PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction: A 10-year follow-up study focusing on mortality and non-fatal events
AUTHORS	Hald, Kathrine; Nielsen, Kirsten; Nielsen, Claus; Meillier, Lucette; Breinholt Larsen, Finn; Christensen, Bo; Larsen, Mogens

VERSION 1 – REVIEW

REVIEWER	Chun Shing Kwok Keele University, Stoke-on-Trent, United Kingdom
REVIEW RETURNED	22-Sep-2017

GENERAL COMMENTS	Thank you for the opportunity to review this article on expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction. This study is a non-randomised cohort study with 10 years follow up. The results show no benefit of the intervention so the clinical impact of the study is limited. Below are my comments. Abstract I think the first sentence needs to be improved. Perhaps: “Cardiac rehabilitation (CR) has been shown to reduce cardiovascular risk.” In the results the estimates have to be provided not just the 95% confidence intervals. Introduction The introduction is generally good but could use some improvements. The first two paragraphs could be combined into one paragraph. The third paragraph needs to be slightly expanded. While referencing reviews is good, there needs to be clearer indication of what exactly cardiac rehabilitation interventions have been explored in the literature and the outcomes they have evaluated. Limitations of the studies in literature should be identified and this should naturally elude to the intervention and outcomes explored in the current study. The fourth paragraph does not clearly define why socially vulnerable means. It should be defined and described. The authors have broken it down in some aspects and its significance but does have one of these factors means they are socially vulnerable (low education, living alone, unclear if anything else)?

	They state that is has relevance in participation in cardiac rehabilitation but they have not stated whether there are previous studies that have done this. I presume the change on the cardiac ward with cardiac rehabilitation based on social vulnerability was because they want to target the groups at highest risk. Is this correct? The definition provided is not satisfactory needs further clarification as to number of factors and severity of individual factors. Methods In the study design, how is the selection between expanded CR and standard CR decided? This is not randomised. Is it just based on the year and whether they were socially vulnerable? Ideally this type of study should be a RCT where the study can be powered and a target sample size calculated. What was the treatment at baseline for the patients? Were patients managed with intervention (i.e. PCI), medications or thrombolysis? These need to be adjusted for and explored if there are baseline differences. A comparison should be made comparing the socially vulnerable and not vulnerable in terms of outcomes prior to the intervention treatment. If the rates of adverse outcomes are similar it will be hard to show any benefit of an intervention. The intervention targets the socially vulnerable group so for this cohort there should be at least demonstration that this group is higher risk. Results The complete follow up over 10 years shows nice work by the researchers. The expanded CR group appears to have higher rates of adverse outcomes compared to standard CR group but they are not statistically significant because of small sample size. Cost analysis of an expanded CR should be included as well. Discussion The results are negative for the intervention which limits the clinical impact of the study. Is the study by Pluss the only study in the literature? The authors state that a number of studies have examined. If there is more than one study, they should be discussed. The authors suggest in the introduction that participation in CR is less in socially vulnerable groups. Perhaps the future work should be on trying to improve engagement in CR as it is not clear that an improved or expanded CR is necessarily needed. Is there a difference in characteristics and outcomes of patients that engage with CR and those who do not? The socially vulnerable may not the problem rather those who do not engage with CR.

	Did the authors look at the same outcomes which showed improvement at one year (medication compliance, lipid profile, blood pressure and body mass index)? This could be discussed. The limitations and future studies reasonably well discussed. In response to the reviewer checklist: 1) Research question is fine. 2) Abstract needs estimates of results not just confidence intervals. 3) Study design ideally should be RCT. 4) Aside from the comment about selection of patients for extended CR treatment it is reasonably well described. 5) Appropriate ethics. 6) Appropriate outcomes. Could use looking at outcomes which improved at 1 year at 10 year follow up. 7) Statistics are fine. 8) More references could be used as the authors only discuss 1 study. 9) The results address the research question to a certain extent but better if RCT. 10) Results are clearly presented. 11) Limited discussions of clinical implications as results are negative. 12) Well written limitations. 13) Research checklist available. 14) No ethical concerns. 15) English is satisfactory.

