

REPLY TO REVIEWER COMMENTS:

The authors reviewed the effect of concomitant administration of ivabradine and beta-blocker on heart failure. The beneficial effects are limited, but reduction of heart rate is significant and plays a crucial role in treatment of heart failure. Unfortunately, the most important endpoint, cardiovascular or all-cause mortality cannot reach to significant level. The authors described reasons of limited effect in LIMITATION such as difference of target heart rate, hypotension and other bias. The authors cannot show enough evidences of effects of ivabradine in this review, but can suggest necessary factors for further study. The manuscript is worth publication.

Reply:

Thank you for the nice comments on our work.

Reviewer 2:

Thank you for asking me to review this systemic review and meta-analysis o Ivabradine + betablockers (BB) versus BBs alone in the Treatment of Systolic Heart Failure. The authors studied 25,659 patients were included and looked at the primary end point of mean heart rate reduction. On a general note the paper read very well and was clearly written. The main concern that I have is with the methodology. I can't see how you can include the main study and then the substudy which includes patients form the main study again as the patients are being counted twice creating significant bias. I think the BEAUTIFUL SHIFT and the other non-SHIFT and BEAUTIFUL substudies only should be included. The second issue I have is with the primary endpoint that has been used in this paper. Why make the primary endpoint mean heart rate reduction when you are

powered for mortality and other more robust end points? You don't need 25,659 patients to work out that the heart rate reduction is better with ivabradine vs a BB alone and this data adds only little. I think the paper is undersold and would make the primary endpoint as close to the original trials as possible and hence the composite of cardiovascular mortality or HF hospitalization. The second issue I had was with the secondary endpoint which is listed as a combined end point of cardiovascular death and rehospitalization for worsening heart failure. Why is rehospitalisation rather than hospitalization? This would suggest that only patients with a previous hospitalization were included in the analysis yet the inclusion criteria does not state this. A number of additional endpoints were studied but why did the authors not look at Heart failure hospitalization separately as was done in both sHIFT and BEAUTIFUL Studies? There seems to be an important error in the conclusion which states that 'In summary, the results of our systematic review and meta-analysis of the published literature supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of <70 bpm per guidelines however the strength of evidence supporting this recommendation is weak'. Should this not be >70 per minute?

Reply:

Thank you for the thorough review of the paper and thank you for the positive comment on the manuscript, your constructive criticism has helped to increase the strength of the paper tremendously. We understand your concern on the methodology of the paper whether sub groups can be included along with the main studies. We agree that that sub groups are not independent of each other and so we have removed the sub groups from

the analysis.

Thank you for the useful suggestion regarding the choice of primary outcome. We have now changed the primary outcome to combined end point of heart failure hospitalization and cardiovascular mortality. We have reported difference in means in heart rate as a secondary outcome.

We apologize for the error, in some places we used the term 're-hospitalization'. This should have been 'hospitalization', we have changed this throughout the manuscript.

We have also added the outcome namely 'Hospitalizations for Heart Failure', we thank you for the suggestion.

Thank you for pointing out the error in conclusion, we agree that it should be >70 bpm and we have changed this in the manuscript.

Again, we sincerely thank the reviewer for helping to improve the strength of the manuscript. We sincerely hope we addressed all your concerns in the revised manuscript.

Reviewer 3:

A useful and interesting paper that should be published after authors make some changes to ensure the article is clearer, easy to read and not too technical statistically. 1. In abstract and text, risk ratio should be written as RR instead of "Mantel-Haenszel(MH)risk-ratio(RR)". An explanation can be then made in the methodology on how Mantel-Haenszel RR differs from the RR presented in other reports. 2. Table 1 contains too much information and should be better presented. 3. Abbreviations used in figures 6MWD and EF should be explained.

Reply:

Thank you for the review and feedback. We have changed MH RR to RR in the abstract and have explained how MH RR differs from RR. We have modified table 1 to look better, we were able to eliminate one column to make the table look better. We have abbreviated the 6MWD and EF in the figures.