Author's response to reviews

Title: The association of hypertriglyceridemia with cardiovascular events and pancreatitis: A systematic review and meta-analysis

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Version: 2 Date: 2 March 2012

Author's response to reviews: see over
Dear Editor,
We thank you for reviewing our manuscript. We also acknowledge the feedback of the referees that will hopefully make this manuscript better and more appropriate for the readership.

We acknowledged all reviewers’ concerns and revised the manuscript. We look forward to hear from you.

MH Murad and co-authors

Reviewer #1
Reviewer: Mitra Mahdavi-Mazdeh
Comment: The authors explained the methodology and also the limitations of their study which are completely correct.
Reply: We thank reviewer #1 for evaluating our manuscript and endorsing it.

Reviewer #2
Reviewer: Yau-Jiunn Lee

Major:
1. The advantage of meta-analysis is to resolve controversial clinical issues by pooling the results of relevant studies. However, based on current literature, it is already known that hypertriglyceridemia is a risk factor to acute pancreatitis. That, to performing a meta-analysis to the topic of association between hypertriglyceridemia and acute pancreatitis was not reasonable and the author also did not make a thesis to this issue in the article. In addition, only one article was suitable for inclusion to investigate the association between hypertriglyceridemia and pancreatitis. Based on the above facts, the author should reconsider the rationale of discussing the issue of association between hypertriglyceridemia and acute pancreatitis.

Reply: We thank reviewer #2 for taking the time to review our manuscript. The reviewer makes the argument that we should omit the evaluation of HTG association with acute pancreatitis because it is known. In reply, we have several reasons to keep this evaluation:

1. The association between HTG and pancreatitis is not settled. The fact that we only have one controlled study underscores this fact. Please note that the association of severe HTG and pancreatitis has been shown in several uncontrolled case series; however, associations with less severe HTG remain unclear.
2. Omitting the evaluation and extensive literature review that we did might be considered a form of publication bias. I think to be explicit and clear, we should present the fact that we only found one study. Therefore, we prefer to keep the acute pancreatitis as an outcome in this systematic review (although this might be an editorial decision and we would delete that outcome if the editor request that). In the revised manuscript, we added more references to the rationale for investigating pancreatitis.

2. The highlight of this study is that the author concluded hypertriglyceridemia was associated with cardiovascular mortality, myocardial infarction and cardiovascular events. In 2007, Sarwar et al. performed a meta-analysis study and found that there was a significant association between triglyceride values and coronary heart disease risk by pooling 29 prospective studies (Circulation. 2007;115:450-458.). Furthermore, Sarwar et al. nicely performed subgroup analyses (grouped by study size, location, population source, duration of follow up, gender, fasting or non-fasting status, analytic methods and HDL-C adjustment) and confirmed the consequence between hypertriglyceridemia and CVD. The results of current article may hardly provide further clinical information.

Reply:
We thank the reviewer for identifying this meta-analysis by Sarwar. In the revised manuscript, we cite this reference. The reviewer is concerned about the fact that the results of our systematic review and meta-analysis are consistent with those of previous reports and therefore, perhaps we didn’t need to do our study. In reply, we provide this counter argument:

1. Please note that although the paper by Sarwar includes a meta-analysis, it is not a systematic review. The focus of that paper was about 2 large observational studies (the Reykjavik and the EPIC-Norfolk studies).
2. It is unclear how or when they searched the literature, but the paper was published in 2008 and submitted to Circulation in 2006. Hence, their literature search must have been before 2006. This means that we are updating the evidence base by at least 6 subsequent years.
3. The fact that our conclusions are consistent to theirs is not a reason to underestimate the value of our work. In fact, having multiple consistent studies is the hallmark of biomedical research. We believe that the consistency of findings should be reassuring and should be presented to evidence consumers.
4. Lastly, the association of HTG and CV risk is not fully settled and remains under debate. Please recognize that a group of experts on the topic (the taskforce of the management of hypertriglyceridemia from the Endocrine Society) is the one who requested, commissioned and funded this review (as we stated in the acknowledgment section of the manuscript).
Therefore, there is a desire of endocrinologists for updated and continuous evaluation of the evidence supporting this association.

Since reviewer 2 brought this issue up, we made revisions in the manuscript to:
1) cite and describe the Sarwar study, 2) highlight the argument for the need of this current evaluation and 3) highlight the origin of the idea (being requested and funded by the endocrine society, which was previously only mentioned as an acknowledgment; however, now we added that statement to the methods section).

3. Obviously, authors did not review the literature extensively, and the 1st paragraph on page 10 describes the strength of current study needed to be revised.

Reply:
Revisions to the strengths section were made as recommended.

Minor:
1. The section of “Introduction” should be reconstructed. In the article, it is hardly to realize the background of performing a meta-analysis to their interested issues (i.e. CVD and pancreatitis). Author mainly discussed the epidemiology, definitions of hypertriglyceridemia across past 20 years and management of hypertriglyceridemia, the detailed controversies and arguments of hypertriglyceridemia in association to the risk of CVD and pancreatitis were lacking. Rewrite this section is required to help readers to understand the rationale of current study.

Reply:
We agree. Revisions to the introduction section made as recommended.

2. The figure of forest plot is difficult to read. The author could make figures of investigated disease separately, instead presented their result as a single figure.

Reply:
We agree. Revisions to the figures made as recommended. Now, each outcome is presented in its own figure depicting its own forest plot.

3. The paragraph of “Result” is too simplified. Please provide detailed information of each analysis (e.g. number of studies included, case number). Moreover, although there were non-significant results, the illustration of subgroup analysis (Table 3) should be provided.

Reply:
We agree. Revisions to the Results section made as recommended.
4. The section of “discussion” should be revised. The most paragraphs were not relevant to the findings of present article, especially in the subsection of “implications”.

Reply:
We agree. Revisions to the discussion section made as recommended.