Author’s response to reviews

Title: Beta-blockers for the primary prevention of anthracycline-induced cardiotoxicity: a meta-analysis of randomized controlled trials

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Author’s response to reviews:

Response to Reviewer 1 (Tao Zhan)

Comment 1: The manuscript's purpose is to evaluate the overall beta-blockers' preventive effect against anthracycline-related cardiotoxicity. It is indeed a question that oncologists would discuss frequently in clinical practice. However, the beta-blocker family has many members, their cardioprotective effects should be analyzed in more specific and quantitative ways. Therefore, meta-analysis of individual beta-blockers would be more justified in terms of methodology in evidence-based medicine.

Reply 1: Because randomized controlled trials showed that carvedilol [1-3], metoprolol [4], and nebivolol [5] all prevented anthracycline-induced cardiotoxicity and we wanted to explore the effects of β blockers and see big picture. Therefore, we included all of these three β blockers in the main analysis. Of course, meta-analysis of individual beta-blocker was important. Thus, we
did the substudy to explore the effects of carvedilol and metoprolol, respectively. (see Results section, line 1-16, page 12.)

Comment 2: Quality assessment is a very essential process before the data pooling is carried out in a meta-analysis. The authors are advised to present more details of quality assessment in the article and, if possible, utilize it in the process of data pooling and further discussion. For example, results of data pooling of studies with different quality grades would be of significantly bias due to the quality heterogeneity.

Reply 2: As the reviewer said, quality assessment was very important. Thus, we used Cochrane collaboration’s tool for assessing risk of bias to assess the quality, which was recommended in Cochrane Handbook for Systematic Reviews of Interventions (version 5.2). The reviewer was right and we should present the details of quality assessment which will help readers understand this meta-analysis. We added the details in the manuscript.

Change in text: Methods section, line 17-19, page 7.

Comment 3: The use of random-effect model is justified only on the basis of ruling out major clinical heterogeneity. We have to admit that clinical heterogeneity is "clinical" and will not be solved by any statistical model. (see line 13-15, page 8). If the data pooling is applicable with the \( I^2 < 50\% \), the fixed-effect model should be utilized to improve the statistical power.

Reply 3: Because of differences in length of follow-up and study participants, some authors [6-8] used random-effect model to rule out heterogeneity. In this meta-analysis, length of follow-up and study participants were not completely consistent and heterogeneity was anticipated. So we chose random-effect model in this analysis. The writing was misleading. We corrected it.

Change in text: Methods section, line 19-20, page 8.

Comment 4: There's difference on the definition of symptomatic heart failure among the included studies, which can also increase the heterogeneity. I suggest the authors explain more about why they still pooled the data of this outcome in the discussion part.

Reply 4: We read the included studies which reported heart failure events and we though the definition of symptomatic heart failure was the same in these 5 trials. So we used this word.
Comment 5: Publications presented in conferences should not be excluded unless they are reduplicative of reports published in journals.

Reply 5: In fact, it’s controversial whether we should include publications presented in conferences or not. There is no specific recommendation in Cochrane Handbook for Systematic Reviews of Interventions (version 5.2). Some experts preferred to include conference paper and some experts wanted to exclude them. Because it’s difficult to assess the quality of the conference paper and the data were limited, we chose to exclude them.

Comment 6: The limitations of the systematic review are very significant. It's not appropriate to conclude that beta-blockers are effective and safe as prophylactic agents against anthracycline-related cardiotoxicity.

Reply 6: After getting the comment from the reviewer, we thought the conclusion was not appropriate. Thus, we deleted it in abstract and changed our words.

Change in text: Abstract section, line 4-5, page 4; Conclusion section, line 21-22, page 21.

Comment 7: Meta-analysis is essentially a type of review utilizing more statistical approaches. Nevertheless, if meta-analysis is not applicable on an outcome, we can still try descriptive analysis instead.

Reply 7: We thought this meta-analysis was applicable and it explored an important issue in the clinical practice. We believed it would help oncologists to make the decision. Of course, we should try descriptive analysis in the future because the meta-analysis focuses on just one problem but descriptive analysis is the review for this field.

Comment 8: There are many problems of English writing in the manuscript. The authors are suggested to improve the writing again or have a native speaker to revise the article.

Reply 8: We reviewed this meta-analysis and corrected all the problems that we found and we found a native speaker to help us improve it. Thank you.

