

06 June 2013

Dear Editor-in-chief,

Please find enclosed the revised manuscript in Word format (filename: 3646-review.docx). We thank the editorial board of the world journal of cardiology for giving us the opportunity to resubmit our manuscript "Atrial Fibrillation in Heart Failure; the Sword of Damocles Revisited" for publication in the World Journal of Cardiology. We thank the reviewers for their helpful suggestions. We feel that these have significantly improved our manuscript and have detailed a summary of the changes below and tracked all changes in the manuscript.

Title: Atrial Fibrillation in Heart Failure; the Sword of Damocles Revisited.

Authors: Muhammad A. Khan, Fozia Ahmed, Ludwig Neyses, Mamas A. Mamas

Name of Journal: World Journal of Cardiology

ESPS Manuscript No: 3646

RESPONSE TO REVIEWERS' COMMENTS

COMMENTS BY REVIEWER 00227622

1. The authors need to read and cite the paper listed on PubMed and published by Gheorghiade M et al online in the European Heart Journal on April 16, 2013 showing in a propensity analysis of the AFFIRM data published by Whitbeck et al (reference 38) that digoxin does not increase mortality. The patients treated with digoxin in this study were at higher risk for mortality. **DONE p9, lines 9-11.**

COMMENTS BY REVIEWER 00227594

This was a very well written and organized manuscript that provides a comprehensive general review of the topic of AF in HF. It covers all the main aspects that should be addressed when discussing the link between the two conditions. Some detail is left out when discussing each aspect, however, I believe the depth is appropriate for a general review. I have only minor comments and suggestions.

1. General Comments Please check throughout for the use of HF vs spelling out heart failure. The abbreviation can be used throughout. **DONE**
2. There are also several sentences which begin with a number (i.e. page 6, line 1...19%). Please correct these. **DONE**
3. Introduction Consider the addition of a sentence which reports the prevalence of AF by type of HF i.e. is the prevalence similar or not between reduced systolic vs. preserved LVEF HF. This is important since the distribution of hypertension as the etiology will obviously vary. **DONE P.3 2ND PARAGRAPH, LINE 5-7.**
4. Page 3, 2nd paragraph – the reference provided for the prevalence of AF stratified by NYHA FC is incomplete since CONSENSUS only covers the FC IV patients.

Suggest adding in additional references to be more complete i.e. SOLVD-P/T, V-HeFT, CHF-STAT, etc to cover FC I-III. **DONE. The Correct References Have Been Updated. P.3 2ND PARAGRAPH, LINE 8-11.**

5. Impact of AF on Prognosis For this section, I think a table summarizing and stratifying the prognostic effect of AF in HF patients would be very helpful. There are a lot of observational and post-hoc analyses of prospective HF studies which have not been discussed in the text. I don't think all of them need to be discussed, however, an inclusive table would allow the reader to see the varied study populations and hazard ratios for mortality. It would also allow the reader to see that not all studies showed AF was independently associated with increased death (V-HeFT, Crigins et al, DIAMOND substudy) for fair balance. **DONE. Please see Tables 1&2 at the end of the article.** Framingham analysis by Wang et al, was also not discussed in the text, but this is an important analysis of the prognostic effect of AF in HF...consider adding. **Done. Wang et al referenced on p.8 2nd paragraph, lines 1-4**
6. Page 5, 2nd paragraph, line 5 – consider adding the actual numbers for hospital LOS so the reader can assess the magnitude of effect **DONE.**
7. Page 7 – consider adding in a short paragraph to describe the effect of HF on AF prognosis. This review correctly describes the interplay between AF and HF as bidirectional, and thus it would be important to include the reverse aspect of prognostic importance (Miyaska Mayo study, Wang - Framingham, Nieuwlast – Euro Heart) **DONE. P.8 2nd paragraph.**
8. Pharmacologic Therapy Consider adding a brief description of the limited data with calcium channel blockers (i.e. diltiazem) for rate control of AF in HF (Am J Cardiol 1991, 1994 potential references). CCBs are referred to earlier but not discussed. **DONE. P9 lines 11-16.**
9. Page 9, 2nd paragraph, line 5 – consider adding “permanent” to clarify the type of AF patients in the RACE II study. **DONE**
10. Page 9, 2nd paragraph, line 7 – please verify whether only 10% of the RACE II population had HF... I recall that it was closer to 35%? **CORRECTED. p.9 2nd paragraph, lines 7-8.**
11. Page 9, 3rd paragraph, lines 6-8 – this sentence is confusing as written; consider revising “It had an overall effect...” **CORRECTED p10.line3.**
12. Page 9, 3rd paragraph – consider adding in a short discussion of the DIAMOND substudy pooled analysis (Circ2001;104:292-6) **DONE. P10, lines 6-14.**
13. Page 10, 1st paragraph – should state that ANDROMEDA did not include HF pts with AF **DONE.p10,line23.**
14. Page 10, 2nd paragraph – sinus rhythm also associated with better outcomes in DIAMOND post-hoc analysis **DONE.p11, line 18.**
15. Page 12, 1st paragraph, lines 3 and 5 – spell out “twice daily” as the accepted abbreviation is not consistent between countries. **DONE**
16. Future Trends Consider adding a short discussion or mention of the potential role of left atrial appendage occlusion devices. Page 16, **DONE.p17,2nd paragraph.**

We hope that this will enable publication of our manuscript in the World Journal of Cardiology.

Kind Regards

Dr Mamas Mamas