Author's response to reviews

Title: The Influence of Gender on the Effects of Aspirin In Preventing Myocardial Infarction

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Author's response to reviews: see over
Response to Reviewers

Many thanks for the very helpful comments of the reviewers. Their comments were helpful in improving the quality of the manuscript. In a point-by-point format, we have provided the responses to the reviewers’ comments.

Reviewer: Gregory Lip

1. Is the search rather limited to PubMed only? What about other important databases e.g. EMBASE, etc.

Our main search engine was PubMed, which was complemented by previous reviews by Weisman (2002), Hayden (2002), Kong (2002), and the Antithrombotic Trialists’ Collaboration (2002) and with EMBASE. EMBASE did not contribute any other citations. We have explicitly stated this on page 4 line 7 to 11 and page 6 line 2.

2. Clarify if non-English literature also searched. State this in the text.

The search was limited to English publications. Please see Page 4, line 6-7.

3. Make more comments on quality of data/studies.

To ensure acceptable data quality, we did the following:

1. We included only those randomized controlled trials that had a Jadad score of 3 or greater and
2. excluded studies that did not have a placebo arm, or had a very short follow-up period (less than 3 months), or co-administered aspirin with another agent, or had very few MI events (fewer than 10).

In the revised text, we have made the inclusion and exclusion criteria more explicit (see page 4 lines 15 to 21).

4. Any information on time course of events? The benefit of aspirin on post-MI seem to be most noted in the early period (eg 30 days) with little benefit afterwards on mortality. A comment is needed here.

Unfortunately, we did not have access to the primary data and as such we could not determine the time course of events. This is an important question that requires additional studies in the future (perhaps a pooled analysis) to address.

5. What about other trials with atrial fibrillation that used aspirin eg AFASAK, PATAF, SAFT etc.
AFASAK-1 was included in the current meta-analysis. AFASAK-2 however was excluded because it did not contain a placebo arm. Similarly, PATAF was excluded because it did not have a placebo arm, while SAFT was excluded because it did not report on MIs and did not have a placebo arm for comparison.

6. *Typo in Table.*

We corrected the typo and re-formatted the Table. Please see Page 16, Table 1.
Reviewer: Daniel Hackam

Major compulsory revisions

...The authors discuss further the implications of their findings-in particular for clinical care. It is unlikely that we will be screening for ASA resistance any time soon in routine practice—would the authors recommend wide use of alternative anti-platelet agents (e.g. plavix, dipyridamole-ASA) in women?

The reviewer raises an interesting and provocative idea that perhaps other antiplatelet agents may be more effective in females. However, to our knowledge, there has been no large scale randomized controlled trials that have evaluated these agents in women (as compared with aspirin). Until such studies are done, it would be presumptuous to recommend other antiplatelet agents for women.

We do agree that more text is needed regarding this subject in the discussion section of the manuscript. Accordingly, in the revised text, we now state that “our findings in the context of the emerging literature regarding possible aspirin resistance in women suggest that clinicians should be cautious in prescribing aspirin in women especially for primary prevention. Whether or not other anti-platelet agents would be more effective for women is unclear. Future clinical studies specifically powered to evaluate sex-specific end points will be needed to determine whether other anti-platelet agents may be more effective in women compared with aspirin.” (see page 9 lines 2 to 8).

Minor Essential Revisions

1. In the last line of the Result section of the abstract, it would be helpful to insert risk reduction in the trials that predominantly included women, to compare with the risk ratio that author have put there for men.

Thank you for the suggestion. In the revised text, we have inserted these data in the abstract (Please see Page 2, lines 20-21).

2. First line, Introduction, Page 3, Thus I would change the “40%” to “50%” and cite VACS here.

We have modified the text according to reviewer’s suggestion. Please see Page 3, line 5.

3. Page 8, the term “belying” should be changed to “underlying”…

We have modified the text according to reviewer’s suggestion. Please see Page 8, line 17.
4. On page 15, Juul-Moller study, the word “Chronic” should be lowercase.

We have modified the text according to reviewer’s suggestion. Please see Page 16, line 16.