## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Safety and Efficacy of PCSK9 Inhibitor (Evolocumab) in Patients with Non-ST Segment Elevation Acute Coronary Syndrome and Non-Culprit Artery Critical Lesions: A Randomized Controlled Trial Protocol (SPECIAL Study) |
| **AUTHORS** | Wang, Yu-wei; Xu, Jie; Ma, Likun; Hu, Hao; Chen, Hong-Wu; Hua, Jing-Sheng; Kong, Xiang-Yong; Li, Dan; Li, Long-Wei; jianyuan, pan; Wu, Jiawei |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ferri, Nicola<br>Università degli Studi di Padova, Department of Medicine |
| **REVIEW RETURNED** | 01-Feb-2024 |

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| **GENERAL COMMENTS** | In the present manuscript the authors described the study design of a clinical trial aimed at investigating<br>the safety and efficacy of Evolocumab in patients with NSTE-ACS and concomitant multivessel CAD (non-culprit artery stenosis between 50% and 75%). This study is, therefore, different from previous studies such as GLAGOV, HUYGENS and ACMAN-AMI. Thus, the rational is valid and the trial very well designed. My statement is supported by the fact that the study received the approval from the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital), with approval number 2023-key-214.<br><br>Minor comments.<br>Statistical analysis is described in the past verb, the authors should change it in future tense.<br>Same thing for the first sentence of methods and analysis “In this single-center clinical randomized controlled trial, 122 patients with NSTE-ACS and concomitant multivessel CAD (non-culprit artery stenosis between 50% and 75%) were randomly assigned to either the evolocumab treatment group or the standard treatment group after completing culprit vessel revascularization”<br>The following sentence is written with different font than the rest of the manuscript “The primary endpoint is the change in minimum FCT from baseline to week 50. Secondary endpoints include changes in plaque lipid arc, lipid length, macrophage grading, lipid levels and MACE during the 1-year follow-up. The authors should correct it.<br>There are minor typos errors that should be correct.<br>I also suggest adding the following reference in the introduction “Pharmacological rationale for the very early treatment of acute coronary syndrome with monoclonal antibodies anti-PCSK9. Ferri N, Ruscica M, Lupo MG, Vicenzi M, Sirtori CR, Corsini A. |

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| | Pharmacol Res. 2022 Oct;184:106439.<br>doi:10.1016/j.phrs.2022.106439. |

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| **REVIEWER** | van Royen, Niels<br>Radboudumc, Cardiology |
| **REVIEW RETURNED** | 04-Mar-2024 |

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| **GENERAL COMMENTS** | Wang, Yu-Wei et al. present a manuscript about a trial protocol whether evolocumab + statin therapy would induce more favourable changes than statin therapy alone to intracoronary atheroma on OCT imaging in patients presenting with non-stemi and multivessel disease. Strength of this trial is that it is a randomized trial and includes patients with more severe coronary narrowing (50-75% DS). Unfortunately, it is not placebo controlled or blinded. Follow-up lasts 52 weeks.<br><br>F. Mensink, MD and J. Los, MD have contributed to reviewing and commenting on this manuscript.<br><br>Major comments<br><br>General<br>- Dates of the study should be included in the manuscript (Requested by BMJ open). It is not clear whether this trial has started, nor what the current status is. Furthermore, write in a consistent tense (present or past), it is not clear what has been done, and what not.<br>- Why would you prescribe rosuvastatin 10 mg/day? This is not considered a high-intensity statin therapy dose. Therefore, patients without evolocumab seem not adequately treated. Therefore, the change of achieving positive results is higher.<br><br>Methods<br>- Will the image-analysis be done by an independent core lab? And will these researchers be blinded for treatment group / sequence of imaging? (baseline vs follow-up)<br>- Primary endpoint is not adequately defined. Is it % change? Or absolute change?<br>- Statistical analysis: With what statistical method is change in FCT assessed? In the text, it seems that comparisons between baseline and follow-up measurements are done with the t-test, however, baseline FCT is also a covariate/confounder, for example ANCOVA could be used. Please elaborate more on your statistical analysis.<br><br>Minor comments<br><br>Abstract<br>- Please add that you perform OCT imaging in the methods.<br><br>Introduction<br>- Line 46: Please add reference to the first sentence.<br>- Line 13: Please use correct form of abbreviation of oxidized low-density lipoprotein (for example ox-LDL).<br>- Line 27: Please provide treatment targets.<br>- Line 33: Sentence build-up seems incorrect.<br>- Is stenosis severity mentioned in the introduction based on angiography or imaging?<br><br>Methods |

