PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical and biological determinants of P-wave duration: Cross-sectional data from the population-based CoLaus|PsyColaus-study
AUTHORS	Bocchi, Federica; Marques-Vidal, Pedro; Pruvot, Etienne; Waeber, Gerard; Vollenweider, Peter; Gachoud, David

VERSION 1 – REVIEW

REVIEWER	Arttu Holkeri Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland
REVIEW RETURNED	11-Apr-2020

GENERAL COMMENTS	The manuscript by Bocchi et al. describes the determinants of P-wave duration on the 12-lead ECG in the Swiss population. The study population is large and study participants underwent extensive baseline examinations. However, some issues should be addressed to improve the manuscript: 1) The concepts of Bachmann's Bundle and interatrial block are not discussed in the manuscript. These should be included in both the Introduction and Discussion sections. 2) The association between left atrial size and P-wave duration, demonstrated in previous studies, should be discussed more extensively. 3) The authors consider the identification of clinical factors associated with prolonged PWD important, as PWD is associated with adverse outcomes and, thus, PWD could be used as a marker for these clinical risk factors, e.g. age, sex, hypertension, obesity, and diabetes. However, these traditional risk factors are easily identifiable in clinical practice and whether PWD as a marker helps to identify these traditional risk factors in clinical practice seems questionable to me. Instead, whether prolonged PWD as a risk marker provides independently incremental value to cardiovascular event risk prediction is worth studying. The Introduction should be revised to clarify this point. 4) Several studies have previously presented average values for PWD in the general population, for example, van der Ende et al. "Population-based Values and Abnormalities of the electrocardiogram in the General Dutch Population: The LifeLines Cohort Study." Clinical Cardiology 2017;40(10):865–72. Therefore, standard values for PWD have been previously published and these previous findings should be considered in the manuscript.

	5) Although the extensive details of the study population have been presented elsewhere, the manuscript should include the basic study population information, including who were invited to the study and what were age inclusion and exclusion criteria. 6) Were the baseline measurements (weight, height, laboratory testing…) conducted during the baseline study in 2003–2006? Or during the second follow-up in 2014–2017? This should be stated more clearly. If the baseline measurements were not obtained at the same time as ECG recordings, it is a major limitation and should be stated. 7) Although the ECG measurement method is published in more detail elsewhere, it should be explained in this manuscript also briefly. The lead or leads used for digital PWD measurement should be stated. The digital and manual measurement accuracies (milliseconds) should be presented. 8) Were there any subjects with pacemakers? Were they excluded? 9) The word “average” (Methods – Statistical analyses, Table 3 legend, Figure 3 legend) should be replaced with mean, median, or mode, whichever was used. 10) Whether the variables associated with PWD in the bivariate analyses were entered each individually or all simultaneously into the multivariable analyses using Model 1 should be stated more clearly. 11) All the prevalences of categorical baseline parameters should be presented in percentages for uniformity and clarity in the Results section. The use of fractions should be omitted. 12) The excluded subjects should not be prioritized in the Results section. The baseline characteristics of the excluded subjects in Table 1 should be omitted or relocated to the Supplement. As subsequently Table 2 contains much of the information of Table 1 (the number of subjects in subgroups), I would recommend the addition of the percentages to Table 2, the addition of the mean ± SD of age to the Results text section, and the removal of Table 1. 13) If the results of the baseline characteristic comparisons between included and excluded subjects are included in the manuscript, the statistical method used in the comparison (t-test and chi-square) should be mentioned in the Methods section. 14) As the number of ECGs requiring manual measurement was relatively high (10.1%), the numbers of ECGs requiring manual assessment due to the digital assessment method’s inability and the number due to extreme values should be presented. Furthermore, the reason for the high number of ECGs requiring manual assessment should be discussed and added to the Limitations. 15) Whether the association between PWD and age and the association between PWD and height were statistically significant should be presented in the text.

