length) is listed as part of the exercise program. This is not typical. Is the intention resistance training through isotonic exercise (muscle contractions with constant load and change in muscle fiber length)?

- Thank you for this comment. We agree, and we have changed the term “isometric” to “isotonic”.

12. Confounding variables: This appears to be a list of descriptive variables of interest rather than confounders.

- Thank you for this comment.

- Indeed, not only the confounding variables are listed, but all the independent variables that are expected to be recorded in this study. Therefore, following the reviewer’s recommendation, we have changed the section heading to “Demographic and clinical measures” (page 15).

13. Table 1- Is visit 0 discharge?

- Thank you for this remark. We apologize for the fact that this point was not clear. Yes, visit 0 is hospital discharge. We have added changes in the text for clarification (Procedure, page 12): “On discharge (visit 0) the cardiac nurse or the physiotherapist will contact the Clinical Research Unit regarding the randomization process. Once the cardiac nurse or the physiotherapist knows the randomization group, they schedule the patient for the first cardiac nurse visit and for the exercise stress test”.

14. Figure 1- What is the “baseline assessment”? I thought baseline data is collected at visit 1.

- Thank you for this remark.

- We have changed table 1 to make the timing of the recording of the study variables consistent with the flow of visits shown in the flow-chart. The baseline assessment (visit –1, inpatient setting) is prior to the randomization visit (visit 0, at discharge).

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
'I declare that I have no competing interests.