Author's response to reviews


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Author's response to reviews:

Dear Editors,

I am deeply grateful for the prompt review and the potentially positive initial response to our paper. I, on behalf of all the authors, would like to thank you and the reviewers of Trials for taking the time and effort to review our manuscript. We appreciate the thoughtful and careful comments of the editors and reviewers. Many of the valuable and constructive points that the reviewers pointed out, were well taken by all of the authors. We have tried to address all of the points that the reviewers have raised. The section below provides a point-by-point response to the issues raised by the reviewers. Each comment has been excerpted and addressed in detail with reference made to the locations of any changes in the manuscript. The revised parts in the new manuscript have been underlined for the convenience of the editors and reviewers.
We believe that the changes have significantly improved the quality of our manuscript and we hope that the revised manuscript better meets the standards the journal.

Thanks so much as always.

Sincerely yours,

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Point-by-point response to editor and reviewer comments

Editorial Requests:

Comment #1
Please include a section explaining your trial status. This should follow the Discussion section. The status of the trial at the time of manuscript submission. The journal considers study protocol articles for proposed or ongoing trials provided they have not completed patient recruitment at the time of submission.

Response #1
The trial status has been added to the revised manuscript. At the initial submission, the recruitment was not completed, but since then, we have completed recruitment and are conducting the follow-ups. [page XX line 1-3]

Comment #2
Please include a competing interests section at the end of the manuscript, before the reference list. If the authors have no competing interests, please state: "The authors declare that they have no competing interests."

Response #2
A competing interests section has been added at the end of the manuscript. [page XX line 4-5]

Comment #3
Please include an Authors? Contributions section at the end of the manuscript, before the reference list. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and
coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Response #3
An author contribution section has been added at the end of the manuscript.

[page XX line 6-15]

Comment #4
As your research involves humans please include a statement of ethical approval in the Methods section of the manuscript, including the name if the body which gave approval, with a reference number where appropriate. Any experimental research on humans must be in compliance with the Helsinki Declaration

Response #4
In the methods, section, a statement of ethical approval has been added. [page XIV line 15 – page XV line 1]

Reviewer's comment
In general, it is a well-written, clear summary of the protocol that contains the necessary items.

Comment #1.
My major comments concern the sample size and analysis sections. Because this is a noninferiority trial, I think that more information about the selection of the margins would be helpful. Why was a noninferiority margin of 1.5 chosen? If the rate in the PtCr-ESS rate could be as high as 9.5% (or even more), is that not important? In superiority trials of cardiovascular disease, we are often happy if the new treatment is 20% or 30% better (relative benefit), yet here we would accept a 50% worsening as equivalent. A similar relative (though smaller absolute) difference seems to be used for the TAT/DDAT comparison. For the stent comparison, why was a 2:1 randomization ratio chosen? For both analyses, how will missing data be handled?

Response #1
This is a great comment that was well taken by the authors. I believe that the question can be broken into three parts.

First, regarding the noninferiority margin, we do agree that a non-inferiority margin of 1.5 is quite large in certain situations. However, in stent trials, such margin is often used. For example, in the RESOLUTE All Comers trial (Serruys PW et al. N Engl J Med 2010;363:136-46), the noninferiority margin was 1.44 (absolute noninferiority margin of 3.5% with assumed primary endpoint rate of 8%). This trial tested the Endeavor Resolute stent against the Xience V stent and the assumed event rate for both stents was 8% with a 3.5% noninferiority margin. In the present study we used a tighter assumption. We assumed that the primary endpoint rate for the stent comparison would be 6.5% (since event rates are conventionally lower in Korean patients) with a 3.25% non-inferiority margin. Another example is the PLATINUM trial (Stone GW et al. J Am Coll Cardiolo 2011:57(16):1700-8), which compared the Promus Element stent with the Xience
V stent. In this trial the noninferiority margin was also 3.5% (same as the RESOLUTE All Comers trial). Therefore we believe that the 3.25% margin that we assumed for the stent comparison was reasonable compared with other well-known stent trials that used the noninferiority design.

Second, regarding the sampling ratio of 2:1 for the stent randomization, this method was chosen because the PtCr-EES is the newest stent in the market. There is very limited data on how this stent performs. The only other randomized data regarding the PtCr-EES was the PLATINUM trial where only 762 patients were randomized to the PtCr-EES arm. We wanted to have as many patients as possible who would be randomized to the newer stent [PtCr-EES]. The first two issues have been added to the discussion section. [page XVI line 15 – page XVII line 2]

Third is the issue of how missing data will be handled. There are various methods of handling missing data including, multiple imputation, maximal likelihood estimation, or mean substitution. For our study, we will use the multiple imputation method. [page XIII line 10]

Comment #2
Two more minor comments:
i) Because of the many abbreviations and acronyms, it would help to have a table at the back of all of them.
ii) On page X, third line from the bottom: The middle “e” in “treatment” should be deleted.

Response #2
As the reviewer recommended, we have added a list of abbreviations and acronyms at the end of the article [page XXII – page XXIII]. The typo has been corrected. We apologize for the mistake.