Author's response to reviews

Title: Ability of Ambulatory ECG-based T-wave Alternans to Modify Risk Assessment of Cardiac Events

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Author's response to reviews: see over
We appreciate the reviewer’s positive remarks and constructive comments. We have made every effort to comply with the suggestions made or otherwise respond to the criticisms raised.

Reply to Reviewer 1:

**Major comment:** Minor Compulsory Revision: First meta-analysis of TWA studies was published by Rizas and Bauer in Editorial Europace doi:10.1093/europace/eus323. This work should be mentioned in the Discussion. Also authors should more clear define what’s new is in their work compared with above.

Response:

Thanks for your comments. The meta-analysis of TWA published by Rizas and Bauer has been discussed in the discussion section. What’s new in our work has also been mentioned in the revised manuscript.

**Minor comment:** Discretionary revision: the title would sound more accurate as “Ability of ambulatory ECG-based T-wave alternans to modify risk assessment of cardiac events: a systematic review”.

Response:

We appreciate your kind suggestion according to the title of our manuscript. The short one may be more concise.

Reply to Reviewer 2:

**Major comment 1:** AECG-based TWA is described as “not well established” (abstract, line 4) or “a promising candidate” (background, line 53). However, historically, TWA has been noted on AECGs to indicate an ominous finding, for example in the setting of proarrhythmia, and it has long been appreciated as an indicator of the Brugada and long QT syndromes. Thus, these statements should be modified. Recently, it has become possible to measure TWA amplitude precisely.
Response:
Thanks for your constructive suggestion. These statements have been revised in our manuscript.

**Major comment 2:** The authors should consider for possible inclusion in this meta-analysis the study by Ren L-N, Fang X-H, Ren L-D, et al. Ambulatory ECG-based T-wave alternans and heart rate turbulence can predict cardiac mortality in patients with myocardial infarction with or without diabetes mellitus. Cardiovasc Diabetol 2012;11:104-111.
Response:
Thanks for your suggestion according to which above-mentioned reference has been discussed in the background and discussion sections.

**Major comment 3:** Background, line 56; discussion lines 165 to 180: When spectral method studies are described, the term “spectral method” should be used not “exercise-based.” By the way, MMA was used during routine, symptom limited exercise testing in the Finnish Cardiovascular Study (FINCAVAS) in nearly 3600 consecutive patients (Leino et al 2011; 8:385–390).
Response:
Thanks for your suggestion. The term “exercise-based” has been replaced by “spectral method” in our manuscript.

**Specific comment 1:** Background, line 60: The study by Monasterio was not negative.
Response:
In the study by Monasterio (Table 3 in their paper)[1], for the end point of cardiac mortality, the prognostic value of TWA was negative. For the end point of SCD, the prognostic value of TWA was positive. This has been discussed in detail in our manuscript.

**Specific comment 2:** Background, line 60: The study by Arisha et al (2013) was not negative, as TWA produced an ROC = 0.64 for SCD or life-threatening ventricular arrhythmias within 6 months. The Arisha study should be included in the tables.
Response:

Thanks for your suggestion. We didn’t include Arisha’s study[2] because their paper did not provide enough primary data (hazard ratio et al.), and an attempt was made to contact the author, but failed to receive the original data. Therefore, this study was not included in our current analysis.

In Arisha’s study[2], the authors interpreted the predictive performance of TWA1 (ROC-AUC =0.64) as “poor”. Survival analyses confirmed the results obtained by ROC curves analyses. TWA1 and TWA2 were not significantly associated with the incidence of the primary outcome (P = 0.15 and P = 0.96, respectively).

Specific comment 3: Methods, line 85: The authors use the term study and trial interchangeably. The term trial is applied only when an intervention has taken place.
Response:

Thanks for your suggestion. The term “trial” has been replaced by “study” in our manuscript.

Specific comment 4: Statements regarding “no unified classification” and the necessity to “standardize the methodology” regarding “cut off values” in discussion, lines 201-208, should be changed to indicate that there are two standard cut-points for MMA: 47 microvolts, which indicates “abnormal” and 60 microvolts which indicates “severely abnormal” test results, as described in the TWA consensus paper (your reference 1).
Response:

Thanks for your suggestion. Two standard cut-points for MMA have been discussed in detail in our manuscript.

Specific comment 5: It should be appreciated that the positive predictive value varies among study populations and is less important than providing an opportunity for physicians to use TWA magnitude in risk assessment, similarly to how other test results are presented, such as blood pressure.
Response:

Thanks for your comments. The discussion about the “standardize the methodology of TWA
assessment during AECG monitoring” has been deleted in our manuscript. Instead, we add some discussion about the opportunity for physicians to use TWA magnitude in risk assessment.

**Minor comment 1:** The authorship of the article by Hou et al 2013 (reference 19—now “Yu et al”) is mislabeled potentially because of English language listing.

Response:
Yes, the authorship of the article by “Hou et al” has been changed to “Yu et al” (PubMed: http://www.ncbi.nlm.nih.gov/pubmed/21920535)[3].

**Minor comment 2:** Discretionary revision: In the abstract and background, a comment could be made indicating that ambulatory ECG (AECG)-based TWA is an important alternative platform to exercise for risk stratification of cardiac events. The TWA consensus guideline, your first reference, should be cited in this context.

Response:
Thanks for your suggestion. The importance of AECG-based TWA has been discussed in detail in our manuscript.

**REFERENCES**

