Author's response to reviews

Title: Systematic study of the effects of lowering low-density lipoprotein-cholesterol on regression of coronary atherosclerotic plaques using intravascular ultrasound in Western and Asian

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Author's response to reviews: see over
Dear Dr. Marco Pavani,

Thank you very much for your suggestion. We have revised the manuscript according to your comment, and the revised parts were presented in red.

Following are response to your comment:

1.) While the primary end point of this study was the volume change of CAP detected by IVUS, the authors should say if the dosage and percent of LDL-C reduction are considered primary or secondary outcome of their work. In the conclusions they say that "For regressing CAP, Asians need lower dosage of statins or lower intensity LDL-C lowering therapy (by >36%) than Westerns (by 45%) but don't talk about the primary endpoint.

**Answer:** I think that the volume change of CAP detected by IVUS is result, primary end point of this study; and the dosage and percent of LDL-C reduction are measures, not primary or secondary outcome of the study. "For regressing CAP" means the volume change of CAP, the conclusions mean that for the primary end point of this study, the measure for Asian and European is not same.

2.) On page 4 I think that Materials and methods should be better explained.

**Answer:** Materials and Methods include Search strategy and selection criteria, Data extraction and quality assessment, and Data synthesis and analysis. Materials and methods on page 4 is only a brief.

3.) In the selection criteria of the study the authors don't say in the text how they have included 18 trials (line 86). Furthermore in line 66-67 the various groups are not very clearly specified.

**Answer:** After fully reviewing the 20 article, 18 trials cited by the 20 articles were included, and the sentence (line 86) was changed to “the text 20 articles were reviewed in full text, resulting in exclusion of 10 trials and inclusion of 18 additional trials cited by the 20 articles”(the last paragraph of page 6).

The various groups in line 66-67 were detailed in the paper (BMC Cardiovasc Disord 2014; 14:60). In revised manuscript a reference [3] was added after groups (the last paragraph of page 5).

4.) On page six. last paragraph, when the authors write "as in the study (3).......", I think it should be difficult to understand the authors' message.

**Answer:** as in the study (3) suggests a reference for the selection of trials. In revised manuscript, as in the study [3] was deleted (the last paragraph of page 6).
5.) I've not understand how they explain that sensitivity analyses about LDL-C lowering in group >70#100HP mg/dL could lead to regression of CAP with reduction of the CAP volume when the arm of 2009 JAPAN-ACS Ato was omitted and also when the arm of 2009 COSMOS Ros was omitted, but that LDL-C lowering in group#70 mg/dL could not significantly lead to regression of CAP with reduction of the CAP volume when the arm of 2012 ARTMAP Ros or 2012 ARTMAP Ato were omitted?

**Answer:** This is a sensitivity analyses method of STATA statistical analyses. If one of the included trials was omitted, the result of meta-analysis was not changed, which indicated the sensitivity is good. Otherwise, sensitivity is bad.

The result of sensitivity analysis that LDL-C lowering in group >70<100HP mg/dL could lead to regression of CAP with reduction of the CAP volume when the arm of 2009 JAPAN-ACS Ato was omitted is good; that LDL-C lowering in group#70 mg/dL could not significantly lead to regression of CAP with reduction of the CAP volume when the arm of 2012 ARTMAP Ros or 2012 ARTMAP Ato were omitted is bad.

In revised manuscript, the sentence in line77-79 of page 6 was changed to “Sensitivity analyses (exclusion of one study at one time) were performed to determine the stability of the results” (The second paragraph).

6.) I've found (like they have in part analysed in the study limitations ) that different follow up between the various works and especially between western and asian studies (are we sure that late follow-up works the same as for asian people? ), as well as different type of statins and dosage (although considering statin class effect ) are important limits of this meta-analysis.

**Answer:** The difference of follow up period between Asian and Western may influence the result. Different type of statins and different dosage may also have influence the result. The follow up period in Asian was shorter than in Western, and low dosage of statins in Asian can regress CAP, as high dosage of statins in Western can do. So, the difference of follow up period and dosage does not influence our conclusion that for regressing CAP, Asians need lower dosage of statins.

7.) Most of the studies are conducted only in CAD people; should we consider it a bias?

**Answer:** CAP (coronary atherosclerotic plaques) is a mark of CAD, this study mainly investigated CAP change. So, the studies are conducted in CAD people, I don’t think it is a bias.

8.) In the discussion, the authors should try to explain why statins do not have a class effect in their meta-analysis, if there are other possible factor that could influence the results (like different lifestile, different diet or other conditions).

**Answer:** This meta-analysis investigated the class effect (lowering LDL-C) of statins on Asian and European. LDL-C level may be influenced by other factors, such as, lifestyle, diet. Those factors were controlled before statins administration in beginning
each trial. So, those factors have little effect on the results.

