Dear editors and reviewers:

I am pleased to resubmit for publication the revised version of (Manuscript NO.: 75684, Case Report) “Proprotein convertase subtilisin/kexin type 9 inhibitor nonresponses in an adult with a history of coronary revascularization: A case report”. I appreciated the constructive criticisms of the Editors and the reviewers. I have addressed each of their concerns as outlined below and the amendments are highlighted in Red in the revised manuscript. We hope the new manuscript will meet your magazine's standard. Below you will find our point-by-point responses to the reviewers' comments/ questions.

****

Responses to reviewers

Reviewer #1:

Major issue: **comment：**

1) Which APOB mutation was identified in the patient and his mother? Was that mutation crucial for the patient's phenotype? Please discuss.

Response：Thank you very much for reviewing the manuscript. This was a very good suggestion.

1） A APOB heterozygous mutation (c.10700C>T p.T3567M) which was identified in the patient and his mother.

2) The causing mutations (LDLR, PCSK9, and APOB) are well known and well described. ‘The most commonly affected gene, accounting for >90% of cases, involves the low-density lipoprotein receptor (LDLR), followed by apolipoprotein B (APOB) (w5%) and proprotein convertase subtilisin/kexin type 9 (PCSK9) (<1%)’ *(Brandts J, Ray KK. FamilialHypercholesterolemia: JACC Focus Seminar 4/4. J Am Coll Cardiol. 2021 Nov 2; 78(18): 1831-1843. doi: 10.1016/j.jacc.2021.09.004. PMID: 34711342)*

However, the LDL level in FH who caused by APOB gene mutations are significantly lower than the others. My team and I think that mutation WAS NOT

crucial for the patient's phenotype. Moreover, I think we still need to discuss about this in the discuss section. We are glad to add the appropriate text in the revised version.

2) Since an APOB mutation has also been detected, was the patient's case type I FH (OMIM: 143890) or type 2 FH (OMIM: 144010)?

Response： Thank you for suggesting this**.**

We authors think that mutation wasn’t crucial for the patient's phenotype after several discussions. Therefore, these uncertainties didn’t affect the main conclusions of our study.

Minor issues

1) Please correct the phrase "Nonetheless, our patient refused this treatment. as it was too expensive for him." (Page 7)

Response： Sorry for the misunderstanding. We have changed this sentence to "However, the patient refused this treatment. It was too expensive for him."(Page 7)

2) Please correct the phrase "The patient had received aspirin 100 mg QD, clopidogrel 75 mg QD (clopidogrel resistance have been excluded). and simvastatin 20mg QN. before the admission to our hospital."

Response： We changed the sentence accordingly. (Page 7)

3) Please amend the phrase "(Guidelines for the treatment of coronary artery disease)." for a suitable reference.

Response： we have Deleted this inappropriate phrase. And references have been added. (2021 ESC Guidelines on cardiovascular disease prevention in clinical practice) (see reference 8).

****

Reviewer #2:

comment：1.The description of the case is inadequate with respect to clinical

history, Investigation and therapy administered. Please see comments in the file attached.

Response： Thank you very much for your hard work to review the article and valuable comments. More detailed description would be better. We have modified each of these issues in the file attached. At the same time, a few slips of the pen need to be removed. Some details are explained in the following:

1) Despite multiple ACS, the EF is preserved!

Response The original results of B-scan ultrasonography were examined accordingly. Normal ejection fraction was confirmed. Possible explanations for this are the following: a) B-scan ultrasonography (2009) shows the patient's ejection fraction was 66%. The basal value was rather high. b) The patient has good treatment compliance. He was also relatively young. c) Some patients see to remain normal ejection fraction according to some research papers (*Change in Left Ventricular Ejection Fraction Following First Myocardial Infarction and Outcome PMID: 29798797 DOI: 10.1016/j.jacep.2017.12.015*). we are glad to discuss about this if necessary.

2) Genetic testing done for FH diagnosis or not?

Response: a) According to Dutch clinical lipid network, (Family history-1; Clinical history-2; Physical examination-6; Investigation-5;). Total 14-Definite FH＞8.

b) Genetic testing is becoming increasingly common nowadays. However, in 2009, it wasn't popularization in our nation.

3) **comment: For** further clarity please read the PCSK-9 resistance algorithm by Warden et al. Trends in Cardiovascular medicine 2020; 30:179-85.

Response: we apologize for the omission to mention this article in the discussion. Obviously, this was published in 2020; 30:179-85. (after treatment).

a) I think that you are referring to the article 'The P*CSK9 revolution: Current status, controversies, and future directions DOI：10.1016/j.tcm.2019.05.007'*

b) in this review, 'An algorithm to assess possible PCSK9i resistance *has been*

proposed to classify hypo-responders and identify mechanism'. The algorithm was based on measuring plasma PCSK9 concentrations before and after treatment with a PCSK9i.

c) The patient is not well educated and he is not patient enough to complete all the measurements. So, plasma PCSK9 concentrations (after treatment) cannot be obtained.

4) This would be worth discussing. We have discussed about this in the discussion section.

2.Moreover, the attribution of genetic defects to drug resistance needs clarity. Please refer to - B.A. Warden, S. Fazio and M.D. Shapiro. Trends in Cardiovascular Medicine 30 (2020) 179–185 for further clarity.

Response： We appreciate these very constructive comments

1)I think that you are referring to the article *'unusual responses to PCSK9 inhibitors in a clinical cohort utilizing a structured follow-up protocol'*. My team and I read this article carefully and were inspired by it.

