Reviewer A:

The authors present a single centre retrospective observational study across a medium - long term period of follow up. The hypothesis is that high risk plaque on CTCA in a primary prevention population is associated with an increased likelihood of predicting ACS. The paper is well written and despite not being particularly novel in its findings, warrants publication if efforts are made to improve the robustness and validity of the work.

Comment 1

Is this truly a primary prevention population? Indication for CTCA is for those with CVD risk factors and angina equivalent symptoms. Hence, does the presence of OS in this patient population not incorporate secondary prevention subjects? The patients excluded were those who had prior revascularisation. Is revascularisation the yardstick for secondary prevention? To this end it must be questioned whether the paper addresses its hypothesis? Perhaps defining what the authors mean by "primary prevention" would be useful here. Is it those free of OS >70%, free of prior revascularisation, free of clinically documented NSTEMI/STEMI, free of medical therapy for coronary artery disease?

Reply 1

We thank the reviewer for the comments. We agree with the reviewer that this population does not represent a primary prevention cohort. Therefore, we have removed the reference about primary prevention cohort in our manuscript. Instead we have clarified that our population consist of patients who are free of prior revascularisation and prior documented acute coronary syndrome. **The changes have been made on page 14, paragraph 3.**

Comment 2

Data on CTCA intra-observer reliability should be presented. How reproducible and consistent is the assessment of HRP at the site of MLA? This is important given the authors position about the ease and utility of interpreting LAP at site of MLA in their discussion. If this is a practice to be adopted, how reliable is it?

Reply 2

We thank the reviewer for the comment. The assessment of HRP at the site of MLA was highly reproducible with excellent intraobserver and interobserver reproducibility. The intraclass coefficient were 0.92 and 0.91 respectively. We have added this to the manuscript on **page 10, paragraph 1.**

Comment 3

Was multi-regression analysis performed for OS lesion? Was it an independent predictor of ACS? Was their correlation between HRP at site of MLA in predicting culprit lesions for ACS. This data should be presented.

Reply 3

We thank the reviewer for the comment. OS lesion was not an independent predictor (p=0.434) of ACS on multi-regression analysis. **This has been added to the manuscript on page 11, paragraph 4.**

Comment 4

Discussion about emerging methods of CTCA detection for adverse event, such as coupling CT with PET probes and FAI. NB: FAI has recently been demonstrated to outperform HRP as a predictor for adverse events, this should be acknowledged/discussed.

Reply 4

This has now been addressed in discussion.

Comment 5

Minor comments:

Methods: CT coronary angiography 'all patients received sublingual nitroglycerine'. Although this may be a routine for the institution, GTN is omitted infrequently for clinical reasons. Can the authors confirm each of these patients received GTN? If not I would suggest the language be softened.

Reply 5

We thank the reviewer for the comments. We can confirm that the administration of GTN is a routine practice in our institution even in patients with severe aortic stenosis.

Comment 6

In the discussion some commentary about why HRP coupled with OS appears to be a driver of ACS would be welcomed. Historical and histological studies have suggested that OS is not a requirement for ACS, but rather the smaller luminal area seen in OS coupled with plaque rupture/thrombus increases the likelihood of ACS. The authors data seemingly supports this notion.

Reply 6

We thank the reviewer for the comment and suggestion. We have added to the discussion that a sub study from COURAGE trial also found an association between stenosis > 50% and future AMI. In addition, pathological studies have demonstrated that ruptured plaques demonstrated layering from multiple healed plaque ruptures suggesting that silent plaque ruptures and healing may contribute to rapid plaque growth in HRP prior to an event. **We have added this to our manuscript on page 16,**

paragraph 1.

Reviewer B:

Comment 1
This paper is a retrospective replica of the study by Motoyama et al (JACC 2007 and 2015). It does not add anything to these papers. As the papers by Motoyama, it is critically flawed by not accounting for the coronary atheroma burden. If you compared "HRP" vs. none, you may also compare plaque vs. no plaque. Of course, the former is associated with events. The value of "HRP" can only be assessed if the analysis is adjusted for coronary atheroma burden. The authors are encouraged to perform this analysis and resubmit. In its current form, the results are potentially misleading and should not be distributed.

Reply 1
We thank the reviewer for the comment and suggestion. We have performed the assessment of   total coronary atheroma burden quantitatively as well as semi-quantitively (SIS and SSS). Total plaque length (p=0.78), total plaque burden (p=0.58) and in addition, the measures of total atherosclerotic plaque burden such as SIS (p=0.11) and SSS (p=0.09) were not associated with ACS. **We have added the section in the methodology on page , paragraph and results section on page 13, paragraph 1.**