9.) In the discussion, pages 13, first paragraph, the authors should try to better describe which tables the data are related to. 

The main purpose of this meta-analysis has been previously evaluated by other study in literature, also taken in account by the authors in the Discussion (study 32,33), so I don't think it's a original question posed by the authors.

Answer: we added the table 3, 4 in that paragraph in revised manuscript (the last paragraph of page 13).

Study 32 (Am J Ther 2012; 19:164-73) investigated whether there is a differing pattern of systemic exposure to atorvastatin in Asian versus Caucasian subjects by comparison of data obtained from completed pharmacokinetic studies, study 32 demonstrated no differences in the systemic exposure to atorvastatin between Asian and Caucasian subjects;

Study 33 (Acta Pharmacol Sin 2011; 32:116-25) evaluated race differences in the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients using a population pharmacodynamic model generated and validated using published clinical efficacy trials, and study 33 also did not confirm that there was significant difference in the exposure-response relationship for LDL-C reduction between Westerners and Asians.

Our study demonstrated that LDL-C lowering therapy has a different effect on atherosclerotic plaque between Westerns and Asians: for regressing CAP, Asians need lower dosage of statins or lower intensity LDL-C lowering therapy than Westerns.

If the revised manuscript needs further revision, would you please let us know as soon as possible.

Best wishes,

Li YF, Feng QZ, Gao WQ, Huang Y, and Chen YD.
Dear Dr. Salma Esmaeil,

Thank you very much for your suggestion.

Following are response to your comment:

This is a great work, but just a major comment the statistics is very complicated in writing, it should be made simpler.

Answer: thank you very much for your very good suggestion. This study included many data, we provided all of them for reader reference.

If the revised manuscript needs further revision, would you please let us know as soon as possible.

Best wishes,

Li YF, Feng QZ, Gao WQ, Huang Y, and Chen YD.
Dear Dr. Flavia Ballocca,

Thank you for your suggestion. We have revised the manuscript according to your comment, and the revised parts were presented in red.

Following are response to your comment:

Answer the ”Major compulsory revision”
“In the results however these groups are reported for Western, but for Asian the groups are only ≤70, >70≤100 HP and >100 mg/dL”. What is the reason for this difference?
General speaking, according to the levels of LDL-C at follow-up, the arms were grouped to following groups: ≤70, >70≤100 HP, >70≤100 MP, >70≤100 LP, >100 mg/dL. But in Asian group, the level of LDL-C at follow up was not in the range of >70≤100 MP and >70≤100 LP, so, for Asian the groups there are only ≤70, >70≤100 HP and >100 mg/dL.

Answer the “Minor Essential Revisions”
The “to identify the different targets of LDL-C that result in the regression of the CAP for Western and Asian” has been corrected to “identified the different targets of LDL-C that result in the regression of the CAP for Western and Asian”

If the revised manuscript needs further revision, would you please let us know as soon as possible.

Best wishes,

Li YF, Feng QZ, Gao WQ, Huang Y, and Chen YD.
Dear Dr. Alicia Quirós,

Thank you very much for your suggestion. We have revised the manuscript according to your comment, and the revised parts were presented in red.

Following are response to your comment:

Discretionary Revisions
1. In the title, use 'systematic review' instead of 'systematic study'
   **Answer:** The title was changed to “The difference between Asian and Western in the effect of LDL-C lowering therapy on coronary atherosclerotic plaque: a systematic study”
2. When citing references, please do it in order
   **Answer:** OK.
3. In line 106, it is the first time that CHD appear, please define
   **Answer:** we added the full name of CHD in revised manuscript (the second paragraph of page 7).
4. Please use alphabetical ordering in the list of abbreviations
   **Answer:** we rearranged the list of abbreviations according to alphabetical order in revised manuscript (on page 18).
5. The manuscript would benefit from a careful review of the written English

 Minor Essential Revisions
1. According to [A], the I2 suffers the same problem as the Q test in terms of statistical power, especially with a small number of studies (k<20). Please report I2 statistic value and CI.
   **Answer:** all I2 equal to zero, see Table 3.
2. No quality assessment is reported. Has the methodological quality of the studies been checked?
   **Answer:** quality assessment of all trials was evaluated with Jadad quality scale, the results of bias risk of included trials is same to meta-analysis published in *BMC Cardiovasc Disord* 2014; **14**:60. So, the report was not presented in this paper, but reference[3] was presented (See the last paragraph of page 7).
   The sentence “Quality assessments of trials were evaluated with Jadad quality scale.” was added in the second paragraph of page 5 in the revised manuscript.
3. Heterogeneity has been properly investigated in each subgroup analysis although I missed a global heterogeneity check. Would it be possible to get a funnel plot? This can be added in line 110.
**Answer:** It is possible to get a funnel plot. But in this meta-analysis, the publication bias was assessed using the Egger regression asymmetry test (see last column Tab.3), no using funnel plot which is similar function to Egger regression asymmetry test.


