

## Format for ANSWERING REVIEWERS

28th May 2015



Dear Editor,

Please find enclosed the edited manuscript in the attached word file.

**Title:** "Challenging aspects of treatment strategies in heart failure with preserved ejection fraction – “Why did recent clinical trials fail?””

**Authors list:** Peter Moritz Becher, Nina Fluschnik, Stefan Blankenberg, Dirk Westermann

**Name of Journal:** *World Journal of Cardiology*

**ESPS Manuscript NO:** 18233

The manuscript has been improved according to the suggestions of reviewers:

### **Reviewer 1:**

*This is a pertinent review of a topic that continues to evolve. However, the authors have done a nice job assembling content that is currently up to date. Some grammatical editing is required but otherwise most comments should only require minor editing or additions. Throughout manuscript - please re-format for proper paragraphs. There are so many isolated sentences and short paragraphs that should be combined. Nebivolol - nebivolol itself would possibly confer additional benefits due to the NO enhancing action of the drug...suggest adding or discussing this mechanism BB summary (just before ref 18) - "absence" should be "absent"; "carefully" should be "careful" ACEi - mechanism for potential benefit is afterload reduction and reduced wall tension, leading to improved diastolic function (hemodynamic effects on ventricular function have not been included in any of the drug class discussions)...suggest adding PEP-CHF - beneficial effect seen early was lost by end of the study (authors only mention the 1y results) CHARM-P - authors should point out that this was not a true HFpEF population (LVEF cut off 40%, and diastolic fx not assessed) ALDO-HF - more detail to be more consistent with other study discussions? DIG Ancillary - 4th sentence, "o" should be "to"; should be mentioned at there was an early benefit with digoxin (as with PEP-CHF) that was lost by the end of follow-up LCZ696 - why was PARADIGM-HF discussed, it does not relate to the topic of HFpEF (should also be removed from the table)*

We thank the reviewer for his very helpful comments to improve the manuscript.

The mentioned grammatical editing and spelling was corrected.

An additional part of discussion of nebivolol's benefits due to the NO enhancing was included.

Possible hemodynamic effects of ACEi and ARBs were also added to its section.

In the section of CHARM-preserved the including criteria as LVEF 40% and the unknown diastolic dysfunction were mentioned and discussed.

A more detailed discussion concerning the ALDO-HF trial was added.

The requested corrections and suggestions were added in the section named „Digitalis Investigation Group (DIG) ancillary trial“.

The PARADIGM-HF (HFpEF) trial was removed from the table and manuscript.

**Reviewer 2:**

*Well-written and analyzed review. Accept as it is.*

We thank the reviewer for the acceptance of the manuscript.

**Reviewer 3:**

*Hengelo, 22 April 2015 Comments on the ESPS Manuscript NO: 18233 With the title: "Challenging aspects of treatment strategies in heart failure with preserved ejection fraction – "Why did recent clinical trials fail?" written by Becher PM, Fluschnik N, Blankenberg S and Westermann D. - This manuscript gives an excellent and detailed exposition on the performed and current trials and studies related to HFpEF. - It conveys a strong message for future trials directions and set-up and sheds light on how the future trials should be designed and conducted. Page 6: Line 10: Please consider "with" instead of "witch". Page 6: Line 19: Please consider "absent" instead of "absence". Page 7: Line 6: Please consider adding "of" between .... effects and beta-blockers ---. Page 10: Line 21: Please consider changing "syndrome" to "symptom". Page 13: Line 18: Please consider omitting the sentence starting with " In this trial the conducted population" Page 16: Line 22: Please consider altering "did not displayed" to "did not display". Page 31: Line 9: Please consider adding "c" to "shema" to become "scheme". References should be displayed according to the requirements of the journal. With best regards, Number ID: 00211908*

We thank the reviewer for his helpful comments to improve the article.

The mentioned sentences have been edited for spelling and grammar mistakes (page 6: line 19; page 7: line 6; page 10: line 21; page 13: line 18; page 16: line 22; page 31: line 9).

We corrected the references according to the requirements of the journal.

**Reviewer 4:**

*This is a good review about preserved HF. Pages numbers should be added. In the ALDO-HF trial, treatment with mineralocorticoid-receptor antagonists decreases renal function. Section about Phosphodiesterase-5 inhibition should be reviewed. Subtitles should be added in many sections. The second part of the summary should be reviewed. That paragraph with focus on LCZ696 is not supported by the preceding argumentation.*

We thank the reviewer for his helpful recommendations, which definitely helped to improve the manuscript.

We added requested page numbers.

We also reviewed and corrected the sections concerning the ALDO-HF trial, phosphodiesterase-5 inhibition, dual angiotensin receptor blocker-neutral endopeptidase inhibitors (PARADIGM trial was removed), and the conclusion/ summary section. In addition, we added subtitles in the several sections.

Thank you for publishing our manuscript in the World Journal of Cardiology.

Yours sincerely,

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