REVIEWER	Carl J. Lavie, MD Ochsner USA
REVIEW RETURNED	03-Oct-2017

GENERAL COMMENTS	This is a nice study and well-written manuscript that is publishable in a modestly competitive journal. The fact is that modern cardiac rehabilitation is quite effective. The authors could cite recent State of the Art manuscript on modern CR (Kachur S et al Prog Cardiovasc Dis 2017;60:103-114) as well as benefits of cardiac rehabilitation around the globe, even in low income countries (Grace SL et Prog Cardiovasc Dis 2016;59:303-322) as well as the psychological benefits of CR (Blumenthal JA et al Circulation 2016;133:1341-1350 and Lavie CJ et al Canadian Journal of Cardiology 2016;32:S365-S373).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Chun Shing Kwok
Institution and Country: Keele University, Stoke-on-Trent, United Kingdom Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below Dear Editor and Authors,

Thank you for the opportunity to review this article on expanded cardiac rehabilitation in socially vulnerable patients with myocardial infarction. This study is a non-randomised cohort study with 10 years follow up. The results show no benefit of the intervention so the clinical impact of the study is limited. Below are my comments.

Abstract

I think the first sentence needs to be improved. Perhaps: “Cardiac rehabilitation (CR) has been shown to reduce cardiovascular risk.”

Author: The first sentence has been changed according to the reviewer's suggestion.

In the results the estimates have to be provided not just the 95% confidence intervals.

Author: The estimates have been provided according to the reviewer's suggestion.

Introduction

The introduction is generally good but could use some improvements. The first two paragraphs could be combined into one paragraph.

Author: The first two paragraphs have been combined into one paragraph according to the reviewer's suggestion.

The third paragraph needs to be slightly expanded. While referencing reviews is good, there needs to be clearer indication of what exactly cardiac rehabilitation interventions have been explored in the literature and the outcomes they have evaluated. Limitations of the studies in literature should be identified and this should naturally elude to the intervention and outcomes explored in the current study.

Author: Changes according to the reviewer's suggestion have been made in the paragraph.

The fourth paragraph does not clearly define why socially vulnerable means. It should be defined and described. The authors have broken it down in some aspects and its significance but does have one of these factors means they are socially vulnerable (low education, living alone, unclear if anything else)? They state that is has relevance in participation in cardiac rehabilitation but they have not stated whether there are previous studies that have done this.

Author: The sentence about socially vulnerable patients has been removed. Instead we more broadly define patients with low socioeconomic status which is the expression used in the references. Our definition of socially vulnerable patients (low educational level and / or single living) is now only mentioned when introducing the intervention in our study.
The references 9-11 refer to previous studies that have investigated the association between socioeconomic status and participation in cardiac rehabilitation.

I presume the change on the cardiac ward with cardiac rehabilitation based on social vulnerability was because they want to target the groups at highest risk. Is this correct? The definition provided is not satisfactory needs further clarification as to number of factors and severity of individual factors.

Author: It is correct that the intervention aimed to target the patient groups at highest risk. In the text a few lines have been added addressing this and also addressing the background for the design of the intervention as well as reflections concerning implementation.

Methods

In the study design, how is the selection between expanded CR and standard CR decided? This is not randomised. Is it just based on the year and whether they were socially vulnerable? Ideally this type of study should be a RCT where the study can be powered and a target sample size calculated.

Author: Yes, it is based on time and whether the patients were socially vulnerable or not. All patients, regardless of whether they were socially vulnerable or not, received standard cardiac rehabilitation from 2000 – 2002. From 2002 – 2004 all socially vulnerable patients received expanded cardiac rehabilitation (standard cardiac rehabilitation and some extra). All non-socially vulnerable patients still received standard cardiac rehabilitation. Our clinical knowledge tell us that the invasive and medical treatment of patients with myocardial infarction in Denmark did not change from the first time period (2000 – 2002) and to the second time period (2002 – 2004). Thus it is reasonable to compare the socially vulnerable receiving expanded cardiac rehabilitation to the socially vulnerable patients receiving standard cardiac rehabilitation even though the patients did not participate at the same time. Today we agree that the ideal study design would be a RCT. But at the time of the intervention this was found to be unethical.