	16) Whether the association between antiarrhythmic drugs and prolonged PWD in the present study is directly caused by the antiarrhythmic drug or due to the underlying cardiac condition (that the antiarrhythmic drug is used for) is unknown, as echocardiography was not performed and no exact cardiovascular diagnoses were presented. This limitation should be included in the Discussion. 17) The term “metabolic disease” should be revised to “metabolic syndrome” or “metabolic disorder”. 18) The Future Directions section should be revised to project future directions based on the findings of the present study. Currently, the section addresses future directions based on previous studies of PWD and cardiac endpoints. 19) When eyeballing the Figure 3, the green lines do not seem to be appropriate for the average of the PWD value “dots” in the scatter plot. The graph editing should be rechecked. 20) The “underweight” classification is not defined in the Appendix. 21) According to the Appendix, a subject with a BMI of 25 kg/m2 is included in both overweight subjects and normal subjects. The definition should be corrected according to the used method.

REVIEWER	Pyotr Platonov Lund University
REVIEW RETURNED	21-Apr-2020

GENERAL COMMENTS	Bocchi et all performed a descriptive study studying association between P-wave duration and significant comorbidities and other clinical factors on a population based sample from Switzerland. Main findings of the study was observation of significant association between PWD and all tested comorbidities, height and male gender. In the multivariable analysis, age, height, male gender, obesity ,markers and hypertension appeared to be independent factors affecting PWD prolongation. This is an important study, which explores clinical factors underlying PWD in a population-based sample. Comments: * P-wave measurement was performed manually on a well-defined subset of selected P-waves with either the lack of automatic measurements or physiologically short or long P-waves. The number of such cases was about 10% of the entire sample and the methodology clearly differed from the automatic measurements (manual and one-lead based vs automatic, which is based on the global PWD in all 12 leads). The authors chose to pool the manually measured P-waves with the automatically measured. I personally doubt whether this is the best approach. At least more details are needed. Would be acceptable to exclude these cases in order to use unified methodology for all P-waves? Would manual measurements be a solution in case of noisy ECG when computer could not perform the measurement? Were there cases where manual measurements could not be reliably performed? * Plots presented in Figure 3 contain a number of measurements indicating cases with PWD well under 80 ms and as short as 50 ms. I doubt existence of physiological and correctly assessed atrial

	depolarisation waves that in 12-leads present with that short duration. Since all P-waves shorter than 80 ms should have been manually measured and thus verified, I would like to see a discussion in this regard as well as examples of such extremely short P-waves. * From a clinical point of view, the value of this work would be significantly improved if the authors could relate their findings to the conventionally accepted threshold for partial interatrial block (120 ms). From the presented data it appears that about 25% of subjects had IAB, which is very much in line with other population-base works such as Skov et al, JAHA 2018 (10.1161/JAHA.117.008247). This is important. * The finding of association between the use of antiarrhythmic drugs is of very limited value since the authors can not distinguish between different classes of AAD. The authors provide no reference to earlier works on AAD. There is quite a few on beta-blockers, less on verapamil, and few on class I and III. But I doubt this part adds any value to the manuscript at all. It is also possible that some patients might have had paroxysmal AF, and the use of AAD was a proxy for that. * The discussion of mechanisms and pathology behind PWD prolongation can benefit from citing studies that directly assessed relationship between PWD and atrial histology, such as Huo et al., J Electrocardiol 2014 (10.1016/j.jelectrocard.2014.01.011)

VERSION 1 – AUTHOR RESPONSE

Answers to Reviewer: 1, Arttu Holkeri

The manuscript by Bocchi et al. describes the determinants of P-wave duration on the 12-lead ECG in the Swiss population. The study population is large and study participants underwent extensive baseline examinations. However, some issues should be addressed to improve the manuscript:

1) The concepts of Bachmann's Bundle and interatrial block are not discussed in the manuscript. These should be included in both the Introduction and Discussion sections.

We thank the reviewer for this comment. As suggested and also according to point 3) of the Reviewer 2, we introduced the concept of interatrial block (in the Introduction and Discussion, see below).

"A prolonged PWD may reflect the presence of structural cardiac abnormalities (atrial inflammation, fibrosis), which lead to impairment in atrial conduction and interatrial conduction in particular. The latter may promote the development of an interatrial block, reflecting the conduction delay through specific myocardic fibers connecting both atria and known as the Bachmann bundle.(3–5) Interatrial block is characterized by a PWD ≥ 120 ms and a bimodal morphology; it is a distinct entity from left atrial enlargement, although they can be associated.(2, 4)"

"Moreover, we attested that 21% of the study population had a PWD ≥ 120 ms, possibly reflecting an interatrial block, which is in line with other population-based studies.(2)"

2) The association between left atrial size and P-wave duration, demonstrated in previous studies, should be discussed more extensively.