2) In this article, '*Among unusual responders, we found 3 mutations in LDLR and one in APOB, of which 2 LDLR mutations were not present in the group with usual responses*' was described. *'But currently there is no clear insight into the molecular causes of poor response'*. The authors explain why something can a fully blocked PCSK9 not exert an effect on plasma LDL-C levels. One of these reasons (mutations in LDL receptors or its ligands apoB or apoE that render them less susceptible to PCSK9 inhibition). This was similar to our case report. Obviously, case series and case reports usually have the low evidence level of as compared to the original article. However, they can could also serve as a foundation for the beginning of a series of subsequent breakthroughs.

3) we have discussed about this in the discussion section.

3.Please discuss whether PCSK-9 levels were obtained on therapy or off therapy.

Response： Sorry for mislead the content. PCSK-9 levels were obtained prior to

treatment. Duo to the complexity of patients' illness. The affecting factors includes exaggerated PCSK9 secretion must be taken into consideration. We have amended in the text.

4.The LDL graph looks incomplete - please add drug doses below corresponding LDL levels.

Response： We authors thinks it is a very constructive suggestion of this graph, which as shown in the updated Figs.

5. comment

1)The chronology of LDL lowering doesn't fit the picture described. -With simvastatin 20 mg, LDL moved from 402 to 141 (65% Reduction). This is unlikely as Simvastatin 20 mg is moderate dose statin which is expected to have 30%-50% LDL reduction. (ACC/AHA 2018 Cholesterol Guidelines- Grundy et. Circulation. 2018; DOI: 10.1161/CIR.0000000000000625) Do the authors suggest that the patient was a super-responder? if yes, quote the literature.

Response： We agree that this issue deserves more discussion.

In the meantime, the article (*ACC/AHA 2018 Cholesterol Guidelines- Grundy et. Circulation. 2018; DOI: 10.1161/CIR.0000000000000625)* also have been discussed. The original data have been checked very carefully for several times. The data is correct. However, since these lipid data were obtained at another hospital and which was dictated by the patient. We tried to contact the patient. However, as you known, finding a 13 years ago laboratory slip is not an easy task.

We all authors wish that the reviewer will agree to omit the uncertain data in the text and figures.

2)The LDL then bounces back to 289-229-220. Was the patient off or on statin? Is it a case of statin tolerance too? Please explain.

Response： The drug and dose were display in the Figure1. The Patient had been maintained on statin and self-reported no use of other drugs. Maybe a 13 years ago laboratory slip can reveal this.

3) when was PCSK-9 inhibitor initiated - not clear form text or graph?

Response： We have added the date in the text (page 9).

4)what was the criteria used to define hypo-responsiveness to drug- < 10% LDL decline or < 15% LDL decline or < 20% LDL decline?

Response： We were pleased to learn that the reviewer found our dilemma description.

A)'Unusual response was defined as: (1) no response: no changes in LDL-C level at all-time points; (2) delayed response: <30% LDL-C reduction by the third dose, but achieving this threshold at a later time; (3) reduced response: <30% LDL-C reduction at all time points; and (4) lost response: ≥30% LDL-C reduction by the third dose, but displaying <30% reduction at a later time'. **(***Unusual responses to PCSK9 inhibitors in a clinical cohort utilizing a structured follow-up protocol PMCID: PMC8315390 DOI: 10.1016/j.ajpc.2020.100012)*

B）At various time points, LDL level is about 10.25% less compared with the previous results(234-210). The other result is 10.95%. there is a 10% increase according the last result.

So, most of the time, hypo-responsiveness to drug can be defined as **reduced response**. In some other occasions, it can be defined as **lost response.**

c) Maybe **'*hypo-responsiveness*'** is a great option for this situation.

6. It would be more informative to have therapy and corresponding LDL levels side by side in text for better understanding of the case.

Response： We very much agree with the reviewer's comments on this point. Appropriate changes have been made in the figure1. Another table can be added if absolutely necessary.

7.The figure 3 doesn't show angiographically severe stenosis. Please omit the figures or provide a better one.

Response：The reviewer is very professional.

The figure is not rigorous enough. We all authors decided to omit the figures after several discussions.

8. It would be worthwhile to note the course of other patients with this mutation described in reference 16.

Response： We noted this article (*Proprotein convertase subtilisin-kexin type 9 as a biomarker for the severity of coronary artery disease*). However, this article focuses more on the level of PCSK9.

****

Responses to EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

We agree with science editor's good advice.

1 comment： The description of the case is inadequate with respect to clinical history.

Response： According to the editor's good instruction, we have revised the part of clinical history. By doing this, it will help readers better understand.

2. comment：Please refine the discussion section: discuss whether PCSK-9 levels were obtained on therapy or off therapy.

Response： Sorry for this confusion. In the revised version, a detailed description of this was shown in the Discussion section.

3. comment：Please improve the figures as per the reviewers' advice.

Response： we have revised all the figures according to the reviewer's advice.

4. comment：please provide documents following the requirements in the journal's Guidelines for manuscript type and related ethics: （1）Conflict-of-Interest Disclosure Form；（2）Copyright License Agreement.

Response：

I have uploaded the both forms according to the instruction of WJCC.

(2) Company editor-in-chief:

Thank you for your careful work.

comment：Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response： The original image files are provided in the attachment. All the figures were shown in PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

comment：Please check and confirm whether the figures are original (i.e., generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response： All the figures in this article are original. In the meantime, I have added the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

comment：Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response： I have upload funding agency copy of approval document (Doctor start-up fund of Jiangxi provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, NO. 19-236).

We look forward to hearing from you regarding our revise version. We

would be glad to respond to any further questions and comments!