**REPONSE TO REVIEWERS**

**Manuscript Number:** 26888

**Manuscript Title:** Noninvasive diagnosis of vulnerable coronary plaque

*Reviewer # 1919991*

*The manuscript by Pozo et.al. reviews the use of non-invasive imaging approaches in the diagnosis of vulnerable coronary plaque. In general term the manuscript is well written and follows a logical projection, with general views of different diagnostic imaging approaches follow by clinical application both for diagnosis and prognostic outcomes. There is lots of information on different imaging approaches, and their applicability on clinical settings together with advantages and drawbacks of the approach. The manuscript is of pleasant reading for a wide audience of readers interested in the issue.*

We are glad you found the article of enough interest to be published in WJC. We really appreciate your review.

*Reviewer #289422*

*The following sentences need rephrasing for better understanding: These lesions are unfailingly, but in a variable frequency, associated with thrombus formation15 However, although all the studies have shown a good agreement in non-calcified plaque quantification between both techniques38-40, there were contradictory results in plaque*

*composition analysis using predefined Hounsfield unit (HU) ranges, due to overlapping in these values38, 40 Incidence of slow-flow phenomenon in patients with stable was related with the presence of circumferential plaque calcification… Moreover, when coronary PET was evaluated in ACS and stable angina after stent implantation, a higher FDG uptake was noted not only in the culprit lesions but also in the left main and ascending thoracic aorta of the patients with acute coronary events (Figure 7)102. Figures 5,6 and 7, as stated are taken from the literature. Permission from the authors of the articles or the editor is obligatory.*

First of all, we would like to thank your comments. We have rewritten the sentences you pointed out in order to clarify the message. We hope after these changes we have improved the understanding. Regarding the figures, we were waiting for the permissions that finally we could not achieve, so we have chosen new figures. In this case each editorial has given the corresponding permission. These documents have been attached with the present resubmission.

*Reviewer #227522*

*This is an excellent review about the role of imaging techniques noninvasive in the detection of vulnerable coronary plaque. The authors report advantages, limitations and clinical implications of the coronary computed tomography, cardiac magnetic resonance and positrom emission tomography.*

We really appreciate you positive evaluation of the article.

*Reviewer #2474355*

*Pozo et al. from Cardiology Department, Hospital Universitario de La Princesa, IIS-IP, Universidad Autónoma de Madrid, Madrid, Spain review the role of coronary computed tomography, cardiac magnetic resonance and positron emission tomography in the subclinical detection of vulnerable coronary plaque (thin-cap fibroatheroma) with particular interest of their advantages and limitations as well as the clinical implications of the derived findings. They nicely point that CCT may well index plaque characteristics, such as positive remodeling, low attenuation, spotty calcification and napkin-ring sign, whereas CMR may stress plaque morphology characterization along with tissue characterization of the coronary plaques through T1- and T2-weighted sequences and contrast-enhanced imaging. Finally, PET has emerged as a promising molecular imaging technique being able to detect coronary inflammation and even macrophage infiltration in vivo. The MS is in general well writte with some language defects like in the sentence "… given that the presence of vulnerable plaque features not are irredeemably linked to…" that should be corrected. Importantly these Authors underline that "…large population studies are needed to clarify the patient subgroup that may benefit from non-invasive detection of high-risk plaques". My suggestion is to expand this point since, although they describe what the 3 techniques are able to provide, how this might be applied in the pre-clinical definition of what a potentially life-threatening plaque might be, largely deserves future studies, also in terms of cost-benefit ratio which is not a trivial problem in the present context. Therefore, one may not give the impression that these techniques have a real potential applicability as one may hope in detecting vulnerable plaques that may precipitate AMI or sudden death in populations at risk (several hundred thousands in a large European town like Madrid !).*

We have corrected the language mistake you indicated. Finally, we have tried to emphasize the need for further large studies to clarify not only the relevance of these

noninvasive plaque features for acute coronary event prediction but also the cost-effectiveness of these imaging techniques in this field.