We appreciate this relevant observation. Unfortunately, in our study we were unable to correlate the PWD to the left atrial size because echocardiographic data are at the moment missing from CoLaus|PsyColaus study. This represents a limitation as we noted in the study limitations paragraph:

"Another limitation of our study is our inability to support causal association between PWD and structural myocardial abnormalities (atrial enlargement, fibro-fatty infiltration) by the lack of anatomo-histological and echocardiographic information, which was not part of our study design."

3) The authors consider the identification of clinical factors associated with prolonged PWD important, as PWD is associated with adverse outcomes and, thus, PWD could be used as a marker for these clinical risk factors, e.g. age, sex, hypertension, obesity, and diabetes. However, these traditional risk factors are easily identifiable in clinical practice and whether PWD as a marker helps to identify these traditional risk factors in clinical practice seems questionable to me. Instead, whether prolonged PWD as a risk marker provides independently incremental value to cardiovascular event risk prediction is worth studying. The Introduction should be revised to clarify this point.
We are grateful for this remark. In fact, we consider the identification of clinical factors associated with prolonged PWD important, as PWD is associated with adverse outcomes (arrhythmia and cardiovascular outcomes). It is true that the clinical factors for prolonged PWD are well known cardiovascular risk factors but this needed to be first demonstrated in our population. We could hypothesize that prolonged PWD reflect subclinical, but established structural damages to the atrial tissue and thus an advanced disease process. This is what we meant by intermediate phenotype in the section Future Directions. Therefore, we totally agree that PWD could have an incremental value to predict the cardiovascular risk, but our cross sectional design prevents us from calculating this possible added value.

4) Several studies have previously presented average values for PWD in the general population, for example, van der Ende et al. “Population-based Values and Abnormalities of the electrocardiogram in the General Dutch Population: The LifeLines Cohort Study.” Clinical Cardiology 2017;40(10):865–72. Therefore, standard values for PWD have been previously published and these previous findings should be considered in the manuscript.
We thank the reviewer for this important statement. We agree with the fact that several studies, as we did, have presented average values for PWD in a given population (Swiss, Dutch, …). However, no reference value of PWD (“normal value”) has been standardized in an unselected population. As Magnani et al. stated (7), PWD cut-offs of 110-120 ms have been proposed. However, no prospective community-based study has developed reference values by identifying a reference population, articulating measurements of PWD, and then applying those measurements to a broad sample with cardiovascular disease and others covariates identified, for example, in our study. This is what we meant with the sentence: “…limited information is available on the influence of each determinant on the prolongation of PWD and, importantly, no standard value of PWD has been defined in an unselected population”.

5) Although the extensive details of the study population have been presented elsewhere, the manuscript should include the basic study population information, including who were invited to the study and what were age inclusion and exclusion criteria.
We now provide more details regarding the study population. The following statements were added in the methods section:
“In summary, a non-stratified, representative sample of the population of Lausanne, Switzerland, was recruited between 2003 and 2006, including 6733 participants. The following inclusion criteria were applied: a) aged between 35 and 75 years; b) written informed consent; c) willingness to take part in the examination and to provide blood samples.
”Participants were invited to attend the Lausanne University Hospital for data collection at baseline and subsequent follow-ups.”

6) Were the baseline measurements (weight, height, laboratory testing…) conducted during the baseline study in 2003–2006? Or during the second follow-up in 2014–2017? This should be stated more clearly. If the baseline measurements were not obtained at the same time as ECG recordings, it is a major limitation and should be stated.
We thank the reviewer for this accurate remark. All data were collected during the second follow-up (2014-2017). Hence, the analysis was restricted to this period. We added the following statement in the methods section:

“Participants were invited to attend the Lausanne University Hospital for data collection at baseline and subsequent follow-ups. Each visit included a health questionnaire, a physical examination, and blood tests.”
“The first follow-up visit was conducted between April 2009 and September 2012 and the second follow-up visit between May 2014 and April 2017. Mean follow-up time was 10.7 (range 8.8-13.6) years for the second follow-up. As ECG data was only collected during the second follow-up, only data collected during the second follow-up was considered.”

