Peer Review File

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Reviewer A

Please discuss the difference between this study and other published studies (HUYGENS and PACMAN).

Reply: Thank you for your comment. Differences between this study and the HUYGENS and PACMAN-AMI trials are as follows:

Firstly, while the HUYGENS and PACMAN-AMI trials focused on patients with acute myocardial infarction (AMI), this study includes individuals at very high risk of atherosclerotic cardiovascular disease (ASCVD) based on risk stratification, encompassing both acute coronary syndrome (ACS) and stable angina in its clinical manifestations.

Secondly, the HUYGENS and PACMAN-AMI trials involved populations from Europe and North America, whereas this study exclusively recruits participants from China, representing the Asian population. The aim is to provide evidence for the application of high-intensity lipid-lowering therapy in Asian populations.

Thirdly, this study explores the pleiotropic effects of PCSK9 inhibitors on atherosclerotic plaques. Additionally, endo-PAT is utilized to measure the reactive hyperemia index (RHI) of patients, assessing the impact of PCSK9 inhibitors on endothelial function.

We have added a description in the discussion section (see Page 10-11, line 237-247).

Changes in the text: Discussion line 237-247.

Reviewer B

This study design paper describes the rationale and methodology for a single-centre, randomised open-label study that will use serial OCT to investigate the effect of evolocumab on plaque composition in patients with “super high risk ASCVD”, a classification term that I am not familiar with and that does not clearly depict the population of patients that actually will be studied. The sample size is very small and almost certainly underpowered. Coupled with the fact that it will be performed in a single centre, is open label and without a placebo comparator, it is unlikely that this study will add definitive, incremental information to a field that has already been well interrogated through the much larger, multicentre, placebo-controlled HUYGENS and PACMAN-AMI studies in recent years. I have the following additional comments:

1. To the best of my knowledge, the term “super high risk" is not conventional terminology. It should be removed/replaced, or at the very least clearly defined as to what it actually means, using published criteria. In the Introduction of page 1, the authors also state “In China, 75.1% of the patients are classified as those with super high-risk atherosclerotic cardiovascular disease (ASCVD).” This also needs a reference.

2. There is quite a lot of misleading information about the potential novelty of this study in the Abstract, Introduction and Discussion. In the abstract, it is stated that: “Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are effective in reducing LDL-C levels, but their effect on local coronary plaque vulnerability remains uncertain.” This is not correct. HUYGENS (which has not been cited here) and PACMAN-AMI showed the effect of PCSK9i on local plaque stability. Similarly, on page 2 in the Introduction, it is stated: “However, the mechanism by which PCSK9i combined with statin improves the vulnerability of local coronary plaque is unclear, which may be

due to lipid reduction that increases the stability of vascular plaque and thus reduces the incidence of MACE(14).” To the contrary, the mechanisms have been well delineated by both HUYGENS and PACMAN-AMI among other studies. The current study is much smaller than these studies and probably underpowered to meet its endpoints. The authors should not overstate what their study will achieve, even if its novelty is that it is specifically targeted to a Chinese population.

3. The failure to reference the HUYGENS study (PMID: 35431172) which showed the effect of PCSK9i on plaque composition in the post MI setting several months before PACMAN-AMI is a major oversight and should be corrected.

4. The authors have not defined how the target vessel / lesion for OCT imaging will be defined. How many vessels will be imaged per patient? Will this include lesions within the stented vessel or only non-culprit, non-stented vessels? What is the stenosis threshold for imaging? How soon after imaging will participants be randomised?

5. References should be provided for how the different OCT parameters will be measured. Will a blinded core laboratory perform analysis? How many analysts? What is the expected inter- and intra-observed reproducibility of the key OCT measurements in your hands?

6. The authors state that their anticipated sample size is based on the assumptions that “The FCT change at 12 weeks is 32 um, and the standard deviation is 30.8 um. Assuming a 20% loss of follow-up rate, 12 patients in each treatment group are asked to provide 90% power at a 2-sided α of .05.” I have performed my own sample size calculation using these predicted numbers and obtained a sample size of 138 participants per group. Furthermore, HUYGENS and PACMAN-AMI were much larger studies than n=12 per group to show their differences in minimum FCT with very similar study design. I therefore have serious doubts about how the authors have obtained their sample size calculations.

