Author's response to reviews

Title: Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials

Authors:

Liu Xue-Hui (liuxuehui0928@sina.cn)
Xu Chun-Yan (514977907@qq.com)
Fan Guang-Hui (fanguanghui59@163.com)

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Author's response to reviews: see over
Re: Manuscript Number: 291077131140805; Title: Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials; Authors: Xue-Hui Liu, Chun-Yan Xu, Guang-Hui Fan

Dear Ms Cruz,

Thank you very much for your letter of 8 March 2014 inviting us to submit a revised version of the above-mentioned manuscript. We have studied the Editor’s and reviewers’ suggestions carefully and have made revision which marked in red in the paper. We also responded point by point to the Editor’s and reviewers’ comments as listed below. About the English writing of the manuscript, we ask for an expert to revise the paper before it was submitted to the magazine and this time we do not know whether it has reached to your magazine's standard. We hope that the revised manuscript is acceptable for publication.

Thank you very much for your continued attention.

Looking forward to hearing from you.

Yours sincerely,

Liu Xuehui

Below are our specific responses to the Editor’s and reviewers’ comments.

**Responses to Editor**

**Comments:** The reviewers believe this meta-analysis warrants publication in the journal. However, several items need to be addressed before it is suitable for publication, including having the manuscript proofread by someone with proficiency in scientific English writing, as well as addressing some methodological concerns which would strengthen the quality of the meta-analysis.

**Responses:** Thank you very much for your valuable and constructive comments. According to Editor’s and reviewers’ comments, we have made thorough editorial corrections in the revised version and proofread the entire manuscript with the help of an expert in English scientific writing. To get more potential information that would strengthen the quality of the meta-analysis, we have contacted the relevant authors via emails. Unfortunately, only one author replied to us up to 27 March 2014. His letter, however, can not provide data regarding this meta-analysis. In addition, we have made corresponding changes that could improve the external validity of the meta-analysis in the abstract and discussion.
Responses to Dr. Louis-Mathieu M Stevens

Comment 1: I believe this manuscript should be published, but a throughout revision by an expert in English scientific writing should be completed before publication.

Response 1: Thank you very much for your positive and constructive comments and suggestions. According to reviewer’s suggestions, we have made thorough editorial corrections in the revised version with the help of an expert in English scientific writing.

Comment 2: It is said that 15 studies were excluded since “they did not evaluate POAF as an outcome”- I would strongly encourage the authors of this meta-analysis to contact the authors of these excluded trial to see if this data is available even if not published.

Response 2: It is just as the reviewer said that we did not contact the authors of these studies to see whether these authors treated POAF as a clinical outcome in their trials. After receiving reviewer’s comments, we have contacted the authors of these studies via email to try to get more potential data. Unfortunately, up to 27 March 2014, two emails were rejected by system automatically, and only one author replied to us. He wrote in the letter that he did not track atrial fibrillation in his trial (Figure 1).

Figure 1 A author’s letter
I did not track atrial fibrillation in my trial. Sorry. Why do you think that NAC will affect this?
Linda Barr

Comment 3: Also, it seems that no authors of the 10 included studies were contacted to inquire about unreported “method of AF assessment”, “definition of AF”, or unreported secondary outcome including ICU and hospital length of stay. I would also strongly suggest the authors to contact the PI of these 10 studies with a limited set of questions in addition to the 15 excluded trials.

Response 3: We agree with the reviewer and we have also contacted these authors via email. However, we only received one letter which replied by system automatically. Hence, we are unable to provide additional information about “method of AF assessment”, “definition of AF” or secondary outcome in the revised manuscript.

Comment 4: There are several typo “Tabled”, “NCA”, “Stains”.

Response 4: We are sorry for these spelling errors. We have checked the entire manuscript for spelling errors and corrected it in the revised version.
**Comment 5**: In Table 1, CLD and COPD describe the same pathophysiology and could all be reported as CLD. ACEI/ARB and “RAI” is the same medication – change “RAI” to “ACEI”.

**Response 5**: We very agree with the reviewer’s suggestions that using CLD report both CLD and COPD, and changing “RAI” to “ACEI” in the Table 1. These changes have been done in the revised version.