Response to Reviewer 2 (Ying-kun Guo)

Comment 1: Results: the quality of the included studies seems too high. I wonder if the items in Cochrane collaboration's tool are truly met in each study. Please clarify. Please check with the
Cochrane collaboration's tool item by item in the included studies. The authors should give more details about the bias in the included studies.

Reply 1: We added the details of Cochrane collaboration's tool. And two independent authors checked the tool item by item and we confirmed the result of quality assessment in our manuscript. And we reported publication bias as the Cochrane Handbook for Systematic Reviews of Interventions (version 5.2) recommendations. (see Results section, line 6-10, page 10)

Change in text: Methods section, line 17-19, page 7.

Comment 2: Methods: a reference should be cited for "I2 was >50%, heterogeneity was considered to exist".

Reply 2: We added the reference. Thank you.

Change in text: Methods section, line 1, page 9.

Comment 3: Methods (Statistical analysis): "These four trials [5, 7, 8, 12] were excluded as a sensitivity analysis." The word "excluded" is quite confusing, please check the sentence and make sure it has expressed what it means.

Reply 3: We checked the sentence and change it.

Change in text: Methods section, line 13, 16, page 9.

Comment 4: Conclusions: one of the conclusions that the authors have drawn is that beta-blockers can alleviate cardiomyocyte injury, but there is no relevant method or result have been mentioned in the article that can come to such a conclusion.

Reply 4: We found that β blockers were associated with lower risk of cTnI elevation >0.04ng/ml and cardiac biomarkers were reliable to detect cardiomyocyte injury. Therefore, we interpreted the results like that. (see Discussion section, line 5-9, page 10)

Comment 5: Conclusions: the authors claim that the beta-blockers are safe with cancer patients. However, this study did not present relevant method or result about the toxicology of beta-blockers in these groups of patients.
Reply 5: We found that there was no marked difference in adverse events (RR 0.94, 95% CI 0.56 to 1.59) between β blockers and placebo. Therefore, we interpreted the results like that. (see Results section, line 3-4, page 12). And one reviewer said “The limitations of the systematic review are very significant. It's not appropriate to conclude that beta-blockers are effective and safe as prophylactic agents against anthracycline-related cardiotoxicity”. So we deleted it and changed words.

Change in text: Abstract section, line 4-5, page 4; Conclusion section, line 22, page 21.

Comment 6: Results: to express participants undergoing carvedilol treatment, the word "receive" should be used instead of "accept".

Reply 6: We changed words.

Change in text: Results section, line 4, page 10.

Comment 7: Please specify the primary end-points and secondary end-points.

Reply 7: We specify the primary end-points and secondary end-points.

Change in text: Methods section, line 2-14, page 8.

Comment 8: Supplemental Table 1, Characteristics of the included randomized controlled trials, is preferred to be presented in the main text instead of being placed in the Supplemental material, since it contains important information of this study.

Reply 8: We presented the Supplemental Table 1 in the main text

Change in text: Results section, line 8-9, page 10; Supplementary data, page 11-13.

Response to Reviewer 3 (Alessandra Ghigo)

Comment 1: The efficacy of beta blockers in patients diagnosed with anthracycline-induced cardiotoxicity is well documented (Zamorano et al, 2017 - PMID 27565769). Authors should discuss this point more extensively and highlight which is the major novelty of their study, that I presume is the efficacy of beta blocker in a preventive setting. This concept however reads between the lines and should be better emphasized.
Reply 1: We wanted to discuss the effects of beta blockers in the primary prevention. And we made some changes and emphasized it in the discussion.

Change in text: Discussion section, line 3-5, page 14; line 2-5, page 15.

Comment 2: The structure of the manuscript is imbalanced. Results are concise while the discussion is wordy and presents several grammatical errors.

Reply 2: We thought it’s important to get the result and it’s more important to interpret it. So it seemed a little wordy. We deleted some unnecessary words and sentences and corrected grammatical errors.

Comment 3: The structure of the manuscript is imbalanced. Results are concise while the discussion is wordy and presents several grammatical errors.

Reply 3: We thought it’s important to get the result and it’s more important to interpret it. So it seemed a little wordy. We deleted some unnecessary words and sentences, rephased it, and corrected grammatical errors.

Comment 4: Supplementary figure legends should be expanded to contain all the information necessary for a full comprehension of the results at first sight.

Reply 4: We added necessary information in supplementary figure legends.

References


