

## **Author's response to reviews**

**Title:** Effect of statin therapy on the progression of coronary atherosclerosis

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### **Author's response to reviews:**

April 15, 2012

Editor

BMC Cardiovascular Disorders

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Manuscript TITLE: Effect of statin therapy on the progression of coronary atherosclerosis

Dear editor:

Thank you very much for the review and constructive suggestions. We have tried to answer point-by-point the comments and questions raised by the reviewer. The changes were incorporated in the revised manuscript.

We believe that our manuscript has improved after the revision and hope that it now meets the expectation of the editor and the reviewers.

If you have any questions, please do not hesitate to contact me.

We added Yanli Sun and Xiang Ban as co-authors for their sufficient contribution in the revised manuscript.

Hope the answers provide enough details to fulfill expectations of the Editorial Board.

Looking forward to a positive decision,

Sincerely yours,

Bo Yu, MD. PhD

Response to Dr. Grzegorz Kopec's comments:

We are grateful for this positive review.

General comment

Question 1: Style and language are not appropriate - the paper is very difficult to read, it needs significant improvement; authors should chose the time (past or present) they use in the consecutive paragraphs.

Answer: The manuscript has been edited by a very experienced medical editor whose native language is English.

Specific comments:

Background

Question 2: sentence 3: in patients with CAD we do not use primary prevention,

Answer: We have deleted it.

Question 3: I suggest not using "plaque component volume" but plaque composition"

Answer: The term "plaque component volume" has been replaced by "plaque composition" in the revised manuscript.

II. Methods:

Question4: 4.1 last sentence: why these papers were manually checked? Is the sentence necessary? What does it mean?

Answer: This is an excellent question. Abstracts of conferences, recently published editorials, review articles as well as the reference lists of identified articles were usually unavailable in the selected online electronic databases. We manually checked this content to avoid missing relevant studies.

Question5: 4.2 the first criterion is not clear; please clarify.

Answer: The first criterion was that IVUS and/or VH-IVUS examinations were done at baseline and repeated at follow-up. We have changed the description of the first criterion in the revised manuscript.

Question6: 4.3 First sentences - how did the authors review the "hidden financial assistance situation"? - was this necessary for the study?; there is no further discussion about it

Answer: We have deleted the phrase "hidden financial assistance situation" according to comments from both reviewers.

Question7: 4.6. Authors say that they calculated MD - they should explain the abbreviation

Answer: We have explained the abbreviation "MD" (mean differences) in the revised manuscript.

### III. Results:

Question8: sentence 1. Comment: what do the authors mean by "statins in 3 groups"? Probably it should be stated "different statins in 3 groups"

Answer: The phrase "statins in 3 groups" was replaced by "different statins in 3 groups".

Question9: sentence 2. Comment: the word "definitely" is unnecessary

Answer: We have deleted the word "definitely".

Question10: sentence 3. It is said: "The rest 4 groups did not definitely excluded patients with ACS." Comment: it is not clear who was included in the studies

Answer: The remaining 4 groups were mixed groups, and included patients with SAP and patients with ACS.

Question11: sentences 5-9: authors should show not only the mean values of age, LDL-C and so on but also SD.

Answer: We have added the SD values of age and LDL-C.

Question12: Last sentence: instead "increase or decrease" it should be used: "change"

Answer: The phrase "increase or decrease" was replaced by "change".

### IV. Discussion:

Question12: 3rd sentence: "decrease in plaque size while achieved LDL-C levels are 70-100 mg/dl or less; while achieved LDL-C levels are greater than 100 mg/dl; there is no significant decrease." it should be written "decrease in plaque size only when LDL-C < 100 mg/dl".

Answer: The sentence "decrease in plaque size while achieved LDL-C levels are 70-100 mg/dl or less; while achieved LDL-C levels are greater than 100 mg/dl; there is no significant decrease." was replaced in part by "...decrease in plaque size will occur only if LDL-C is < 100 mg/dL".

Question13: 6th and 7th sentence the authors say that plaque composition did not change during statin therapy and give only one possible explanation which is "low statistical power". The authors should discuss this important observation in a separate paragraph; if they think that the statistical power was the reason they should prove it.

Answer: We have rewritten this paragraph and discussed this result in a separate paragraph.

Question14: Authors use one paragraph to review pleiotropic effects of statins; instead they should explain how pleiotropic effects influence their results,

Answer: We have rewritten this section to explain how pleiotropic effects may have influenced our results in the revised manuscript.

Question15: Table 1 - authors should explain under the table "I2"

Answers: We have added the explanation under Table 1.

Response to Dr. Gregory Makris's Comments:

We are grateful for this positive review.

Question1: Despite the interesting subject the authors fail to link it properly with the current clinical needs and identify the clinical implications of their findings. We generally know that the pleiotropic effects of statins have a beneficial role on plaque stabilization however the underlying mechanism and how we will take advantage of this property remain an issue of debate.

Answer: We have rewritten the Introduction and Discussion sections.

