Author’s response to reviews

Title: Relationship between ALDH2 Genotype and In-stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention

Authors:

Lizhi Lv (provlizhi@126.com)
Weijie Ye (463111153@qq.com)
Peiyuan Song (song_ng_peiyuan@126.com)
Yubin Chen (470643668@qq.com)
Jing Yang (fccyangj3@zzu.edu.cn)
Congmin Zhang (fcczhangcm@zzu.edu.cn)
Xiaoping Chen (chenxp74@hotmail.com)
Fanyan Luo (drlfy@163.com)

Version: 2 Date: 15 Mar 2019

Author’s response to reviews:

Dear Editor:

We would like to thank the editor for giving us a chance to resubmit our paper, and also thank the reviewers for providing constructive suggestions that helped us regarding English language and for improving the quality of the paper. We are submitting a revised version of our manuscript titled “Relationship between Aldehyde ALDH2 Genotype and In-Stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention” (BCAR-D-18-00746), which has been modified according to the editor’s and reviewers’ suggestions. Efforts were also made to correct mistakes and improve the English of the manuscript. We modified the manuscript using tracked changes in Word.

Sincerely,

Lizhi Lv, M.D
The following is a point-by-point response to the editor’s and two reviewers’ comments.

Editors:

Question 1. Please refer to our guideline for manuscript preparation. For instance, the reference format, the legend or footnote for the tables and figures.

Answer: Thank you for your advice. We amended the manuscript according to the guidelines for manuscript preparation.

Question 2. Improvements to the English language within your manuscript is requested for further consideration for publication. Please, follow our language suggestions in our guideline to revise your manuscript.

Answer: Thank you for your advice. We have improved the English language according to the language suggestions.

Question 3. Please, be careful with usage of professional terms. For instance, in Abstract, Results, “68.7% of patients had the wild type……”, please be clear, wild type homozygotes, heterozygotes, and mutant homozygotes. “Wild type” and “mutant type” mainly are used to refer “allele”, not genotype. Please consider to revise through the manuscript. Since the low frequency of minor (mutant) allele, for the main analyses, I presume the author combined the heterozygotes with minor allele homozygotes and compared with wild-type allele homozygotes. Please, clarified in the Methods, Tables and Figures.

Answer: Thank you for your correction. We revised the manuscript and addressed these questions.

Question 4. The Introduction is tediously long and redundant. Quite lots of information could be removed or moved to the Discussion. In the Introduction, please simply explain the rationale and background to do the study.

Answer: Thank you for your advice. We removed some content from the Introduction and moved some content to the Discussion.
Question 5. Methods, please, also refer to Comment 7 of our Reviewer 1, a clear flow-chart about the inclusion and exclusion of the study subjects should be provided.

Answer: According to comment 7 of Reviewer 1, we provided in Figure 1 a flowchart for the inclusion and exclusion criteria.

Question 6. Methods, both logistic model and cox model had been used for the analyses. The author should clarified which method had been used for which analyses in the Methods section, and in the legend or footnote of the tables correspondingly.

Answer: We modified the statistical analysis in the Methods section (lines 207-211) and in the footnotes for the tables.

Question 7. Methods, since cox model had been used. Time of ISR diagnosis turns to be relevant. Please, report exactly the time when the repeated coronary angiography were performed for the patients.

Answer: We have the exact time when the patients repeated coronary angiography. But according to your question 14, the time of repeated coronary angiography could not represent the time when ISR occurred. Thus, it is not appropriate to use the Cox model for this analysis.

Question 8. Methods, “All subjects provided their informed consent” were repeatedly mentioned in the Page 10, line 44 and page 11, line 11. However, this part were missed in the Declarations. Please, also specify if the patient provide written consent?

Answer: We deleted this part in the Methods and added it to the Declarations on lines 474-479.

Question 9. Methods, Please clarify why the covariates were included in current study, if a stepwise regression was applied.

Answer: Thank you for your question. Regarding the selection of independent variables, we did not apply stepwise regression based on other papers. We added this to the Methods, lines 215-217.
Question 10. Results, the criteria for defining cigarette smoking, alcohol drinking, hypertension, diabetes mellitus and hyperlipidemia should be clarified either in the method or in the table footnotes where they are relevant. By the way, there was a typo for “hyperlipidemia” in Table 1. In the table footnote, please also clarified all abbreviations. At the end of the manuscript, a list of overall abbreviation should be provided.

Answer: Thank you for your advice about criteria for risk factors and abbreviations. We added this part to the Methods, lines 162-166. At the end of the manuscript, we provided a list of abbreviations on lines 441-467.