7) Although the ECG measurement method is published in more detail elsewhere, it should be explained in this manuscript also briefly. The lead or leads used for digital PWD measurement should be stated. The digital and manual measurement accuracies (milliseconds) should be presented.
According to your remark, for which we are grateful, supplementary information have been added to the paragraph “Electrocardiography”, as follows:
“Digital ECGs were stored in an anonymised database of SEMA Data Management System (V3.5, Schiller AG, Baar, Switzerland). ECG measurements, including PWD values, were determined in milliseconds (ms) by Schiller AG algorithms based on all 12-leads and the reconstitution of an average beat.”

8) Were there any subjects with pacemakers? Were they excluded?
In fact subjects with pacemakers were not included in our study. The exclusions criteria have been better reported (see below) and the Figure 1 has been modified.
“Participants were excluded from the analysis if they presented 1) no sinus rhythm or paced rhythm on the study ECG or Wolff-Parkinson-White ECG pattern (present on the digital or manual analysis); 2) missing or non-interpretable ECG (artefacted, unstable baseline, inverted electrodes) and 3) missing phenotypic data.”

9) The word “average” (Methods – Statistical analyses, Table 3 legend, Figure 3 legend) should be replaced with mean, median, or mode, whichever was used.
The word “average” has been replaced with “mean”.

10) Whether the variables associated with PWD in the bivariate analyses were entered each individually or all simultaneously into the multivariable analyses using Model 1 should be stated more clearly.
Each variable significantly associated with PWD in the bivariate analysis, taken singularly, and then adjusted for age, height and gender was used for Model 1. This has been better clarified in the corresponding paragraph:
“Model 1 was applied for each individual variable significantly associated with PWD in the bivariate analysis and adjusted for age, height and gender. Model 2 included all variables significantly associated with PWD in Model 1, including age, height and gender.”

11) All the prevalences of categorical baseline parameters should be presented in percentages for uniformity and clarity in the Results section. The use of fractions should be omitted.
As proposed, in the result section, the prevalence of categorical baseline parameters has been presented in percentages; use of fractions has been omitted.

12) The excluded subjects should not be prioritized in the Results section. The baseline characteristics of the excluded subjects in Table 1 should be omitted or relocated to the Supplement. As subsequently Table 2 contains much of the information of Table 1 (the number of subjects in subgroups), I would recommend the addition of the percentages to Table 2, the addition of the mean ± SD of age to the Results text section, and the removal of Table 1.
We thank the reviewer for this statement. Table 1 (excluded participants) has been relocated to the Appendix. We added the percentages and the mean age ± SD of Table 1 in Table 2.

13) If the results of the baseline characteristic comparisons between included and excluded subjects are included in the manuscript, the statistical method used in the comparison (t-test and chi-square) should be mentioned in the methods section.
T-test and chi-square were used to compare included and excluded participants and this is now mentioned in the methods section as follow:
“T-test for continuous variables and chi-square for categorical variables were used to compare included and excluded participants as well as participants with a PWD < or ≥ 120 ms.”

14) As the number of ECGs requiring manual measurement was relatively high (10.1%), the numbers of ECGs requiring manual assessment due to the digital assessment method’s inability and the number due to extreme values should be presented. Furthermore, the reason for the high number of ECGs requiring manual assessment should be discussed and added to the Limitations.
The number of ECG requiring a manual measure due to the digital assessment method’s inability and the number due to extreme values have been presented. The Limitation paragraph has been modified.
“A total of 351 ECGs, i.e. 10% of the ECGs, needed a manual determination of PWD according to the previously mentioned criteria: 101 (29%) for extreme automatically calculated PWD (> or < 2 SD), and 250 (71%) for automatic assessment inability.”
“…a significant number of ECG (10%) needed a manual determination of PWD; this might have biased the results. However, even after exclusion of the manually analysed ECGs, associations remained unchanged.”

15) Whether the association between PWD and age and the association between PWD and height were statistically significant should be presented in the text.
Association between PWD and age or height is presented in the text (paragraph: association of PWD with demographic, clinical and biological markers and discussion). Figures 3a and 3b illustrate the linear and positive association of PWD with age and height, respectively.

16) Whether the association between antiarrhythmic drugs and prolonged PWD in the present study is directly caused by the antiarrhythmic drug or due to the underlying cardiac condition (that the antiarrhythmic drug is used for) is unknown, as echocardiography was not performed and no exact cardiovascular diagnoses were presented. This limitation should be included in the Discussion.
Based on this relevant statement and according to point 4) of the Reviewer 2, the association between antiarrhythmic and PWD has been removed from our analysis. Multivariable analysis (Model 2A and 2B) has been repeated without including antiarrhythmic. Results are shown in Table 2.

