Author’s response to reviews

Title: Sex dependent risk factors for mortality after myocardial infarction: individual patient data meta-analysis

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Author's response to reviews: see over
Response to reviewers comments

Dear dr. D'Souza,

Thank you for sending us the helpful and detailed comments of both reviewers; we appreciate their rigorous reading of our manuscript “Sex dependent risk factors for mortality after myocardial infarction: individual patient data meta-analysis”. We have revised our manuscript according to the concerns of the reviewers. Below we have listed all reviewers comments and our responses to these (italicized). Changes in the manuscript are visible with track changes.

During revision we noted that we have been inconsistent in reporting sample characteristics. In the results section we described means of the original data (p11), whereas in table 1 (p25) we reported means of the imputed data. We apologize for this inconsistency. We have adjusted table 1 so that we consistently report sample means of the original data set.

We have answered the editorial requests by providing the email addresses of all authors together with their institutional addresses, and included the contributions of all authors in the ‘author contributions’.

We hope you want to consider our revised manuscript for publication in BMC Medicine.

Best wishes, on behalf of all authors,

Hanna van Loo
Report reviewer 1:

BMI is not the best predictor of mortality, waist circumference is definitively better.

We agree with the reviewer that BMI is paradoxically related to death after myocardial infarction: contrary to expectation, several studies (including this study) have found that MI-patients with a higher BMI have improved survival (e.g. Bucholz EM, Rathore SS, Reid KJ et al., Body Mass Index and Mortality in Acute Myocardial Infarction Patients. The American Journal of Medicine (2012), 125, 769-803). Thus, BMI is a predictor of mortality, but it is unclear whether it has an independent effect or whether its effect is dependent on confounding variables (e.g. malnutrition, or lean body mass). Whether waist circumference is a better marker of cardiovascular risk in patients after myocardial infarction is unclear as few studies have investigated this. A recent study comparing BMI and waist circumference predicting mortality after myocardial found that waist circumference is not a stronger predictor for all-cause mortality than BMI. However, patients with a combination of a low BMI and high waist circumference had increased 1-year death rates, which could indicate an interaction effect (Zeller M, Steg PH, Ravisy J et al., Relation between Body Mass Index, Waist Circumference and Death after Myocardial Infarction, Circulation (2008), 118, 482-490). So, it would have been interesting to see if we could observe the same in our sample, but waist circumference was not measured in all included studies. We have mentioned waist circumference in the discussion as one of the data limitations and added the reference to Zeller et al. (p15).

Further details about the predictors used for multiple imputation and whether only one or multiple data sets (i.e., multiple imputation) were used for analyses.

We provided further details on the predictors used in the multivariate imputation, and that we imputed one data set (p8).

Authors need to do their best for explaining in very clear and lay terms the methodology that they have used. They need to use terms that can be understood by the usual average reader of the journal who is not a specialist in advanced multivariable modeling.

We have adjusted our methods section in the manuscript, and especially clarified the section on lasso penalized regression (p8-10).

Authors need to represent graphically the most important interactions that they have found in order to clarify their meaning, magnitude and direction. The current Figure 1 is complicated and it is not easy to understand. It is essentially a Table instead of a Figure.

We have added figures as additional files (figures 1-4) to the manuscript with plots of survival curves showing the four significant interaction effects between sex and age, sex and depression, sex and LVEF and Killip class and beta-blocker use. We plotted survival curves for different strata adjusted for all other risk factors (as included in table 3). We decided not to exclude figure 1 from the manuscript given that reviewer 2 was positive about this addition (see “Other comment” reviewer 2).
There is not any mention or explanation on whether these interactions are only quantitative or they are also qualitative (because they change the direction of the association). The magnitude (size) of the differential effect is perhaps more important than just to state that the interaction term was statistically significant.

We agree that effect sizes are more important than p-values, and we performed two stratified analyses in order to find the differential effect size of age<50 years, a poor LVEF and depression score in men and women, and the effect of beta-blocker use in patients with and without heart failure (p13-14). In all cases, the magnitude of the risk factors was different, but not the direction of the association. We have added this observation to the results section (p14). We hope that this, along with the additional figures, clarifies the differential effects of the risk factors in different groups.

The main limitation is that you could not include all relevant predictors in your analyses such as blood pressure or heart rate or ECG findings. There is no mention of educational attainment, marital status or socioeconomic status that can act also as predictors of mortality.

We agree with the reviewer that important predictors are missing due to data limitations. We have added socioeconomic status, marital status and educational attainment (with a reference) to our description of missing predictors (p15), in addition to blood pressure, heart rate and ECG findings in the limitations section, which we already described.