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| | - Please check study design flow charts for grammar mistakes. Current quality is rather poor.<br>- When is informed consent obtained? Before PCI or after culprit PCI?<br>- Will you correct for possible differences in baseline values of the primary endpoint?<br>- Line 12: This line seems rather subjective, please rewrite.<br><br>Discussion<br>- Page 15, line 5: I think you won't be able to explore plaque volume, as the penetration depth of OCT is limited. To test the hypothesis if plaque volume will change, IVUS or cardiac CT are preferred.<br>- Please mention in your discussion other ongoing studies on the same topic. For example, the ongoing FITTER study (NCT04141579) investigates change in non-culprit FFR by evolocumab in the same patient group. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1

In the present manuscript the authors described the study design of a clinical trial aimed at investigating the safety and efficacy of Evolocumab in patients with NSTE-ACS and concomitant multivessel CAD (non-culprit artery stenosis between 50% and 75%). This study is, therefore, different from previous studies such as GLAGOV, HUYGENS and ACMAN-AMI. Thus, the rational is valid and the trial very well designed. My statement is supported by the fact that the study received the approval from the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital), with approval number 2023-key-214.

Minor comments.

Statistical analysis is described in the past verb, the authors should change it in future tense. Same thing for the first sentence of methods and analysis "In this single-center clinical randomized controlled trial, 122 patients with NSTE-ACS and concomitant multivessel CAD (non-culprit artery stenosis between 50% and 75%) were randomly assigned to either the evolocumab treatment group or the standard treatment group after completing culprit vessel revascularization"

Reply: Thank you for your valuable comment. I'm deeply sorry for making that mistake. I have checked it carefully and corrected.

The following sentence is written with different font than the rest of the manuscript "The primary endpoint is the change in minimum FCT from baseline to week 50. Secondary endpoints include changes in plaque lipid arc, lipid length, macrophage grading, lipid levels and MACE during the 1-year follow-up. The authors should correct it.

Reply: Thank you for your valuable comment. I'm really sorry for making that mistake. I have checked it carefully and corrected.

I also suggest adding the following reference in the introduction "Pharmacological rationale for the very early treatment of acute coronary syndrome with monoclonal antibodies anti-PCSK9. Ferri N, Ruscica M, Lupo MG, Vicenzi M, Sirtori CR, Corsini A. Pharmacol Res. 2022 Oct;184:106439. doi:10.1016/j.phrs.2022.106439.

Reply: We are sincerely appreciative of the reviewer's constructive and valuable advice. According to the suggestion of reviewer, we have added this relevant article "Pharmacological rationale for the very early treatment of acute coronary syndrome with monoclonal antibodies anti-PCSK9. Ferri N, Ruscica M, Lupo MG, Vicenzi M, Sirtori CR, Corsini A. Pharmacol Res. 2022 Oct;184:106439.doi:10.1016/j.phrs.2022.106439."as a reference in the introduction section.

Dear Reviewer,
Thank you for the valuable comments and suggestions regarding our manuscript（Manuscript ID：bmjopen-2023-083730） entitled “Safety and Efficacy of PCSK9 Inhibitor (Evolocumab) in Patients with Non-ST Segment Elevation Acute Coronary Syndrome and Non-Culprit Artery Critical Lesions: A Randomized Controlled Trial Protocol (SPECIAL Study)”. All the authors have discussed these comments and revised the manuscript accordingly. Point-by-point responses to the reviewers’ comments are listed below. All changes made in the revised manuscript were highlighted with red.

Reviewer 2
Manuscript summary
Wang, Yu-Wei et al. present a manuscript about a trial protocol whether evolocumab + statin therapy would induce more favourable changes than statin therapy alone to intracoronary atheroma on OCT imaging in patients presenting with non-stemi and multivessel disease. Strength of this trial is that it is a randomized trial and includes patients with more severe coronary narrowing (50-75% DS). Unfortunately, it is not placebo controlled or blinded. Follow-up lasts 52 weeks.

Major comments
General
- Dates of the study should be included in the manuscript (Requested by BMJ open). It is not clear whether this trial has started, nor what the current status is. Furthermore, write in a consistent tense (present or past), it is not clear what has been done, and what not.
Reply: Thank you for your valuable comment. Actually,the SPECIAL trial has been implemented in April 2023. We have added that infromation in the revised manuscript and corrected the tense problem in the revised manuscript.