17) The term “metabolic disease” should be revised to “metabolic syndrome” or “metabolic disorder”.
The term “metabolic disease” has been replaced with “metabolic syndrome”.

18) The Future Directions section should be revised to project future directions based on the findings of the present study. Currently, the section addresses future directions based on previous studies of PWD and cardiac endpoints.
We thank the reviewer for this remark. The future directions section has been revised:
“Based on our results, it would be interesting to know the evolution of the participants according to their PWD. Data from echocardiography or other imaging techniques, as well as post-mortem materials, could be useful to prove the fatty or fibrotic infiltration of the atria or left atrial enlargement. Moreover, future work could determine if preventive interventions (e. g. lifestyle and dietary intervention) based on the PWD have positive effects on clinical outcomes. The ongoing follow-up of the CoLaus|PsyCoLaus cohort would provide some information in the near future.”

19) When eyeballing the Figure 3, the green lines do not seem to be appropriate for the average of the PWD value “dots” in the scatter plot. The graph editing should be rechecked.
The Figure 3 has been revised.

20) The “underweight” classification is not defined in the Appendix.
The “underweight” classification is now better detailed:
“Obesity was defined as BMI ≥ 30 kg/m2, overweight as BMI ≥ 25 and < 30 kg/m2, normal as BMI ≥ 18.5 and < 25 kg/m2 and underweight as BMI < 18.5 kg/m2.”

21) According to the Appendix, a subject with a BMI of 25 kg/m2 is included in both overweight subjects and normal subjects. The definition should be corrected according to the used method.
The definition is now corrected. Please see our answer to query #20.

Answers to Reviewer: 2, Pyotr Platonov
Bocchi et all performed a descriptive study studying association between P-wave duration and significant comorbidities and other clinical factors on a population based sample from Switzerland. Main findings of the study was observation of significant association between PWD and all tested comorbidities, height and male gender. In the multivariable analysis, age, height, male gender, obesity ,markers and hypertension appeared to be independent factors affecting PWD prolongation. This is an important study, which explores clinical factors underlying PWD in a population-based sample.

1) P-wave measurement was performed manually on a well-defined subset of selected P-waves with either the lack of automatic measurements or physiologically short or long P-waves. The number of such cases was about 10% of the entire sample and the methodology clearly differed from the automatic measurements (manual and one-lead based vs automatic, which is based on the global PWD in all 12 leads). The authors chose to pool the manually measured P-waves with the automatically measured. I personally doubt whether this is the best approach. At least more details are needed. Would be acceptable to exclude these cases in order to use unified methodology for all P-waves? Would manual measurements be a solution in case of noisy ECG when computer could not perform the measurement? Were there cases where manual measurements could not be reliably performed?
We thank the reviewer for this comment. In our study, we decided to measure the PWD manually in two different cases:
1. When the algorithm was unable to provide a PWD value (e.g. artefacted ECGs, unstable baseline, inverted electrodes); 101 ECGs were analysed; in 41 of them, a sinusal rhythm was present. The remainder were excluded.
2. For extreme PWD, defined as < 80 ms (< 2 standard deviations) or > 150 ms (> 2 standard deviations); 250 ECGs were analysed, of which 10 were excluded.
Of all ECGs analyzed manually, only 6 could not be manually analyzed (artefacted ECGs) and were therefore excluded.
Considering this, we agree with the fact that the methodology to measure PWD was clearly different between manual and automatic approach. However, we assumed that this number of ECGs would not influence our results. Indeed, following your remark, we repeated the multivariable analyses after excluding all the 351 ECGs analyzed manually. The results have not changed. Age, height, gender, hypertension and obesity markers (abdominal obesity, BMI) were positively associated with PWD. Results are available in Supplemental Table 3.

2) Plots presented in Figure 3 contain a number of measurements indicating cases with PWD well under 80 ms and as short as 50 ms. I doubt existence of physiological and correctly assessed atrial

depolarisation waves that in 12-leads present with that short duration. Since all P-waves shorter than 80 ms should have been manually measured and thus verified, I would like to see a discussion in this regard as well as examples of such extremely short P-waves.
We are thankful for this remark. Among the pool of ECGs (< 2 SD or < 80 ms) that were manually analyzed, only 30 had PWD < 80 ms. In 12 of them, PWD was really short (~ 60 ms manually measured, between 54 and 76 ms automatically calculated). The figure 3 has been revised (no more plots indicating cases with PWD as short as 50 ms are present). We annexed two ECGs as an example with a short PWD (54-60 ms).