Mayor Compulsory Revisions
1. Research question: The research question as it is posed at the end of the Background section is divided into two questions and the therapy is used as a general term although the type and dose is studied in the results section. I would recommend the authors to expand this paragraph so that the research question is clearly stated. Besides, it should match with the ideas outlined in the conclusions section. As stated in [B], a well-framed clinical question must include a population, intervention, comparator and outcome, as well as design.

**Answer:** Both investigating the difference between Western and Asian in the effect of LDL-C lowering therapy on the progression of the CAP and identifying the different targets of LDL-C that result in the regression of the CAP for Western and Asian are to explorer the difference between Western and Asian in the effect of LDL-C lowering therapy on CAP. The former was focused on statins, the latter focused on LDL-C levels. These two questions are two aspects of main research question: the difference between Western and Asian in the effect of LDL-C lowering therapy on CAP.

2. Methodology and study design: A comparison between groups is not considered although it is the main goal of the article… The conclusion may not be valid. The statistical method for the assessment of the difference between Asian and Western populations is not stated in the part devoted to describe the methods. The results shown are not sufficient (and do not seem to support) the main conclusion: 'There was a different effect of LDL-C lowering on CAP between Westerns and Asians'. How did you compare the effect between the two populations?

**Answer:** yes, no statistical method was used for the assessment of the difference between Asian and Western populations. There is no statistical method which can be used for comparison between the results of two meta-analyses.

In revised manuscript comparison between Western and Asian in using statins was added (See the third paragraph of page 6, the first paragraph of page 13, the second paragraph of page 16). Table 7 was added in revised manuscript.

Finding the difference between Asian and Western by meta-analysis is the main goal of this study. We presented the difference between Asian and Western in the effect of LDL-C lowering therapy on CAP by results of meta-analysis: in groups <70mg both of Asian and Western, the meta-analysis showed that LDL-C lowering by respective 47.2%, 49.4% can regress CAP. In groups >70≤100HPmg, the meta-analysis showed that only in Asian LDL-C lowering by 36.1% can regress CAP, LDL-C lowering by 43.2% in Western cannot regress CAP; In groups>30≤40%, the
meta-analysis showed that only in Asian LDL-C lowering by 36.0% can regress CAP, LDL-C lowering by 37.0% in Western cannot regress CAP (Table 3, 4). It was concluded that there was a different effect of LDL-C lowering on CAP between Westerns and Asians.

3. Confounders: Could follow-up duration be a confounder? It is clearly associated to race and the authors affirm that treatment duration might have some effect on CAP regression. Make sure there are no other confounders. The last conclusion of the abstract could be a spurious conclusion, taking into account that there might be confounding factors related to the mentioned difference, such as associated BMI or difference in clinical practice/guidelines.

**Answer:** Yes, the follow-up duration might have some effect on CAP regression, but has little on the meta-analysis of subgroup. The follow up duration in Asian was shorter than in Western, and low dosage of statins in Asian in short time can regress CAP, as high dosage of statins in Western can do in a long time. So, the difference of follow up duration hardly influences our conclusion that there was a different effect of LDL-C lowering on CAP between Westerns and Asians, and for regressing CAP, Asians need lower dosage of statins.

BMI might influence statins dosage. Generally speaking, BMI of Asian is smaller than Western, so, Asian need lower dosage of statins to regress CAP, this meta-analysis provided the evidence for Asian to treat coronary artery disease with statins. Asian should have their own guideline of using statins, and Asian doctor might not practise according to the guideline of European or American.

4. Clinical relevance of the results: Are the reductions reported clinically relevant? Statistical significance does not mean clinical relevance.

**Answer:** The results have an important clinical meaning, and suggest that Asians need lower dosage of statins or lower intensity LDL-C lowering therapy than Westerns for regressing CAP to prevention of coronary artery disease.

5. Contribution: Most of the results reported are equal to the ones reported in [3. BMC Cardiovasc Disord 2014; 14:60]. It is not clear to me the added contribution of this article to the results reported in [3. BMC Cardiovasc Disord 2014; 14:60].

**Answer:** We added new information in this meta-analysis. Trials included in this meta-analysis were same to those reported in [3. BMC Cardiovasc Disord 2014; 14:60], and most of the results in this meta-analysis are similar to those reported in [3. BMC Cardiovasc Disord 2014; 14:60], but not the same. This meta-analysis was paid attention to the difference between Asian and European, which is lack in the report in [3. BMC Cardiovasc Disord 2014; 14:60].

If the revised manuscript needs further revision, would you please let us know as soon as possible.

Best wishes,

Li YF, Feng QZ, Gao WQ, Huang Y, and Chen YD.