

Peer Review File

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Reviewer A

I appreciate the author's efforts. The authors describe the pathology, prevention methods, treatment methods, and future directions of postoperative atrial fibrillation (POAF) well. This information about POAF may be available for cardiothoracic surgeons to improve the clinical outcomes. However, this review may require the revision as following reasons.

COMMENT 1: The authors describe the prevention strategy of POAF consisted of preoperative, intraoperative, and postoperative. Moreover, medication therapies of beta-blocker, amiodarone, and the other drugs were also described. These contents may be overlapped. Then, the authors would be better off formulating prevention methods, treatment methods, and anticoagulation therapy more clearly

REPLY 1: Thank you for the favorable and insightful comment. To provide a comprehensive approach, we thought that the content was more intuitively organized according to the different phases of a case: preoperative, intraoperative, and postoperative. The reviewer's suggestion is appreciated, and we have modified Table 2 to delineate more clearly the prevention and treatment/anticoagulation steps. We think that this provides a blend of both approaches.

CHANGES IN THE TEXT: Changes made to Table 2 with column designations for "POAF Prevention," "POAF/AF Treatment," and "Stroke Prevention."

COMMENT 2: The authors would be better off adding the schematic figure of summary including levels of evidence (like a visual abstract), which provided easy reading and understanding of POAF for readers.

REPLY 1: Thank you for this comment. We have removed the current Figure 1 and submitted an alternative figure that serves as a summary figure.

CHANGES IN THE TEXT: New Figure 1 added.

Reviewer B

COMMENT 1: I have read with interest this Review article, as POAF is the most common complication after cardiac surgery, as the authors state. In this article, Suero et al. provide a pretty good revision for POAF management in all phases of care, pre-, intra- and postoperative periods.

Moreover, Table 2 seems to be useful for those caregivers with doubts in the management, as it represents a summary of recommendations derived from the review of guidelines, RCT, etc.

However, I would like to highlight some aspects:

REPLY 1: We appreciate the Reviewer's response and overall comment on the quality of the manuscript. We believe that the value of Table 2 is not that it shows that any intervention is necessarily novel, but that it provides the grade of recommendation assigned by multiple societies in a single table. This can help clinicians who practice different elements of AF prevention and treatment but who may not be aware of the level of support for each practice in societal guidelines.

COMMENT 2. Title page: *I can't find the Word count of the manuscript, neither of the figures and tables.*

REPLY 2: We agree with the Reviewer and did not realize the word count and figure/table count needed to be included. We have made this change.

CHANGES IN THE TEXT: Word and figure/table counts added to Line 32.

COMMENT 3. Keywords: *The authors are supposed to specify from 3 to 5 keywords, but they provide only two.*

REPLY 3: We appreciate the suggestion and have added three keywords: cardiac arrhythmia prevention, rhythm control, and rate control.

CHANGES IN THE TEXT: Additional keywords added as above (lines 65-66).

COMMENT 4. Introduction: 3.1. The Introduction section must include Background, Rationale and knowledge gap and Objective of the study. They explain the context of POAF as a background; however, they don't define which gap of knowledge they found to justify the study. This may be, for example, non-standardized practice in POAF management among institutions, discrepancies among some studies and absence of strong recommendations in current guidelines. On the other hand, the Objective is well stated in the last paragraph of the Introduction.

REPLY 4: Thank you for the suggestion to include any gaps in knowledge that this review seeks to fulfill. We have also reformatted the Introduction into Background, Rationale, Knowledge Gap, and Objective sections.

CHANGES IN THE TEXT: A statement regarding the gap in knowledge that this review fills has been added to the Introduction section. The Introduction has been reformatted as requested. (Lines 68-81)

COMMENT 5: *In sentence 62-63, they should include “anesthesiologists” as they are part of the care team, not only intraoperatively, but also in the intensive care unit (in some centers).*

REPLY 5: Thank you for the comment. We have made this change to be more inclusive in our representation.

CHANGES IN THE TEXT: Anesthesiologists have been added to the list of providers (Line 74).