- Why would you prescribe rosuvastatin 10 mg/day? This is not considered a high-intensity statin therapy dose. Therefore, patients without evolocumab seem not adequately treated. Therefore, the change of achieving positive results is higher.
Reply: Thank you for the insightful comments from the reviewer, which I deeply appreciate. I agree with your perspective. However, we must confront the reality that a significant number of high-risk cardiac patients worldwide have not received intensified lipid-lowering treatment, resulting in their LDL-C levels not achieving the target values recommended by guidelines. Data released by the ACC in 2023 indicates that as many as 72% of high-risk patients have never reached the LDL-C targets set by the guidelines, with only 2% of patients having received combination lipid-lowering therapy. The Dyslipidemia International Study-China (DYSIS-China) revealed that 88.6% of patients were treated with statin monotherapy, with an LDL-C attainment rate of 19% at hospital admission for ACS patients, which only increased to 37% after a 4-month follow-up[1, 2]. Results from the China Cardiovascular Disease Quality Improvement Project show that the LDL-C attainment rate among ASCVD patients treated with statins is merely 33.6% [3]. This may be associated with adverse drug reactions such as liver damage and myalgia following intensified statin treatment, affecting patient compliance[4]. Given the current state of lipid control, we chose Rosuvastatin 10mg/day as the standard lipid-lowering treatment protocol, which more closely mirrors the real-world statin treatment landscape and to a certain extent, better reflects the impact of adding alirocumab to statin treatment on patient outcomes in the real world. Nonetheless, we cannot deny the limitations of treating with Rosuvastatin 10mg/day, which indeed represents one of the weaknesses of our study, and we hope to address this in future research.

Methods
- Will the image-analysis be done by an independent core lab? And will these researchers be blinded for treatment group / sequence of imaging? (baseline vs follow-up)

Reply: We appreciate the insightful and profound comments made by the reviewer. The answer is yes. All imaging performed will be electronically transferred to the central core laboratory at the First Hospital of the University of Science and Technology of China, Anhui Provincial Hospital. And all the analysts are blinded to the treatment status of the patient and to imaging timepoint (baseline/follow-up). This part of the explanation has already been supplemented in the methodology section.

- Primary endpoint is not adequately defined. Is it % change? Or absolute change?
Reply: Thank you for your valuable comment. We apologize for not being able to give a precise definition. The primary endpoint is the absolute change in minimum FCT. We have corrected in the revised manuscript.

- Statistical analysis: With what statistical method is change in FCT assessed? In the text, it seems that comparisons between baseline and follow-up measurements are done with the t-test, however, baseline FCT is also a covariate/confounder, for example ANCOVA could be used. Please elaborate more on your statistical analysis.
Reply: It's a very constructive and thought-provoking comment! We wholeheartedly concur with the reviewer's recommendation to employ ANCOVA for negating the influence of baseline discrepancies on our findings. Accordingly, we have implemented the suggested adjustments in the revised manuscript.

Minor comments
Abstract
- Please add that you perform OCT imaging in the methods.
Reply: Thanks for your profound and thought-provoking comment, we have added the relevant content to the corresponding part of the revised manuscript as suggested.

Introduction
- Line 46: Please add reference to the first sentence.
Reply: We thank the reviewer for the valuable comment. We have made the corresponding changes in the revised manuscript as suggested.

- Line 13: Please use correct form of abbreviation of oxidized low-density lipoprotein (for example ox-LDL).
Reply: Thank you for your valuable comment. I'm deeply sorry for making that mistake. I have checked it carefully and corrected.

- Line 27: Please provide treatment targets.
Reply: Thank you for your valuable comment. The treatment target for LDL-C levels is <70 mg/dL. We've highlighted it in the revised manuscript.

- Line 33: Sentence build-up seems incorrect.
Reply: Thank you for your valuable comment. I'm deeply sorry for making that mistake. I have checked it carefully and corrected.

- Is stenosis severity mentioned in the introduction based on angiography or imaging?
Reply: We thank the reviewer for valuable comments. The stenosis severity mentioned in the introduction is based on angiography.

Methods
- Please check study design flow charts for grammar mistakes. Current quality is rather poor.
Reply: We are sincerely appreciative of the reviewer's constructive and valuable advice. I'm deeply sorry for making that mistake. We have scrutinized the study design flowchart and made corrections.

- When is informed consent obtained? Before PCI or after culprit PCI?
Reply: We sincerely appreciate the reviewer's valuable comment. We will obtain informed consent from the patient after PCI.