**Comment 6**: Please add the figure of the subgroup analysis of studies with short-term NAC vs long-term NAC.

**Response 6**: According to reviewer’s suggestions, we have added the two figures in the revised manuscript.

**Comment 7**: Format all p-values with the same number of decimal (I would recommend p-values with 3 decimals everywhere—if the p-values is 0.0004, simply report <0.001)

**Response 7**: This has been done by us in the revised manuscript according to reviewer’s recommendation.

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**Responses to Dr. Frederic Jacques**

**Comment 1**: Altogether, few corrections should be performed to make this review article receivable.

**Response 1**: Thanks very much for your suggestions. We have revised the entire manuscript with the help of an expert in English scientific writing according to reviewer’s comments.

**Comment 2**: Overall, the manuscript is well written and well organized. The question is well defined, the data is as sound as the available literature on the subject, the title and abstracts are appropriate. The methodology section is well described. However, not being a statistician myself, the details of the validity of the statistical analyses should undergo statistical review before accepting the manuscript.

**Response 2**: Thank you very much for your positive and constructive comments and suggestions. We have reviewed the statistical analyses again with the help of our colleague who has rich experience in conducting meta-analysis. In addition, we have contacted some authors of relevant studies to get more significant data that would strengthen the quality of the meta-analysis. Unfortunately, we are fail to obtain additional information regarding this meta-analysis.

**Comment 3**: In addition to that and even though statistics support the conclusion, the
message should be changed to improve the external validity of the paper, or at least its perception.

**Response 3:** We are sorry for the misunderstanding due to unclear descriptions in our previous manuscript. We agree with the reviewer and have made corresponding changes in the abstract and discussion. For example, the sentence (PubMed, Embase and Cochrane Center Register of Controlled Trials were searched from the date of their inception to 1 July 2013 for relevant studies) in “Abstract: Methods” was changed into “PubMed, Embase and Cochrane Center Register of Controlled Trials were searched from the date of their inception to 1 July 2013 for relevant randomized controlled trials, in which NAC was compared with controls for adult patients undergoing cardiac surgery”.

**Comment 4:** More specifically, the message about the reduction of all-cause mortality should be softened given the small number of events. The input of a statistician in that regard might also be of benefit.

**Response 4:** We agree with the reviewer’s suggestion, because all-cause mortality is really a small number of events in both NAC and control group. We have changed the relevant message with the help of our colleague in the discussion. We described that “this meta-analysis demonstrates that prophylactic NAC apparently reduce the incidence of all-cause mortality” in revised version. After changing, it might soften the message about the reduction of all-cause mortality. Whether prophylactic use of NAC could really reduce all-cause mortality needed to be explored in future larger RCTs.

**Comment 5:** In “Results: Identification of eligible studies”, “article” or “manuscript” would be better than “records”. In “Results: Characteristics of eligible studies”, “Male” should not have a capital “M”, “infRAction” should be “infARction”. At the end of the discussion, “potentially” should be “potential”.

**Response 5:** We have made corresponding corrections in the revised version.

**Comment 6:** In “Results: Primary analyses: Incidence of POAF” and in “Discussion”, there are two sentences starting with the word “Despite” that I found hard to understand but it did not seem related to the use of this word.

**Response 6:** Thank for very much for you constructive comments. We have changed these two sentence in the revised version. For example, “Despite a trial enrolled several patients with a prior AF, the pooled outcome did not change obviously without the trial” is replaced by “A trial enrolled some patients with a history of AF, but the pooled results did not change when this trial was excluded”.

**Comment 7:** In “Results: Primary analyses: Incidence of POAF”, “Seven of the 10 included studies (…)” should be “Seven studies (…)” as it was previously stated that the paper was related to the 10 selected studies among the 115 screened.

**Response 7:** In the revised revision, we have made corresponding editorial changes.
Comment 8: The paper would benefit from eradicating subjective words such as “well”, “novel” or “encouraging”, and also from eliminating unnecessary “the” or “a” at various places.
Response 8: We have deleted these words in the revised version.

Comment 9: Authors should simplify long sentences that do not add valuable information. For example, the phrase “Recently, a published trial, the largest sample size of its kind, demonstrated(...)” would be simpler to understand written “Recently, a large trial demonstrated (...)”
Response 9: Thanks very much for your valuable comments. According to your suggestions, we have simplified these long sentences that do not add valuable information in the revised version.

Comment 10: The use of the words “half” or “the rest” should all be replaced by numbers.
Response 10: In the revised version, we have made correction according to your suggestions.