COMMENT 6. *Pathogenesis of POAF: The authors comment some structural and calcium-metabolism factors involved in POAF pathogenesis, but do not mention the role of oxidative stress, which can have also influence on POAF development. As a matter of fact, some groups have tried antioxidant therapies as a preventive treatment, although with no strong results.*

REPLY 6: Thank you for this comment. While we tried to edit down this section in the interest of word economy, we acknowledge that a comment is warranted on oxidative stress and reactive oxygen species and their role in the pathophysiology of POAF. We appreciate the suggestion.

CHANGES IN THE TEXT: The potential role of reactive oxygen species (ROS) is briefly described in the Pathogenesis section.

“Oxidative stress with increased circulation of reactive oxygen species has also been implicated in the development of POAF through several mechanisms.” (Lines 154-155)

COMMENT 7. Intraoperative strategies:

In paragraph 226-230, the authors recommend posterior pericardiotomy should be performed to prevent POAF. However, I think there is not enough evidence, and this strategy is not widely extended. For example, some surgeons prefer not to open the pleura, if possible, to avoid pneumothorax and pleural effusion after surgery. So, I wouldn't put this statement as a recommendation. Perhaps something to be considered.

REPLY 7: Thank you for this insightful comment. Despite the existing variability in practice regarding posterior pericardiotomy (PP), our interpretation of the literature suggests that PP is a viable option for preventing POAF and, as such, should be considered whenever technically feasible. The NNT for PP is 7, which is comparable to that of beta blockers and amiodarone—cornerstone prevention strategies in the perioperative period. This is consistent with the most recent 2023 ACC/AHA/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation, which declares PP a Class IIA recommendation (Joglar. CIRCULATION. 2023).

In the PALACS trial (Gaudino. LANCET. 2021), the incidence of pleural effusion was 32% in the no-PP group versus 30% in the PP group, with only 1% of patients in either group requiring drainage. In the meta-analysis by Soletti (of 18 RCTs) reporting on pleural effusion, the difference was 23% in the PP

group compared with 17% in the no-PP group, but there was no difference in the frequency of pleural effusion needing drainage. Thus, while there may be a higher incidence of pleural effusion in patients who have undergone PP, it does not appear to be of clinical significance. Moreover, the clear benefit in reduced pericardial effusion and reduced POAF appears to outweigh the pleural effusion risk. Indeed, in CABG patients, who represent the largest cardiac surgical population, the placement of a left pleural tube is routine. We have also found that a soft drainage catheter (Blake drain. Johnson & Johnson. Ethicon. Raritan, NJ) works well in cases in which the left chest has been entered only for the sake of the PP. We agree with the reviewer that surgeons may have several theoretical concerns that make them reluctant to accept PP as a treatment option. Our hope is that continued dissemination of POAF reduction outcomes with PP will encourage further adoption.

We have downgraded our recommendation at this point to state that PP is reasonable (a Class IIA recommendation) instead of that PP should be performed (a Class I recommendation). This is consistent with the 2023 ACC/AHA/HRS Guidelines. (Joglar. CIRCULATION. 2023).

CHANGES IN THE TEXT: Lines 243-249 now read as follows:

“Posterior pericardiectomy is currently included as a recommendation with limited evidence in both American (39) and European (40) guidelines. However, these recent trials demonstrating a benefit in reducing POAF have led the authors of the 2023 American guidelines to make PP a Class IIA (B-R) recommendation for patients undergoing CABG, aortic valve replacement, or ascending aortic replacement surgery (19). Given the ease with which it can be performed, PP is reasonable when feasible.”

COMMENT 8. End of Main text: The authors do not comment either strengths or limitations they find with their review.

REPLY 8: Thank you for this comment. The purpose of this article is to provide the target audience with a comprehensive review of the current literature with regard to the prevention and management of POAF. We have added a paragraph on the strengths and weaknesses of our review.