7. The Discussion begins with the following “To date, the study populations using intravascular imaging to assess the effect of PCSK9i have been mostly differentiated according to the clinical manifestations of CAD. There is a gap in the study of specific populations at risk for ASCVD. Therefore, the inclusion of patients with super high-risk ASCVD in this experiment is an innovation.“ Firstly, it is not at all clear what the authors mean by super high-risk ASCVD. Secondly, it is not apparent how their study design (other than specifically targeted to a Chinese population) is different from preceding studies in this field and therefore how it is actually innovative. Are they dealing with post-ACS patients (like HUYGENS and PACMAN-AMI) or patients with stable coronary disease, or both? Please elaborate.

Reply: Thank you for your insightful comments.

1. The Chinese Lipid Management Guidelines (2023) define very high-risk atherosclerotic cardiovascular disease (ASCVD) as having had ⩾2 severe ASCVD events or 1 severe ASCVD event combined with ⩾2 high risk factors. We have added corresponding descriptions and citations to the original text (see page 2, line 37-49).

2. Misleading information in the original manuscript has been modified, and the sample size required for the study has been recalculated with the help of statistical experts to improve the scientificity of the study.

3. We have added the differences between this study and HUYGENS 'and PACMAN-AMI's studies in the discussion section (see page 11-12, line 240-250).

4. We have added the definition of OCT imaging lesions in the methods section: three blood vessels will be scanned by OCT. OCT imaging will be performed on plaques with non-left main artery and

non-culprit lesions with a visual angiographic estimate of 20%-70% diameter stenosis. If there are more than two eligible lesions, the lesion with the most severe stenosis will be selected as the target lesion for OCT analysis (see page 7, line 167-173).

5. This study will not require a blinded core laboratory perform analysis, and a total of 3 OCT technicians performed the analysis. Inter-observed stability will be achieved through back-to-back analysis by two experienced OCT technicians and verification by a third technician. Intra-observed stability wille be achieved through matching target lesions between baseline and follow-up OCT and comparing based on the distance from the landmarks (see page 6, line 142-144, and page 7, line 169-171).

6. We have recalculated the sample size needed for the study with the help of statistics experts. Each group will require 120 patients (see page 11, line 215-220).

7. This study include ASCVD patients at very high risk of developing MACE in the future, including clinical manifestations of ACS and SAP at the time of inclusion (see page 11-12, line 243-250).

Changes in the text: line 37-49, line 167-173, line 215-220, line 240-250.

Reviewer C

The authors presented the protocol for a randomized controlled trial with the goal to assess the impact of evolocumab on thin-cap fibroatheroma in patients with super high-risk atherosclerotic cardiovascular disease with optical coherence tomography. The manuscript is with merit, but several aspects need improvement before publication can be considered. The authors should omprove English language, grammar and style (please correct typos, such as “stain” instead of “statin”, line 40, as example). The authors should also revise the manuscript for use of abbreviations (abbreviations should be explained the first time used, i.e. OCT should be explained as optical coherence tomography). Other comments:

- Introduction line 50: please provide a section explaining briefly what OCT is, what it measures, principle of operations, and summary of current evidence of its use
- The authors should expand the introduction and provide more evidence about the background of the study, highlighting what is known on this specific topic from the literature with more citations
- Methods: it seems the manuscript is a draft with missing information, for example “XXX” at line 69: please provide accurate details
- What type of consent the participants will give? Written or oral? Please add this information to the manuscript
- The authors should add a section on the potential limitations of the study

Reply:Thank you for your comment. We have invited native speakers with medical backgrounds to refine the article. We have added the principle and evidence of OCT expand the introduction section (see page 3, line 78-88). This research will give participants written consent form (see page 4, line 114-114. We have added a limitation section (see Page 13, line 292-299). As for “missing information”, this is because the journal adopts a double-blind peer review process, where the editor redacts author-related information from the original manuscript. We ensure that the manuscript information remains complete.

Changes in the text: line 78-88, line 114-114, ine 292-299.

Reviewer D

Comment #1: please add a line in the title stating that this is a description of the study design rather

than the actual results

Comment #2: please comment on power-calculation of sample size. A sample size of n =12 seems extremely low

Reply:Thank you for your comment.

1. We have revised the title to “Assessing the impact of evolocumab on thin-cap fibroatheroma and endothelial function in patients with very high-risk atherosclerotic cardiovascular disease: a study protocol for a randomized controlled trial”.

2. Upon re-examining the results of previous studies and guided by statistical experts, we recalculated the sample size. For each group, 120 patients will be required (see page 11, line 215-220).

Changes in the text: line 1-3, line 167-173, line 215-220.