

Dear Editors and Reviewers,

We would like to thank you for your kind comments and valuable suggestions to our manuscript entitled: **“The relationship between coronary calcium score and high-risk plaque/ significant stenosis”**. We are sending it back for your attention. In this letter, we are providing the response to specific comments directly. We are looking forward to your comments in order to improve our manuscript.

Sincerely,

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## **Detailed Response to Reviewers**

Reviewer 211908

1. We appreciate your acknowledgement.

Reviewer 214240

1. How were patients recruited? Consecutive patients?

Thank you for your comment. We added the next sentence in the Methods section.

“Most patients were referred to our hospital for the evaluation of coronary artery disease because of multiple risk factors and/or symptom of chest pain.”

2. There is a negative correlation between increasing LDL-C and increasing CCS.

Thank you for your comment. We have no clear explanation. About 55% to 60% of patients in each group underwent statin therapy. Intensity of statin therapy might affect these results.

Reviewer 504181

1. We appreciate your acknowledgement.

Reviewer 233953

1. Addition of a reference

We agree with the reviewer and added the next reference in the References section as reference 3.

**Youssef G**, Budoff MJ. Coronary artery calcium scoring, what is answered and what questions remain. *Cardiovasc Diagn Ther* 2012; 2: 94-105. [PMID:24282703 DOI: 10.3978/j.issn.2223-3652.2012.06.04.]

Reviewer 26520

1. Because vulnerable plaques are not usually calcified, the prevalence of high-risk plaque does not increase although CCS increases.

Thank you for your comment. It might be one reason of this phenomenon. However, it's not proven. On the other hand, because the progression of coronary atherosclerotic change is not homogeneous in the three major coronary arteries, high-risk plaque may develop even when the CCS is high. Thus it might be possible that large calcium in patients with high CCS mask the presence of high-risk plaque.

2. Why the patients were referred for CCTA?

Thank you for your comment. We added the next sentence in the Methods section.

“Most patients were referred to our hospital for the evaluation of coronary artery disease because of multiple risk factors and/or symptom of chest pain.”

3. The definition of high-risk plaque and its prognostic significance.

Thank you for your comment. Thomsen et al. performed a systematic review and meta-analysis to study the characteristics of high-risk plaque and its association of prognosis [Eur Heart J Cardiovasc Imaging 2016;7:120-129]. ACS patients had significantly higher number of non-calcified plaque and spotty calcified plaque compared with stable angina (SA) patients. Remodeling index was higher in culprit lesions in ACS compared with SA and compared with non-culprit lesions in ACS patients. The associated risk of future ACS was significantly higher in high-risk than in low-risk plaques. Thus, CCTA can non-invasively characterize high-risk vulnerable coronary plaques and can predict future ACS events in patients with high-risk plaques. Therefore, we think that the prognostic value of high-risk plaque is well established.

As a reviewer suggested, there are too few events to suggest the validity of our definition in our study. However, the reason is obvious, which is the low number of patients and the short follow-up period. In addition, our patients are at low risk for coronary events, because these patients have no known CAD, which means

subclinical CAD. Moreover, we prescribed high-intensity statin therapy for patients with high-risk plaque. We think that these are the reasons why there are too few events in our study. Our experience also suggests that diagnosing high-risk plaque when no calcium is present is not difficult.

Therefore, we added the next sentence in the limitation section.

“We think that it is difficult to demonstrate differences in hard cardiac events among the four groups, because the number of patients and follow-up period were not sufficient. In addition, our patients are basically at low risk for coronary events, because these patients have no known CAD, which means subclinical CAD. Moreover, we prescribed high-intensity statin therapy for patients with high-risk plaque. We think that these are the reasons why there are too few events in our study.”

4. Inclusion of coronary revascularization in MACE is misleading.

Thank you for your comment. As stated in the limitation section, we used strict criteria for the selection of patients who underwent coronary revascularization. We selected coronary revascularization only for patients with either moderate to severe ischemia on myocardial perfusion imaging or fractional flow reserve less than 0.75. Many studies demonstrate that these patients are at increased risk of coronary

events, and benefit from coronary revascularization. Actually, only half of patients with significant stenosis on CCTA underwent coronary revascularization. Therefore, we think that inclusion of coronary revascularization is valid.

Thus, we added the next sentence in the limitation section.

“We selected coronary revascularization only for patients with either moderate to severe ischemia on myocardial perfusion imaging or fractional flow reserve less than 0.75. Many studies demonstrate that these patients are at increased risk of coronary events, and benefit from coronary revascularization.”

5. The conclusion should be altered.

Thank you for your comment. As we showed in discussion section, our point is that we clearly showed the relationship between coronary calcium score and high-risk plaque/ significant stenosis. There was each study which showed the relationship between coronary calcium score and significant stenosis, and coronary calcium score and high-risk plaque, respectively. However, no previous study comprehensively showed the relationship between coronary calcium score and high-risk plaque/ significant stenosis.