CHANGES IN THE TEXT: We have added the following paragraph (Lines 570-575):

“The strength of this review is its thorough, evidence-based discussion of postoperative atrial fibrillation (POAF) after cardiac surgery with the use of landmark randomized trials, systematic reviews, and societal guidelines. In addition, the multispecialty background of the authors (cardiac surgery, anesthesiology, cardiology, and critical care) provides a broad perspective. The

limitations include the broad scope of the review, which did not allow deeper investigation into potentially important areas.”

COMMENT 9. *Acknowledgment section: The authors have forgotten this section, and a Funding subsection. If no funding was used, “None” should be stated.*

REPLY 9: Thank you for this comment; we recognize our inadvertent omissions.

CHANGES IN THE TEXT: An Acknowledgement section and Funding subsection have been added.

(Lines 26-28)

Reviewer C

COMMENT 1: *The authors submit a review article on postoperative atrial fibrillation (POAF) in which they broadly cover multiple aspects of POAF. Subtopics included pathogenesis, patient risk factors, POAF impact on patient outcomes and treatment strategies to reduce POAF incidence as well as management of POAF that has occurred. The conclusions of the review are that there are multiple avenues to reduce the common complication of POAF after cardiac surgery.*

REPLY 1: Thank you for the comment. We agree that there are multiple options for intervention and that a comprehensive, deliberate strategy is necessary. There are preoperative, intraoperative, and postoperative preventive measures that can be taken to reduce patients’ overall risk of developing POAF.

CHANGES IN THE TEXT: No changes required.

COMMENT 2: *Overall, the submission is well written. Coverage of each subtopic is somewhat superficial given the breath of the review; at the same time, the broad coverage of POAF adds length to the submission. In this reviewer’s opinion, a more focused review of issues directly pertaining to POAF management may shorten the submission and align better with the stated objectives outlined on lines 64-67 of the submission.*

Consider removing or editing verbiage that is peripheral to the management of POAF. Included would be the subsection on pathogenesis (lines 132-142), operative strategies to address preoperative atrial fibrillation (lines 195-203), the topic of left atrial appendage occlusion (lines 243-257), and the subsection on AI in POAF (lines 507-539). Tables 2 and 3 would need to be revised accordingly.

REPLY 2: Thank you for this gracious comment on the quality of the writing. We acknowledge that to be more comprehensive, it was necessary to cover some topics in less depth. We have edited down the sections on pathogenesis (by 1 line), operative strategies (2 lines), left atrial appendage occlusion (7

lines), and AI (10 lines) to create a more succinct review of POAF. We did not dispense with this material altogether because including such topics may expand the target audience to include members of the surgical and biomedical engineering communities, who may be inspired to make future contributions to the management of this complex disease process.

We edited Table 2 substantially to delineate more clearly a preventive POAF/AF treatment or anticoagulation intervention; we did not edit Table 3 because the content was preserved. While the distinction between POAF and preexisting AF is clear, for many clinicians, it is logical to take a comprehensive approach to managing AF. We want clinicians to think about both preexisting AF and POAF. For example, clinicians should understand the role of LAA occlusion in treating patients with preexisting AF (Class I indication according to 2023 ACC/AHA guidelines) as opposed to patients with preexisting AF, for whom LAAO does not have a formal recommendation because the supportive data are limited.

CHANGES IN THE TEXT: Several sections have been edited throughout the manuscript.

The changes include efforts to be more concise in the pathogenesis, intraoperative strategies, LAA occlusion, and artificial intelligence sections, as requested. Moreover, Table 2 was edited to make the points explained above.

COMMENT 3: *For Table 2, consider simplifying the table by removing the 2nd column (appropriate candidates); this column seems unnecessary.*

REPLY 3: Thank you for this comment. We have removed that column from Table 2 and replaced it with Prevention, Treatment, and Stroke Prevention columns consistent with the suggestion of Reviewer 1.

CHANGES IN THE TEXT: TABLE 2 revised.

