World Journal of Cardiology Editorial Office

RE: Manuscript NO: 42942

MS TITLE: ***"Percutaneous Devices for Left Atrial Appendage Occlusion: A Contemporary Review."***

Dear Editor in Chief,

Enclosed please find our response to the comments of the reviewers on the manuscript cited above. In the letter the comments from reviewers are presented in bold font, while our responses are in regular font. We have attempted to address all comments of the Reviewers comprehensively.

We appreciate the opportunity to re-submit this revised manuscript and hope that our responses and revisions are acceptable to the Editors and Reviewers. We are grateful to the Editors and Reviewers for their helpful and insightful comments and believe that the manuscript has been greatly improved.

Sincerely,

M Chadi Alraies, MD

Reviewer #1:

In general, LAAO is an alternative approach for thromboembolic event prevention in AF. Therefore, I suggest being cautious in using "therapy" (page 2, para 1), "treatment" (page 2, para 3) throughout the manuscript.

The authors agree with this suggestion. We removed the terms "therapy" and "treatment" as recommend by the reviewer #1. We used the term "approach" instead.

Page 4, para 1. May consider quoting recent Australia guideline on AF as well which stated is pretty similar to ESC recommendation "LAA occlusion may be considered for stroke prevention in patients with N-VAF at moderate to high risk of stroke and with contraindications to oral anticoagulation therapy".

We quoted the Australia guideline reference as recommended by reviewer #1. The following sentence was added in the revised manuscript: "Similarly, National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand state that LAAO may be considered for stroke prevention in patients with non-valvular AF at moderate to high risk of stroke and with contraindications to OAC (GRADE quality of evidence: Low; GRADE strength of recommendation: Strong)."

Page 4, para 3. The key finding in Blackshear and Odell paper supporting LAA obliteration to reduce stroke in non-valvular afib was that 91% of nonrheumatic AF-related LA thrombi were from LAA and only 57% of rheumatic afib. Please revise the relevant sentence to reflect this key point supporting LAAO in non-valvular afib.

The authors agree with this point. We revised this sentence after reviewing Blackshear and Odell paper. The following sentence was used in the revised manuscript: "Approximately, 5 to

15% of AF patients have atrial thrombi on Transesophageal echocardiography (TEE), and 91% of those thrombi are located in the LAA in patients with nonrheumatic AF.

3. Page 8, para 2, typo: "randomely"

The typo was fixed.

4. Page 8, Para 3: The primary efficacy endpoint….., please specify the endpoint (f stroke, systemic embolism (SE), or cardiovascular/unexplained death)

We specified the primary efficacy endpoint as recommend by reviewer #1

5. Page 9, para 2: CAP and CAP2 data suggested "higher rate of ischemic stroke in Watchman group (1.6 vs 0.9 events/100 PY, p = 0.05)" --- the primary purpose of LAAO is to prevent ischemic stroke from embolization originated from LAA. With increased ischemic stroke rate in patients with Watchman LAA, it defects the primary purpose of LAAO. Please elaborate your augments of the benefit of LAAO by taking this into consideration.

This is a good point. One explanation of this finding may relate to technical failure of the device. Compared with the meta-analysis of PROTECT AF and PREVAIL trials by Reddy et al, the difference in ischemic stroke rate was not observed between LAAO and warfarin groups at longer and combined follow-up of 5 years. We added the following paragraph in the revised manuscript: **"**Although the rate of all-cause stroke was similar between both arms, the reduction in hemorrhagic stroke with Watchman device was balanced by a relative increase in ischemic stroke rates. This may relate to possible technical failures of the device: failure to completely obliterate LAA flow, anatomical remodeling of the LAA ostium over time resulting in more leaks, or the development of thrombus on the device. Compared with the pooled results of PROTECT

AF and PREVAIL trials mentioned above, the difference in ischemic stroke rate was not observed between LAAO and warfarin groups at longer and combined follow-up of 5 years."

6. Page 14 conclusion paragraph: "new and effective treatment" to be changed to "a reasonable alternative approach".

The change was done.

7. Page 14 conclusion paragraph: for the conclusive statement about WATCHMAN device, "Watchman device……", it might be better to quote the FDA approved label for clarity. "The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores, are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin."

We quoted the FDA approved label for Watchman device in the conclusion section of revised manuscript as recommended by reviewer #1.

Reviewer #2: This is a nice overview of Percutaneous Devices for Left Atrial Appendage Occlusion.

Thank you - the authors appreciate the positive feedback.

The authors should be more specific on the clinical characteristics of patients who underwent LAA occlusion in different studies. The correct selection of patients suited for this kind of Treatment is provide optimal Outcome for the patients. Thus, clinical

charcteristics of patients included in previous studies and the clinical characteristics of a Patient optimally suited for an LAA occlusion should be stated by the authors.

We agree with this point. We added clinical characteristics of patients included in the previous studies as suggested by reviewer #2.

In Addition, some typos and Errors should be taken care of.

The authors reviewed the manuscript and fixed all typos and errors.

Reviewer #3: This is an excellent systematic review about percutaneous devices for left atrial appendage occlusion. This manuscript is nicely structured and well written. I have no question about this manuscript.

Thank you - the authors appreciate the positive feedback.

Reviewer #4: Please follow the instruction for author for this journal or at least follow the PRISMA guideline to provide a standard shape of this review

We reformatted the review article to follow PRISMA guidelines as recommended by reviewer #4.

Reviewer #5: Dear author, The author represents the review manuscript which is aiming to evaluate percutaneous devices for left atrial appendage occlusion. The article is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly.

Thank you - the authors appreciate the positive feedback.

The most discussable options in the article are:

1) **I would kindly ask you to elaborate your info regarding devices which were presented at ESC 2018 and TCT 2018. You will find out the information in the relevant websites.**

We included 2018 literature and information from ESC 2018 and TCT 2018 about LAAO as recommended by reviewer #5

2) **I trust, the table 1 could be elaborated with the main advantages and disadvantages for each device.**

This a good point. We included the advantages and disadvantages of each device in text.

3) **There must be the Future Perspective at the end, but please be objective.**

We added future perspective about LAAO in the conclusion section of the revised manuscript

Thank you,

M Chadi Alraies, MD