- Will you correct for possible differences in baseline values of the primary endpoint?
Reply: Thanks for your profound and thought-provoking comment. Yes, we will correct for possible differences in baseline values of the primary endpoint. To achieve this, we plan to use ANCOVA (Analysis of Covariance), which will allow us to adjust for baseline differences effectively and ensure that the observed effects are due to the intervention rather than initial disparities.

- Line 12: This line seems rather subjective, please rewrite.
Reply: Thank you for your valuable comment. We have rewritten it and highlighted it in the revised manuscript.

Discussion
- Page 15, line 5: I think you won't be able to explore plaque volume, as the penetration depth of OCT is limited. To test the hypothesis if plaque volume will change, IVUS or cardiac CT are preferred.
Reply: Thanks for your profound and thought-provoking comment, we agree with the reviewer that the OCT is unable to explore plaque volume. We have made changes accordingly.

- Please mention in your discussion other ongoing studies on the same topic. For example, the ongoing FITTER study (NCT04141579) investigates change in non-culprit FFR by evolocumab in the same patient group.
Reply: It's a very constructive and thought-provoking comment! According to the suggestion of reviewer,we have mentioned this relevant study in the discussion section.

[1] Gitt, A.K., et al., Contemporary data on treatment practices for low-density lipoprotein cholesterol in 3867 patients who had suffered an acute coronary syndrome across the world. Data Brief, 2018. 16: p. 369-375.
[2] Jiang, J., et al., Uncontrolled hyperlipidemia in Chinese patients who experienced acute coronary syndrome: an observational study. Ther Clin Risk Manag, 2018. 14: p. 2255-2264.
[3] Xing YY., et al., Current status of statin use and low-density lipoprotein cholesterol levels in elderly hospitalized patients with acute coronary syndromes aged 75 years and older. Chinese Journal of Cardiovascular Disease.2019(05):351-359.(In Chinese）
[4] Lin, J.L., et al., Real-World Analyses of the Safety Outcome among a General Population Treated with Statins: An Asian Population-Based Study. J Atheroscler Thromb, 2022. 29(8): p. 1213-1225.

**VERSION 2 – REVIEW**

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| **REVIEWER** | van Royen, Niels<br>Radboudumc, Cardiology |
| **REVIEW RETURNED** | 15-Apr-2024 |

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| **GENERAL COMMENTS** | Wang, Yu-Wei et al. present their revised manuscript about the trial protocol of the SPECIAL study. This paper now reads clearly because it has been changed to a consistent tense. Please find the comments on the revised manuscript and replies below.<br><br>J. Los, MD has contributed to reviewing and commenting on this manuscript.<br><br>Minor comments |

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| | Methods:<br>- It is accurate to say that many patients fail to meet their LDL-C therapy objectives. However, this may not be a reason to not treat accordingly. Nonetheless, this limitation has now been well described in the manuscript.<br>- Since written informed consent is obtained after PCI, a second procedure to perform OCT of the non-culprit vessel seems needed. Otherwise, oral informed consent seems needed to perform OCT imaging during the index procedure and written informed consent is obtained afterwards. Please add the applied workflow to the study design.<br>- The updated study design flowchart has not been added to this manuscript.<br><br>Results table<br>- Please adjust “minimal FCT” to “minimum FCT” |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer 2

Wang, Yu-Wei et al. present their revised manuscript about the trial protocol of the SPECIAL study. This paper now reads clearly because it has been changed to a consistent tense. Please find the comments on the revised manuscript and replies below.

Major comments

Methods:

- It is accurate to say that many patients fail to meet their LDL-C therapy objectives. However, this may not be a reason to not treat accordingly. Nonetheless, this limitation has now been well described in the manuscript.

Reply: We sincerely appreciate the reviewer's constructive and valuable advice. However, this is the limitation of our research.

- Since written informed consent is obtained after PCI, a second procedure to perform OCT of the non-culprit vessel seems needed. Otherwise, oral informed consent seems needed to perform OCT imaging during the index procedure and written informed consent is obtained afterwards. Please add the applied workflow to the study design.

Reply: We sincerely appreciate the reviewer's constructive and valuable advice. As detailed in Table 1, within 24 hours of completing culprit vessel revascularization, the Principal Investigator (PI) will confirm patient eligibility and obtain written informed consent. We have updated the study design flowchart accordingly.

- The updated study design flowchart has not been added to this manuscript.

Reply: Thank you for your valuable comment. An updated study design flowchart will be included as an attachment with the revised manuscript.

Results table

- Please adjust “minimal FCT” to “minimum FCT”

Reply: Thank you for your valuable comment. I’m deeply sorry for making that mistake. I have checked it carefully and corrected.