Question 11. Table 1, please clarify why the percentage was reported only in some cells, not for all cells where it was relevant.

Answer: The analysis of continuous variables such as biochemical tests was performed by the t test, and we provided the mean and standard deviation. For categorical variables such as sex, risk factors, coronary artery lesions, medications and ALDH2 genotype, we used the chi-square test, and we provided the contingency ratio.

Question 12. Table 3, there were a typo for the genotype ALDH2 *2/*2, which was mistyped as ALDH2 *1/*1.

Answer: We apologize for this error in Table 3; we have corrected it.

Question 13. Table 4, the results of genetic comparison should be leading with “ALDH2 *2 carriers vs. ALDH2 *1 homozygotes” to avoid any confusion.

Answer: We modified the results of genetic comparison in Table 4.
Question 14. There should be something wrong with the number at risk in Figure 1. At time point 0, how come the number at risk were 100 and 61 for the two groups. I guess they should be 365 and 166. Please, double check all of the numeric results. I also have problem with the rationale of Kaplan-Meier analysis here. Majority of the ISR cases were asymptomatic, and detected because of routinely repeated CAG. Time when defining ISR here was rather depending on the CAG than relevant as time of ISR development. Therefore, cox model assessment elsewhere in the paper would also be not relevant. Please clarify.

Answer: We checked all numeric results. Indeed, majority of ISR cases were asymptomatic and were only detected because of routinely repeated CAG. As we cannot be sure of the exact time when ISR occurred, it is not appropriate to use Kaplan-Meier analysis. Ultimately, we decided to remove this result.

Question 15. Analysis for ISR as a continuous variable could be considered to confirm the findings.

Answer: According to question 14 and our answer, we did not know the exact time of ISR; hence, we cannot analyze ISR as a continuous variable.

Question 16. Please, also carefully address all of the comments from our two reviewers.

Answer: We respond to these comments below.

Reviewer#1:

Blerim Mujaj (Reviewer 1): Title: Aldehyde Dehydrogenase 2(ALDH2) Genotypes and In-stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention

Comments to the authors:

The authors studied the association of between Aldehyde Dehydrogenase 2(ALDH2) Genotypes and In-stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention. This study reports negative results as the association is driven by other risk factors, mainly diabetes. However, study provides clinically important information for the patients, despite their possible genetic background, diabetes is matter of treatment to reduce the risk of restenosis.
Question 1. In the title you have with errors written 'Chineses' and it should be changed to 'Chinese'.

Answer: We apologize for this mistake, and we have corrected this.

Question 2. In the abstract section within the background the authors stated 'In-stent restenosis is a serious adverse result of PCI'. Restenosis per definition is defined as primary PCI complication and not a serious adverse event. Can you elaborate further?

Answer: We apologize for not describing ISR with accuracy, which is defined as a primary PCI complication and not a serious adverse event. We changed the definition on line 28-29.

Question 3. In the abstract section within the background the authors stated, 'PCI which is a significant treatment for CAD'. Primary PCI is recommended treatment for CAD.

Answer: We changed the text on lines 29-30.

Question 4. In abstract section with methods, you do not show the number of patients included in the study. Please do that.

Answer: We add the number of patients included in the study to line 31-33.

Question 5. In introduction section, the authors stated, '. The treatment of CAD mainly depends on drug therapies, including antiatherogenic drugs (such as statins) and endothelial protective drugs (such as ACEIs). Percutaneous coronary intervention (PCI) is an important way to promote the reperfusion of patients who have suffered from acute coronary syndrome (ACS)'. I disagree with first sentence as drug treatment are the treatment options for CAD and PCI is treatment of recommendation if symptoms persist despite the drug treatment. And also, with second sentence as PCI is important treatment in acute only but also in stable CAD if symptoms persist with drug therapy.

Answer: Thank you for your advice. We modified the discussion of therapeutic indications for PCI on lines 64-69.
Question 6. In the method section, the authors used heading as 'Human subjects', please change that to Study population.

Answer: Thank you for your advice. We changed ‘Human subjects’ to ‘Study population’ on line 131.

Question 7. In methods section, it is not clear how many patients have been diagnosed with ACS? How many underwent PCI and how many returned to hospital for re-examination and were diagnosed with re-stenosis? How many met inclusion criteria and how many met exclusion criteria? Finally, to end up with 531 patients included in the study.

Answer: Thank you for your advice. We provided in Figure 1 a flowchart for the inclusion and exclusion criteria.

Question 8. In the method section: Definition of the in-stent restenosis, the authors stated that the Academic Research Consortium considered the definition of ISR. So, the question is what is the role of Academic research Consortium? Does this body provide the treatment guidelines in China? If yes, based on which scientific evidence? Is there any published document? If not, then please refer to most recent guidelines of ESC and AHA.