Question2: The entire manuscript needs editing and probably rewriting in some parts by a native English speaker. I strongly encourage authors to carefully revise the grammar and syntaxes before resubmitting.

Answer: The manuscript has been edited by a very experienced medical editor whose native language is English.

Question 3: Title: Needs shortening: "new insights through meta-analysis" is unnecessary.

Answer: We have shortened the title in the revised manuscript.

Abstract:

Question4: Needs shortening as well and restructuring including a Method section-include limitations of research and that further research is needed. It also needs rephrasing at some points.

Answer: We have shortened and restructured the Abstract section.

Background:

Question5: 2nd paragraph needs rephrasing.

Answer: The second paragraph has been rephrased in the revised manuscript.

Question6: Explain why this research is necessary and how is clinically relevant.

Answer: We have rewritten this section.

Methods:

Question7: For some reason it appears after the conclusions. Please bring this section after introduction. Needs editing as well

Answer: The Methods section has been edited and placed after the Introduction section.

Question 8: Why search date ranges from 1990 to 2010 and not 2012?

Answer: This study was designed in October 2010. We searched online

databases up to October 2010. The literature search was accomplished independently by two well-trained reviewers. Discussions were initiated between the two reviewers if there were discrepancies between their search results. Abstracts of conferences, recently published editorials, review articles as well as the reference lists of identified articles were checked. We spent 6 months selecting the eligible literature, extracting data, analyzing the data, and interpreting of the results. After completing these process, we spent 6 weeks preparing the manuscript. Several meta-analysis studies were published »1 year before submission of our article (e.g., Filion et al. BMC Cardiovasc Disord. 2010, 10:24; Rod et al. BMC Cardiovasc Disord 2009, 9:13; Pasquale et al. Hypertension. 2007; 49:792-798; Matthias et al. JAMA. 2006; 295: 2046-56; Katharine et al. BMC Cardiovasc Disord. 2005; 5:11).

Question 9: Please update search Inclusion criteria need to be more specific. Please define what you mean by plaque components.

Answer: We have updated the information regarding inclusion criteria. "Plaque component volume" has been replaced by "plaque composition" in the revised manuscript. We have defined the meaning of plaque composition.

Question 10: Where are the exclusion criteria? Improve the flow chart?

Answer: We have added information regarding the exclusion criteria in the revised manuscript. We have also improved the detail of the flow chart.

Question 11: "Financial situation ...hidden" this doesn't have to be here.

Answer: We have deleted the phrase "hidden financial assistance situation" according to comments from both reviewers.

Question12: In the study selection all the reasons for the excluded studies can be summarized in the flow chart.

Answer: We have added all the reasons for excluding the studies in the flow chart.

Question13: End points: Need to be carefully defined

Answer: The endpoints were carefully defined.

Question14: Statistical analysis: please describe how you did the subgroup analysis and the stratification you mention later on in the results section.

Answer: We have described how we did the subgroup analysis and the stratification analysis in the Methods section.

## RESULTS:

Question15: A second table summarizing the study finding needs to be added. At the moment you only have one table with the table characteristics. Please also include quality scoring for the included studies.

Answer: We have added a table summarizing the study findings in the revised manuscript (Table 1). We have also added the quality score in Supplementary Table 1.

Question16: First paragraph is too long.

Answer: We have now divided the first paragraph into two paragraphs.

Question17: Funnel plots are mentioned but are not included anywhere in the manuscript or the graphs.

Answer: We have added the funnel plot as Figure 3 in the revised manuscript.

Question18: The type of statins was not studied? If not why and if yes what where the results?

Answer: We tried to carry out a subgroup analysis according to statin type. As described in the revised manuscript, of the 22 groups, atorvastatin was used in 8 groups, rosuvastatin in 3 groups, simvastatin in 3 groups, pravastatin in 3 groups, pitavastatin in 1 group, fluvastatin in 1 group, and different statins in 3 groups. Six groups were obtained when groups were stratified by statin type. Unfortunately, in 5 of the 6 subgroups, there was significant heterogeneity. Taking into account the significant heterogeneity in the subgroups, we did not undertake a subgroup analysis by statin type in the present study.

## Discussion

Question19: The whole section needs editing by native speaker.

Answer: The entire section was edited by a very experienced medical editor whose native language is English.

Question20: Commend a bit more on relative literature and on the clinical implications of your research.

Answer: We have rewritten the Discussion section.

Question21: No suggestions for further research are mentioned.

Answer: We have rewritten the Discussion section to describe the implications of our findings for further research.

Question22: Explain the various plaque components and their potential significance on plaque stability. Please expand on this using relevant literature.

Answer: We have explained the various plaque compositions and their potential significance on plaque stability.

Question23: "The results of this meta are robust" please rephrase! The whole 2 paragraphs after that need rewriting.

Answer: "The results of this meta are robust" was deleted and the entire paragraph rewritten.

Question24: The limitation section needs rewriting as well.

Answer: The limitations of our study have been rewritten in the revised manuscript.