Please include always (also in the tables) the 95% CI for the areas under the ROC curves.

We included bootstrapped confidence intervals for the areas under the ROC curves (table 2).

Please correct: Sonofi-Aventis Groupe // Sanofi-Aventis Groupe

Thank you for noting this, we corrected the name (p17).

Report reviewer 2:

Van Loo and colleagues present the results of meta-analysis (patient level) of interaction between risk factors following myocardial infarction. The manuscript is exceptionally well written, the analyses rigorous, and the results provide novel information not found in the existing literature while confirming in a convincing way previously reported interactions.

Major Compulsory Revisions: None

Minor Essential Revisions:
1) The method discuss categorization of depression into three classes based on z-scores (with highest value being top quartile), yet the results discuss 40% having an increased depression score based on standard cutoffs. Please clarify. I personally appreciate the additional presentation of the categorical cutoff measure, but it would help to have a sense of what thresholds were used. It would also be helpful to report in the methods what depression measures were collected in each study (could also consider table for this).

*We have clarified the description in both the methods and results section (p7 and p11). We have indicated the most often used depression interview schedules and questionnaires, and gave examples of standard cut-off values. For a full overview of questionnaires and cut-off values we included references to Meijer et al. (2013), who provides a full overview in an additional table.*

2) Table 1 refers to “increased depression score” yet this is a baseline variable. “Increased” implies the value changed over time. Please reword (e.g., “elevated”) in a manner that doesn’t imply that a prospective change over time was observed. Please also clarify whether smoking refers to current smoking.

*We adjusted “increased depression score” into “elevated depression score” and added “ever” to smoking (table 1).*

3) The protective effect of the lowest quartile of depression is fascinating and suggestive that these symptoms are relevant even outside the pathological range. Perhaps this can be at least briefly discussed. It may argue for not simply focusing on depression as a categorical disease in conveying risk. It is interesting to think that even within the normal range lower levels of depression might be protective.

*Our study indeed suggests that a lower depression z-score predicts lower mortality rates as compared to the reference class (depression z-score in the two intermediate quartiles) and the patients with the highest depression scores, and might suggest that there is a linear relationship between depression score and mortality risk (as opposed to only an increased risk above a certain cut-off). We have noted this in the results section (p13).*

4) Please clarify the following from the discussion: “For instance, why is depression more strongly related to all-cause mortality in men than in women? A study in one of the datasets included in MINDMAPS suggested that men with depression are more likely to have a poor LVEF than women with depression.[37] Thus, depression seems to reflect more severe heart disease in men but not in women, which could explain why depressed men are more at risk for all-cause mortality than depressed women. This example illustrates that the interpretation of interactions should be done in the context of possible confounders.” In Table 2, I was under the impression that the interactions were tested controlling for other variables (such as LVEF and Killip class), thus the sex differences observed seem unlikely to be fully explained by severity. If I’m misunderstood, please clarify in the manuscript accordingly.

*Thank you for noting this unclear description. To test the interaction effect between sex and depression, we have indeed controlled for LVEF and other measures of severe heart disease, and in spite of that, the interaction between depression and sex was (borderline) significant (table 2, 4). Although the interaction between sex and depression is attenuated by LVEF (and thus is partly explained by the fact that depressed men have a poorer LVEF than depressed women), LVEF does not fully explain the interaction effect. We have clarified this part of the discussion by noting that other potential confounders could underlie the remaining interaction effect (p17).*
Discretionary Revisions:

1) Antidepressant use appeared harmful and I wonder if this was due to collinearity with depression (and lack of a protective effect). Could the authors at least report the percentage of those in the highest quartile of depression treated with antidepressants? If low, this is reassuring. If collinearity appears potentially problematic, please consider reporting a sensitivity analysis that either excludes antidepressants from the models or collapses it into the high depression group (perhaps as a categorical group by merging with increased depression score).

*Only 10.7% of the subjects in the high depression quartile used antidepressants, and there were no indications of collinearity (phi coefficient 0.11). We added this information to the results (p11).*

3) Highest quartile of depression is difficult to extrapolate to other research studies and clinic. Can the authors comment on what this approximates with one or two of the more commonly used depression scales used.

*Thank you for this suggestion. We have included means and standard deviations of the depression scores on the Beck Depression Inventory-1A for the subjects in the highest, intermediate two, and lowest quartiles in the results section (p11) and table 1 (p26).*

Other Comment:

1) Figure 1 is a very nice addition to the manuscript.

*Thank you.*