
Dear reviewers:

We appreciate your time, effort and valuable suggestions in reviewing our manuscript. We have incorporated the suggested changes in our revised manuscript. We attached a copy with changes highlighted. Below we provide pointwise response to your comments.

Reviewer: 00227470

Comments to the Author

Thank you for this concise overview of studies on PDE inhibitors in end-stage heart failure. The idea of combining PDE inhibitor with BB therapy is attractive and clinically tried (see Constantinescu et al, Eur J Heart Fail 2014). As the authors correctly point out, more research is needed. I ask the authors to cite the paper I mentioned here and this would be my only comment.

Response:

We have incorporated the suggested reference in revised manuscript (ref no.34)

Reviewer: 00100945

Comments to the Author

Very nice review. A little too long. NO special comment.

Response: We appreciate your encouraging remarks. The manuscript is revised and we have made concise without removing concepts and evidences which we sought out to present.

Reviewer: 00227375**Comments to the Author**

This is an excellent review about the role of phosphodiesterase inhibitors in the management of end-stage heart failure, especially the beneficial effects of combining milrinone infusion and beta-blocker therapy. I have a few minor comments about this manuscript. Please consider the following comments. (Comments) 1. Page 10, lines 2-5 The corrected QT interval was significantly prolonged in the monotherapy group (mean \pm 436 \pm 29 msec before vs 469 \pm 28msec after; $p=0.002$), whereas the interval remained unchanged in the combination group. Most notably, survival at 3 years was 65% higher in the combination group versus the milrinone monotherapy group ($p<0.001$). Judging from the original article, I think the authors probably make a mistake. Correct “436 \pm 29 msec” to “436 \pm 13 msec”. Correct “65%” to “59%”.

Response: We appreciate your time and positive comments. We apologize for the inconvenience. We have made the suggested corrections in our revised manuscript as rightly pointed out by you.

Reviewer: 02445850**Comments to Authors**

The authors reviewed the main studies evaluating the use of milrinone in end-stage heart failure. In particular, they focused on the use of milrinone in order to initiate and titrate b-blockers in advanced heart failure. This is a very attractive option, though prospective randomized controlled clinical trials are needed. We congratulate the authors for the comprehensive examination of the role of PDEI agents in end-stage HF. The second case-report raises some questions. The patient received a CRT device. It can be argued that improving clinical status and left ventricular systolic function during follow-up is due mainly to biventricular stimulation rather than milrinone.

Response: We appreciate your time and encouraging comment. The second case highlights the fact that combination of milrinone and BB therapy is not cardiotoxic and does not counter positive impact of already established heart failure therapy.