Author's response to reviews

Title: Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction

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Author's response to reviews: see over
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Assistant editor Rikki Graham  
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Dear Assistant editor

Enclosed you will find a revised version of the manuscript:

*New title: Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction*

*Old title: Health-related quality of life after myocardial infarction: the role of left ventricular function*

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We would like to thank the three reviewers for their comments which we have found very useful. The reviewers’ comments have contributed to clarify and improve the revised version of our manuscript.

In addition to the manuscript we have enclosed a document in which we have responded to all comments and given an account of all changes we have made in the manuscript. The changed text is red, deleted text is stroked out, added text is underlined.

All authors have read and accepted the final version of the revised manuscript.

Corresponding author: Kjell I. Pettersen,

On behalf of the authors,  
Yours sincerely

Kjell I. Pettersen, MD
Response to reviewers’ reports.

Ad Reviewer 1 (David R Thompson)

Comment #1
Can LVEF predict HRQoL or is it just an association; if it can is it the LVEF or the cardiac event itself?

Response:
As one should be cautious with regard to stating causality on the basis of results from observational studies, we have now found it more appropriate to use the term association and determinants instead of predictors. In line with this changes have been made throughout the manuscript.
Our data suggests that LVEF is a determinant, but some influence from the cardiac event itself can not be ruled out. In the revised manuscript we have elaborated on this issue, in the second paragraph of the ‘Discussion’.

# 2
What are the clinical implications of these findings?

Response:
We observed an association between LVEF and later HRQoL. An implication of this is that medical treatment aimed at restoring heart function is important for maintaining HRQoL. A new sentence has been added at the end of the Conclusion.

# 3
Why did the authors use the EQ-5D and not the SF-36, or SF-12? Also, what about the Visual Analogue Scale of the EQ-5D – was this used, and if so where are the data, and if not, why?

Response:
In this paper we wanted to use a condition-specific and a generic questionnaire. The EQ-5D also gives utility scores, which aggregate the disutility of having had a myocardial infarction into one number. We also have SF-36 scores available, which could have been presented in two dimensions, MCS and PCS, or possibly could be converted to utilities through the SF-6D algorithm (John Brazier). However, this would require more space, and we think this would add little to the results obtained from the EQ-5D. Further, the utility algorithm for the EQ-5D is better documented than for the SF-6D.
The results using the Visual analogue Scale of the EQ-5D were obtained and in the revised manuscript they are presented in Table 2 and in multivariate analyses in Table 3. Text has been added in the Questionnaire section, in the three first paragraphs under ‘Results, Health-related quality of life’, and in the ‘Discussion’.
Ad Reviewer 2 (Phyo Kyaw K Myint)

Major Compulsory Revision #1
The current title put focus on LV function as determinant of HRQoL after MI. Although authors tried to quantify the role of LV function in HRQoL by excluding LVEF from the model the current title may be an over-interpretation. Authors perhaps should use somewhat modest title.

Response:
We see the point and have changed the title to: ‘Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction’, in accordance with the reviewer’s suggestion.

#2
A flowchart with eligible population, exclusions and reason for exclusion, would provide an overall picture of the study at a glance for readers in assessing the robustness and also highlight the representativeness of the paper

Response:
As suggested by the reviewer, we have added a flowchart describing the patient population in more detail.

#3
754 patients from 15 hospitals were thought to be eligible. Of them 406 (54 %) had LVEF measured. At follow-up 408 returned the questionnaire. Of them, 256 had data on LVEF. It appears to me that one third of patients (n=101) came from a single hospital which routinely measured LVEF using MUGA. This raises the question of true representativeness of the sample across the whole population. Site specific data in appendix would improve transparency of the manuscript and helping the readers to make judgment of representativeness of the sample.

Response:
As stated above, we have added a flowchart showing the patient population. If the editor wants an appendix with site-specific information we can provide it.
In supplementary analyses, we have added individual hospital variables in the final multivariate models. However, in none of these analyses were hospital variables important predictors for HRQoL. Adding these analyses would add to the length of the paper and therefore we would prefer not to include them. Changes not made.

#4
It is interesting that in this series, a history of peripheral vascular disease predicts higher EQ-5D score, which is opposite of what one would expect to see. Authors should provide how the
history of peripheral disease was collected and why they have decided to include in the models. Also what is their thought on such findings.

Response:
Information on peripheral vascular disease was, as for the other cardiovascular morbidities, collected from the patients’ medical record, and is based on ICD codes or other explicit statements in the medical records. In the revised manuscript we have added a sentence about this in ‘Review of medical records’.
All cardiovascular diagnoses collected can affect HRQoL, especially when assessed with a generic instrument, and were thus added in bivaraible regression analysis. Peripheral vascular disease had p < 0.25 in bivaraible regression analysis and was reported in the final model because it came out as an independent determinant of EQ-5D Index score in the final multivariable regression analysis. Our thoughts on this finding have now been added in the 7th paragraph in the ‘Discussion’.

