ANNALS OF PALLIATIVE MEDICINE

Peer Review File

Review Comments

This study evaluated the correlation of LDL-C with AF in a Chinese population of hypertension. The authors concluded that they found lower LDL-C was associated with increased AF. They performed multiple strategies on statistics. The correlation remained significant on the multivariate logistic regression, however some of the data interpretation and discussion were not appropriate. There are still major shortcomings as followings:

1. How was LDL-C concentration determined? Was it calculated or directly quantified? With which assay?
Reply 1: The LDL-C concentration was directly quantified by direct enzymatic colorimetric method by a Beckman Coulter AU analyzer. Reference: Garoufi A, Drakatos A, Tsentidis C, et al. Comparing calculated LDL-C with directly measured LDL-C in healthy and in dyslipidemic children. Clin Biochem. 2017;50(1-2):16-22. Changes in the text: N/A.

2. Table 1. The incidence of AF in this study population was relatively low, approximate 1%, which is much lower than other clinical studies. The reason behind the low AF incidence of the study population needs to be discussed.
Reply 2: We have modified as advised (Page 11, line 214-217)
Changes in the text: Second, in the present study, AF was diagnosed by ECG at the baseline but not by the 24 hours ECG, which might missed up paroxysmal or subclinical AF and lead to the relatively low incidence of AF.

3. The usage of statin was significantly higher in AF group than in non-AF group. This was not mentioned.
Reply 3: We have modified as advised (Page 8, line 140-141)
Changes in the text: The statin usage was significantly higher in AF group than in non-AF group.

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4. Table 2. What is the rationale to divide LDL-C into quartiles? The TC, LDL-C, HDL-C, use of statin was linked with LDL-C quartiles; what is the rationale to analyze the correlation among those factors?

Reply 4: We divided LDL-C into quartiles in order to investigate more details of the association between LDL-C and AF. And we examined the baseline characteristic of each LDL-C quartiles before we tried to analyze the relationships between LDL-C quartiles and AF.

Changes in the text: N/A.

5. Table 3. It is strange that systolic blood pressure was negatively associated with AF in the univariate regression.

Reply 5: We found this inconsistent with previous studies. There are two reasons could possibly explain. First, in present study, the participants with AF had lower baseline blood pressure than those without AF. Second, the incidence of AF is relatively low in the current study.

Changes in the text: N/A.

6. The study population has almost 20% diabetes. What are the differences regarding disease co-morbidities compared with studies: ALLHAT, ARIC, EMSA, and FHS that have consistent and inconsistent results?

Reply 6: In ALLHAT, 35.5% participants with diabetes at baseline, 11% for MESA(2000-2002), 8% for FHS(1995-1998), and approximately 10% for ARIC(1987-1989). Due to different study populations and study design, the disease co-morbidities are different among different studies.

Changes in the text: N/A.

7. The relationship of LDL-C and inflammatory reaction is of debate and of doubt. The related discussion may require adjustment.

Reply 7:   We have modified as advised (Page 10-11, line 199-203)

Changes in the text: First, some researchers considered that high levels of LDL-C might have an anti-inflammatory effect (27,28), and AF was closely associated with inflammatory reaction (15). Low level of LDL-C probably contribute to the pathogenesis of AF via enhancing inflammatory response.

8. A latest article addressed the concept of cardiac lipotoxicity in which heart tissue uptake of lipoproteins is increased as such the circulatory lipids may be reduced (Lee et al. Int. J. Mol. Sci. 2020, 21, 891). The imbalance of lipids distribution

(among tissue and circulation) may be another explanation for the paradoxical correlation between LDL-C and AF.

Reply 8: We have modified as advised (Page 11, line 208-212)

Changes in the text: In addition, a latest article purposed the concept of cardiac lipotoxicity in which heart tissue uptake increased lipoproteins, therefore the circulatory lipids may be reduced. The imbalance of lipids distribution among tissue and circulation may be another explanation for the paradoxical relation between LDL-C and AF (33).

9. The authors neglect important evidence on significant benefit from statin treatment on AF risk reduction. The statement "The lipid lowering therapy with side effect of AF" is inappropriate.

Reply 9: We agreed that this statement was inappropriate and we have deleted this sentence. (Page 12, line 226-227)

Changes in the text: ~~Nevertheless, present study indicated that lipid lowering therapy should avoid the side effect of AF.~~

10. There remain some limitations to the study: Lack of thyroid function test; ordinary electrocardiogram may not detect paroxysmal or subclinical AF; lack of data reflecting central obesity; lack of heart function.

Reply 10: We have modified as advised (Page 11, line 217-219)

Changes in the text: Third, we did not examine the levels of inflammatory biomarkers, and did not performed tests on thyroid function, heart function, and did not obtain the data of central obesity.

11. Vague words such as seem, more likely, … have to be avoided.

Reply 11: We have modified as advised (Page 8, line 138-140)

Changes in the text: Participants with AF were older, had higher prevalence of CAD and had lower levels of LDL-C, TG and TC compared to those without AF (all P<0.05).

12. Prevalence should be incidence. These two terms should not be misused.

Reply 12: We have modified as advised ((1)Page 3, line 44-45 (2)Page 12, line 223-224)

Changes in the text: (1) Lower levels of LDL-C was associated with increased ~~prevalence~~ incidence of AF in a Chinese community hypertensive population. (2) In conclusion, we found that lower levels of LDL-C were associated with increased ~~prevalence~~ incidence of AF in a Chinese community hypertensive population.