COMMENT 4: *I believe would be important to include the criterion used for establishing the diagnosis of POAF – consider mentioning the definition used in the Society of Thoracic Surgeons database as well as differing criterion used in other studies to establish the diagnosis. The impact of these varying definitions on management and outcome also deserve comment.*

REPLY 4: Thank you for this comment and suggestion. While there is heterogeneity with respect to the definition of POAF, the Society of Thoracic Surgeons database defines POAF as new-onset AF “lasting longer than 1 hour and/or requiring treatment” (Matos. JTCVS 2021). We reference several systematic reviews, such as Caldonazo’s, which examined 57 studies to show the association between POAF and adverse outcomes after cardiac surgery. It would not be feasible to review each of those studies to determine the variations among definitions of POAF.

CHANGES IN THE TEXT: STS definition added (Lines 70-71).

“The Society of Thoracic Surgeons defines POAF as new-onset post-surgical atrial fibrillation that lasts for more than 1 hour and/or requires treatment.”

COMMENT 5: *More actionable concluding statements would strengthen the conclusions. Assuming the authors have an opinion on the most effective strategies to prevent or treat POAF, consider specifically stating these in your conclusions.*

REPLY 5: We appreciate the thoughtful comment regarding clear, actionable items.

CHANGES IN THE TEXT: The Conclusion has been modified (Lines 578-585) as follows:

“Postoperative atrial fibrillation is the most common complication after cardiac surgery. Specific interventions in the preoperative, intraoperative, and postoperative phases of care can provide an opportunity for reducing the incidence of this complication. Most promising are those interventions that have been shown in randomized trials to have a number needed to treat (NNT) of fewer than 8 patients, indicating an especially high-yield intervention. A comprehensive approach to POAF prevention would incorporate preoperative amiodarone, perioperative beta-blockers or amiodarone, and posterior pericardiectomy at the time of surgery. Randomized, multicenter trials of this combination approach should be considered in the near future.”

COMMENT 6: *What methodology did the authors use to identify potential sources used in their review? ideally, this would be reproducible. If possible, include the decision algorithm as a Figure in the submission.*

REPLY 6: We did not approach this manuscript as a systematic review, narrative review, or scoping review. The authors performed literature searches on the most recently published evidence in the field of POAF by using the search strategy listed below.

Including a figure representing the methodology for this literature search would add length to the paper. There are already systematic reviews available on this topic for which a search algorithm would be more germane.

Search Strategy Designed for Medline OVID (Primary Database)

Postoperative AFIB Prevention

1. Postoperative Complications/
2. exp Atrial Fibrillation/ or exp Atrial Flutter/ or Arrhythmias, Cardiac/
3. 1 and 2

4. ((postop* or "post-op*" or "after surgery" or postsurg* or "post-surg*" or postprocedur* or "post-procedur*" or "new onset" or "sudden onset") adj3 ("atrial fibrillation*" or "auricular fibrillation*" or "a-fib*" or "atrial flutter*" or "auricular flutter*" or arrhythmia* or "irregular heart rhythm*" or "irregular heartbeat*" or "irregular heart contraction*" or "irregular cardiac contraction*")).ti,ab,kw.
5. 3 or 4
6. exp Cardiac Surgical Procedures/
7. ("cardi* surg*" or "heart surg*" or cardiosurg* or "cardio-surg*" or "cardi* operation*" or "heart operation*" or "coronary artery surg*" or "heart valve surgery*" or "open heart surg*" or "coronary artery bypass graft*" or "aortic valve replacement*" or "mitral valve repair*" or "mitral valve replacement*").ti,ab,kw.
8. 6 or 7
9. exp Secondary Prevention/ or Primary Prevention/
10. (prevent* or avoid* or reduce* or eliminate* or avert*).ti,ab,kw.
11. 9 or 10
12. 5 and 8 and 11
13. limit 12 to yr="2000 -Current"
14. limit 13 to English language

CHANGES IN THE TEXT: None

COMMENT 7: *The currently included Figure 1 appears too general to add much to the specific topic of POAF management; consider deleting.*

REPLY 7: Thank you for this comment. We have created an alternative figure.

CHANGES IN THE TEXT: The legend for the new figure reads as follows:

“Summary of preoperative, intraoperative, and postoperative phases of care along with future technologies for preventing and treating postoperative atrial fibrillation after cardiac surgery.”