What was the treatment at baseline for the patients? Were patients managed with intervention (i.e. PCI), medications or thrombolysis?
These need to be adjusted for and explored if there are baseline differences.

Author: At baseline all patients in the study received invasive and medical treatment following European guidelines according to their individual needs. No differences in treatment regimes were made.

A comparison should be made comparing the socially vulnerable and not vulnerable in terms of outcomes prior to the intervention treatment. If the rates of adverse outcomes are similar it will be hard to show any benefit of an intervention. The intervention targets the socially vulnerable group so for this cohort there should be at least demonstration that this group is higher risk.

Author: All patients in the study were admitted with first episode myocardial infarction and all patients received and participated in standard or expanded cardiac rehabilitation which started while the patients still were admitted. Thus no patients in the study died or suffered from a recurrent event before they had completed the intervention. Also, we aimed to investigate the long-term effect of the intervention. Because of the above argumentation we have not made a comparison of the outcomes in the study at baseline.

Results

The complete follow up over 10 years shows nice work by the researchers.
The expanded CR group appears to have higher rates of adverse outcomes compared to standard CR group but they are not statistically significant because of small sample size.

Cost analysis of an expanded CR should be included as well.

Author: Unfortunately data are not available for us to do a cost analysis. We found no significant long-term effect of the intervention on the outcomes in question, suggesting that it would not be cost-

effective to implement the intervention in regards to the hard endpoints such as mortality and recurrent events.
Discussion

The results are negative for the intervention which limits the clinical impact of the study.

Is the study by Pluss the only study in the literature? The authors state that a number of studies have examined. If there is more than one study, they should be discussed.

Author: "A number of studies" have been changed to "Two studies". The other study is Giannuzzi et al. (reference 8) which is also mentioned in the introduction. A discussion about the study has been added in the 'Comparison with other studies'-paragraph.

The authors suggest in the introduction that participation in CR is less in socially vulnerable groups. Perhaps the future work should be on trying to improve engagement in CR as it is not clear that an improved or expanded CR is necessarily needed. Is there a difference in characteristics and outcomes of patients that engage with CR and those who do not? The socially vulnerable may not the problem rather those who do not engage with CR.

Author: In the publication which investigated one-year outcomes in our study (reference 18) attendance was also investigated. The cardiac rehabilitation attendance rates were significantly higher (P-value < 0.001) among the patients who received the expanded cardiac rehabilitation intervention compared to the socially vulnerable patients who received standard rehabilitation. This indicates that it is possible to improve the socially vulnerable patients through expanded cardiac rehabilitation.

Did the authors look at the same outcomes which showed improvement at one year (medication compliance, lipid profile, blood pressure and body mass index)? This could be discussed.

Author: At the moment data regarding the outcomes medication compliance, lipid profile, blood glucose levels, blood pressure and smoking status is being collected and will hereafter be analyzed and hopefully presented in another publication. In the present publication we focus on the hard endpoints such as mortality and recurrent events.

The limitations and future studies reasonably well discussed.

Reviewer: 2
Reviewer Name: Carl J. Lavie, MD
Institution and Country: Ochsner, USA
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below This is a nice study and well-written manuscript that is publishable in a modestly competitive journal. The fact is that modern cardiac rehabilitation is quite effective. The authors could cite recent State of the Art manuscript on modern CR (Kachur S et al Prog Cardiovasc Dis 2017;60:103-114) as well as benefits of cardiac rehabilitation around the globe, even in low income countries (Grace SL et Prog Cardiovasc Dis 2016;59:303-322) as well as

the psychological benefits of CR (Blumenthal JA et al Circulation 2016;133:1341-1350 and Lavie CJ et al Canadian Journal of Cardiology 2016;32:S365-S373).

Author: The studies suggested above have been cited in the 'Introduction' (Lavie et al. 2016; reference 5) and in the 'Future research' (Blumenthal et al. 2016; reference 19, Grace et al. 2016; reference 20 and Kachur et al. 2017; reference 21) of the article.