3) From a clinical point of view, the value of this work would be significantly improved if the authors could relate their findings to the conventionally accepted threshold for partial interatrial block (120 ms). From the presented data it appears that about 25% of subjects had IAB, which is very much in line with other population-base works such as Skov et al, JAHA 2018 (10.1161/JAHA.117.008247). This is important.
We thank the reviewer for this important comment. As a consequence, further analyses were conducted. In our sample, the prevalence of PWD ≥ 120 ms was 21% (741 participants with such a PWD, confidence interval 20-23%). These participants are likely to have at least a partial interatrial block, but we did not review the morphology of the P wave and could not be conclusive on this point. Results and comparison between participants with a PWD < or ≥ 120 ms are presented in the Supplemental Table 2 of the Appendix.

4) The finding of association between the use of antiarrhythmic drugs is of very limited value since the authors can not distinguish between different classes of AAD. The authors provide no reference to earlier works on AAD. There is quite a few on beta-blockers, less on verapamil, and few on class I and III. But I doubt this part adds any value to the manuscript at all. It is also possible that some patients might have had paroxysmal AF, and the use of AAD was a proxy for that.
Based to this relevant remark and according to point 16) of the Reviewer 1, the association between antiarrhythmics and PWD has been removed from our analysis. Multivariable analysis (Model 2A and 2B) has been repeated without including antiarrhythmic. Results are shown in Table 2.

5) The discussion of mechanisms and pathology behind PWD prolongation can benefit from citing studies that directly assessed relationship between PWD and atrial histology, such as Huo et al., J Electrocardiol 2014 (10.1016/j.jelectrocard.2014.01.011)
Following this relevant comment and according to point 2) and point 18) of the Reviewer 1, we revised the section “Limitations” and “Future Directions”. Unfortunately, we were unable to study this association between PWD and atrial histology because of a lack of echocardiographic or other imaging techniques, and of post-mortem data. We hope that the ongoing follow-up of the CoLaus|PsyCoLaus cohort would provide some information in the near future.

VERSION 2 – REVIEW

REVIEWER	Arttu Holkeri Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland
REVIEW RETURNED	27-Jun-2020

GENERAL COMMENTS	The authors have nicely answered my previous comments. The authors have revised the manuscript well according to the comments or, in some cases, adequately explained and reasoned the lack of need for revisions.

	I have no further comments.

REVIEWER	Pyotr Platonov Lund University, Sweden
REVIEW RETURNED	10-Jul-2020

GENERAL COMMENTS	I am satisfied with the responses provided in regard to the issues I raised. An additional publication on P-wave values from a population-based sample (this time based on the Finnish data: Eranti et al. Orthogonal P-wave Morphology, Conventional P-wave Indices, and the Risk of Atrial Fibrillation in the General Population Using Data From the Finnish Hospital Discharge Register, Europace 2020), which is directly relevant to the topic the authors study, came up published in June and is referable. The authors may wish to cite/discuss this one. Otherwise not further comments.

VERSION 2 – AUTHOR RESPONSE

Answers to Reviewer: 1, Arttu Holkeri

1) The authors have nicely answered my previous comments. The authors have revised the manuscript well according to the comments or, in some cases, adequately explained and reasoned the lack of need for revisions.

I have no further comments.

We thank the Reviewer 1 for the thorough evaluation of the manuscript and his relevant comments that have helped us to improve our work.

Answers to Reviewer: 2, Pyotr Platonov

1) An additional publication on P-wave values from a population-based sample (this time based on the Finnish data: Eranti et al. Orthogonal P-wave Morphology, Conventional P-wave Indices, and the Risk of Atrial Fibrillation in the General Population Using Data From the Finnish Hospital Discharge Register, Europace 2020), which is directly relevant to the topic the authors study, came up published in June and is referable. The authors may wish to cite/discuss this one.

Otherwise not further comments.

We are grateful for the useful and very enriching comments. We have taken into consideration this latest and recent publication by citing it in our manuscript (introduction and furure direction sections).