Answer: Thank you for your advice. The academic Research Consortium did not provide treatment guidelines in China; we deleted this part. We defined ISR according to recent literature (lines 168-175).

Question 9. In following sentence you did to similar document (reference 14) but the PCI field has been improved so much that the reference of year 1999 might be inappropriate today. Please additionally refer to most recent important guidelines issued by ESC and AHA.

Answer: Thank you for your advice. We have referred the new guideline by ESC to explain PCI.
Question 10. Next, the authors stated 'The results of the luminal narrowing and the in-stent restenosis were confirmed by two experienced interventional cardiologists according to guidelines for cardiovascular diagnoses. Can you please explain the experience of cardiologists? Did you perform intra-and-inter reader reproducibility? And according to which guidelines the cardiologist confirmed diagnoses?

Answer: Thank you for your advice. The experience of cardiovascular specialists is defined by their surgical experience, whereby each cardiologist performed more than 300 PCI surgeries each year. We did assess intra- and interreader reproducibility. The cardiologist confirmed diagnoses according to ESC guideline.

Question 11. In Statistical analysis section, the authors mentioned 'Interaction terms with p value'. Did you test any interaction term? (interaction terms ?)

Answer: We apologize for this error. We did not test any interaction term; we merely want to express that a p value less than 0.05 was considered to be statistically significant. We have revised lines 218-219.

Question 12. All tables need improvements. Please provide a footnote to each table to describe the univariate and multivariate models.

Answer: Thank you for your advice. We have improved all tables.

Reviewers2#:

İhsan Alur, MD (Reviewer 2): Dear Editor,

Manuscript Number BCAR-D-18-00746 entitled "Relationship of Aldehyde Dehydrogenase 2 (ALDH2) Genotypes and In-stent Restenosis in Chines Han Patients after Percutaneous Coronary Intervention" has been reviewed. First of all I want to thank the writers of this article for their planning and performed such an important study. I would like to congratulate for your work. The study and methodology of the study is well-designed. Results are consistent with the literature. I think that the important results have been achieved and that these results are a serious contribution to the literature. This work will contribute to intensive research in cardiovascular diseases I think.
My comments are included at the bottom of this letter.

Question 1. It appears to be that 2 and 16 references are written the same. It needs to be corrected.

Answer: Thank you. That mistake has been corrected.

Question 2. It appears to be that 17 and 18 references are written the same. It needs to be corrected.

Answer: Thank you. That mistake has been corrected.

Question 3. I have not found the articles mentioned in the second (2nd reference) and seventeenth (17th reference) references in the literature. I've scanned 'Pubmed' and 'Google' but I haven't found these articles.

Answer: Thank you for your advice. Downloaded references were sent to the editor in supplementary material named as “reference 1” and “reference 2”.

Question 4. The 'Reference' section of the article should be written in the 'Word' format and should be rearranged according to the journal's writing rules.

Answer: Thank you for your advice. We checked the References according to the journal's guidelines.

Question 5. In the 'Abstract' section of the 'Conclusion' section, the word 'postoperative' was misused in the sentence " but it was a significant association with this post operative ". The word 'after the procedure' is would be more appropriate.

Answer: Thank you for you advice. We changed the word 'postoperative' to 'after the procedure' on line 52.
Dear Editor:

We would like to thank the editor for giving us a chance to resubmit our paper entitled “Relationship between Aldehyde ALDH2 Genotype and In-Stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention” (BCAR-D-18-00746). We modified the manuscript according to your suggestions.

1. FORMATTING CHANGES: we upload a clean version of revised submission.

2. DECLARATIONS SECTION:

We completed the declaration section.

For the “Availability of data and materials” section, we presented our data within additional supporting files.

For the “Authors' information”, we completed the information of all the authors.

Sincerely.

Lizhi Lv, M.D
Dear Editor:

We would like to thank the editor for giving us a chance to resubmit our paper titled “Relationship between Aldehyde ALDH2 Genotype and In-Stent Restenosis in Chinese Han Patients after Percutaneous Coronary Intervention” (BCAR-D-18-00746). We modified the manuscript according to your suggestions.

1. Itemized replies to all previous comments from our Reviewers and Editor: we presented all responses to the comments.

2. A version of your manuscript tracing all of the changes you made: we upload clean version of revised submissions named as “clean version xxx”. And the version of manuscript, figure and table tracing all of the changes we upload with name of “changes xxx”.

Sincerely.

Lizhi Lv, M.D