#5
Along the similar line, it is not clear to me which variables were included in the models and (a) what are the rational for inclusion-e.g. education level (b) how did authors ascertain these variables. This needs to be described in the method section. Also authors should have mentioned which variables were excluded due to high correlation

Response:
In the analysis we first included age, sex, education, and LVEF. Then, as a second step we added all the other predictor variables with p < 0.25 in bivariable analyses. However, we only report the final models in the text and in table 3. We have described how we assured previous cardiovascular diagnoses in the response to ‘Major Compulsory Revision 4’. Information on education was collected through three questions inquiring about the highest level of completed basic, higher, and vocational education. From the responses we calculated expected number of year of education. There was no way to ascertain this variable further.
The rationale for including education in the multivariate models even if it was not an independent predictor of HRQoL in this set is that education is one of the sociodemographic variables known to influence responses on HRQoL instruments.
No variables had bivariable correlation >0.70 and thus no variables were excluded on this basis. We have reformulated the second paragraph in ‘Statistical analysis’ in order to make it easier to understand the different steps in the statistical analysis.

#6
I don’t think adding the time between index MI and HRQoL is a suitable approach. Intervention such as re-vascularisation (yes/no) and major life events (yes/no) may be an alternative option to consider in multi-variately adjusted models as crude adjustments. Alternatively, would there be enough power to examine them by stratification. i.e. stratified analyses by event such as MI and re-vascularisation.

Response:
We agree that the time from the MI to measuring HRQoL is not the best measure for events affecting HRQoL. We asked patients about new cardiovascular events and revascularization.
However, we did not ask patients about other major events and thus we used time as a substitute variable and think this was the best analysis we could undertake. Too few patients had suffered new MI or had been treated with revascularization justifying stratified analyses. Therefore no changes have been made in the revised manuscript.

**Minor Essential Revision #1**
There are some typographical errors.

**Response:**
We have corrected several typing errors.

**#2**
Authors repeatedly refer to the data of the whole cohort. After referring to the flow diagram as suggested above, probably easier to readers to follow if authors concentrate on actual number of patients included in this analysis.

**Response:**
See response to Major Compulsory Revision 3.

**#3**
Why intermediate LVEF instead of low LVEF was independent determinant of a lower EQ-5D score? What the authors’ thoughts are?

**Response:**
That intermediate and not reduced LVEF was an independent predictor of reduced EQ-5D score in our series was an unexpected result. There might be several reasons for this result. Most likely the reason for reduced LVEF not being an independent predictor of reduced EQ-5D is a combination of two different possible explanations. First, EQ-5D, being a generic instrument, may be less sensitive to changes than the disease specific KCCQ and thus might not be able to differentiate between patients with intermediate and reduced LVEF as well as the KCCQ. Second, the number of patients with reduced LVEF who responded to the EQ-5D was 30 compared to 53 in the intermediate group. This leads to reduced statistical power and the difference in EQ-5D score between patients with normal and reduced LVEF has to be larger than for patients with normal and intermediate LVEF for reduced LVEF to be significantly associated with reduced EQ-5D score.

We have already commented on generic versus condition-specific instruments in the third paragraph of the ‘Discussion’, and in order to provide a more compete discussion, have added a comment on statistical power at the end of the paragraph.

**Discretionary Revision #1**
Current introduction (Background) requires revision to justify the study.
Response:
We have chosen a brief and to the point introduction, which still includes the essential information to justify the aim of the study. We have considered expanding the introduction. However, our preference is a brief introductory background and then takes the opportunity to discuss at greater length in the discussion.

Ad reviewer 3 (Roger Davis)

Minor Issue #1
In the demographic section, it is not clear what test was used to compare LVEF levels between the respondents and non-respondents. The test used should be specified. Since the summary is presented categorizing LVEF into 3 groups, I am assuming that a chi-square test of independence was used (as that is the only test prescribed for categorical data). That test is not the best choice, as it does not take the ordering of the categories into account. There are a number of better alternatives. There is a test of trend for ordinal categories, or one could use a Wilcoxon rank-sum test on the categories. Another option is to use the actual LVEF values and test using a t-test of a Wilcoxon rank-sum test.

Response:
Changes made as suggested by the reviewer.

#2
In table 1, localization is a categorical variable with 3 possible values. Instead of doing separate test comparing proportions for each location, there should be a single test done. Specifically, to compare LVEF measured versus LVEF not measured, you should do a chi-square test of independence on the 2 x 3 table of LVEF measured (yes/no) by localization. For LVEF level by localization, you could do a Kruskal-Wallis test (essentially a non-parametric analysis of variance)

Response:
Changes made as suggested by the reviewer.

Editorial #3
Throughout the paper, you should use ‘multivariable’ rather than ‘multivariate’.

Response:
Changes made as suggested by the reviewer.

#4
Instead of ‘R2’ you should use ‘R²’ or ‘R-square’
Response:
Changes made as suggested by the reviewer.

#5
Methods section of Abstract: ‘KCCQ clinical summary score was’ should be ‘KCCQ clinical summary scores were’.

Response:
Changes made as suggested by the reviewer.

#6
Second paragraph of Questionnaire section: ‘and its psychometric properties is documented’ should be: ‘and its psychometric properties have been documented’.

Response:
Changes made as suggested by the reviewer.

#7
Statistical analysis: change ‘bivariate’ to ‘bivariable’ or ‘unadjusted’.

Response:
Changes made as suggested by the reviewer.

#8
Statistical analysis: ‘multicolinearity’ should be ‘multicollinearity’.

Response:
Changes made as suggested by the reviewer.

#9
Statistical analysis: change ‘stepwise forward’, to ‘forward stepwise’.

Response:
Changes made as suggested by the reviewer.

#10
First paragraph of discussion: ‘10 an 17 points respectively’ should be ‘10 and 17 points respectively.

Response:
Changes made as suggested by the reviewer.