Reviewer's report

Title: Anti-inflammatory and Morphologic Effects of Pitavastatin on Carotid Arteries and Thoracic Aorta Evaluated by Integrated Backscatter Trans-esophageal Ultrasound and PET/CT: A Prospective Randomized Comparative Study with Pravastatin (EPICENTRE study)

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Reviewer: Daniele Panetta

Reviewer's report:

This article reports on a clinical study (EPICENTRE) which aims to evaluate the outcome of a 6 month treatment with pitavastatin in hyperlipidemic patients. The effects of pitavastatin are compared with those of pravastatin in terms of plaque morphology indicators (integrated backscatter and intima-media thickness) as measured by TEE (in aorta) and TTE (in carotid artery) as well as markers of plaque inflammation measured by 18-FDG PET/CT. Biohumoral results are also reported.

General assessment

This article is well structured and falls within the scope of Cardiovascular Ultrasound. Unfortunately, its significance is severely impaired by the small numerosity (N=20) of the patients enrolled (as correctly pointed out by the authors in the “Study limitations” section). Besides this, there are some aspects of the PET protocol that need some clarification as better explained below in this report.

The higher lipid-lowering effect of pitavastatin vs pravastatin has been reported elsewhere: the authors should cite, for instance: Sponseller CA et al, Clin Ther. 2014 Aug 1;36(8):1211-22. doi: 10.1016/j.clinthera.2014.06.009. Nevertheless, I think that the direct comparison in terms of plaque morphology and inflammation is an original aspect of this study and deserves attention. The significant correlation between LDL cholesterol and imaging biomarkers of plaque severity is also worth to be discussed, even though the above mentioned problem of sample size cannot be neglected as far as consensus is concerned.

There is some concern on the statistical analysis. I’ve found just a bit surprising that the significance threshold (p<0.05) was reached for the cIBS changes in the pitavastatin (PI) group (-20.1+/−5.0 dB to -19.6+/−7.0 dB) but not in the pravastatin (PR) group (-19.6+/−7.0 dB to -18.9+/−4.4 dB). With such a low number of patient, it would be more convincing if the author can graphically represent their results of cIBS and TBR (e.g. in a scatter-plot and/or box-plot). The authors should refer to the specific comments below to improve their manuscript.

Major Compulsory Revision
1) cIBS changes and statistical significance.

I understand all the problems related to the sample size in a clinical study. Of course my first suggestion would be to wait for a higher number of patients, because some reader may think that for N=10/group the study can be underpowered and thus even a p<0.05 doesn’t mean by itself that your results are “robust” (i.e., they could change for small changes of the dataset). If it’s not possible for you to increase the size of your sample (as I imagine), for such a small number of patient it would be more convincing if you could graphically represent your results of cIBS and TBR (e.g. in a scatter-plot). Figure 1 reports the % changes of TBR and cIBS in a pooled form, so it’s impossible for the reader to infer which points are from the PI group and PR group. I strongly suggest to double-check your statistical analysis.

2) Measurement of SUV_max and TBR with 18F-FDG-PET.


Anyway, I’m not sure that the only assessment of the TBR_max in such a small ROI (1 cm diam) in the carotid artery is enough to assess the whole inflammation burden. It is also well know that tracer quantification in small objects (e.g., plaques < 1cm) is biased by partial volume artifacts. For this reason, I think that also the TBR_mean (measured as the blood-normalized SUV_mean) should be reported as calculated on a larger volume of interest covering the arterial bed. Probably your choice of such a small ROI was due to the high residual activity in neighboring pixels due to the short injection-to-imaging time: can you add more comment on this?

3) Reproducibility of the ROI selection in PET.

You say that the identification of the target plaque in PET at baseline was done manually by selecting the region with the highest uptake of FDG, whereas you’ve used CT as a reference for TEE. Could you please add more comments on the use of CT plaque images for the selection of your ROI's in PET? Can you say whether the landmark-based identification of ROIs after six month still leads to the region with the highest uptake of FDG? In other words, in how many cases you can still find the target plaque manually after six months? Again, I think that the small size of the ROI chosen for PET quantification can affect the reproducibility of your measurements, and this is why I suggested to report also TBR_mean in larger ROI's in the point 2) above.

Minor essential revisions
4) Please add more information on your PET/CT imaging protocol. More specifically, please add info on the reconstruction algorithm (FBP or iterative) and types of correction (attenuation, decay time, etc) which have strong impact on quantification. Add also the total duration of the scan.

Discretionary Revisions
(mainly stylistic suggestions)

5) ABSTRACT - Conclusions: “… The pravastatin treatment had less of an effect…”. Did you mean “was less effective”?

6) METHODS - PET/CT image acquisition and analysis: “… Patients were injected with 18F-FDG 3.7 MBq (0.1 mCi) /kg…”. Change to “… were injected with 3.7 MBq/kg (0.1 mCi/kg) of 18F-FDG…”

7) DISCUSSION - 3rd paragraph: “It is know that plasma hs-CRP concentrations are associated with high cardiovascular risk”. Change to “It is known that _high_ plasma hs-CRP concentrations…”

(really optional)

8) You have CT images for all patients for both baseline and follow-up: why not reporting also the Ca (Agatston) score? Perhaps your CT protocol was not diagnostic as it was used only for PET attenuation correction, but I’m just guessing. Could you add some comment on this?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.