Author’s response to reviews

Title: Optimal Strategy of Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction due to Unprotected Left Main Coronary Artery Occlusion: study protocol for a randomized controlled trial

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Author’s response to reviews:

Dear Editors:

We have read the decision letter and reviewer’s comments. The suggestions are really helpful and we have revised our manuscript. The responses to the reviewer’s comments are listed here. All the changes in the revised manuscript have been marked by red and the locations are indicated after each response.

1. As there are 30 hospitals involved in this study, are all these hospital in the same city? Or in the same region of China, like the south or the north? Are they all third-grade class-A hospitals? It might be better to have some more details of these 30 hospitals.

Thanks a lot for the reviewer’s comment. The participating centers are mostly located in southern China (20 of 30), while several other hospitals (10 of 30) from northern districts are also involved. Most of them are 3A hospitals (25 of 30). All centers can perform primary PCI in 24 hours for 7 days a week and had a minimum volume of 500 PCI procedures annually. Coronary care unit and surgery backup are available in all the centers involved. We described the
detailed information about the 30 hospitals in the revised manuscript (red mark, P4 L20-L27), and also listed them in the Supplementary Table 1.

2. Are all these 30 hospitals required to randomize a certain number of patients to participate in the study?

Thanks a lot for the reviewer’s comment. In this study, there is no such requirement for each single center. As LM-AMI patients are very rare and it is difficult to ensure a hospital could randomize a certain number of eligible patients. We include 30 centers in order to accelerate the process of enrollment and such requirement may prolong the enrollment process.

3. Has the randomization been stratified in consideration of the hospitals?

Thanks a lot for the reviewer’s comment. In this study, the hospitals are not considered as a covariate for stratification, because all participating centers can perform primary PCI in 24 hours for 7 days a week and had a minimum volume of 500 PCI procedures annually. Coronary care unit and surgery backup are available in all the centers involved. Additionally, chest pain centers and quick-reaction systems of PCI for AMI patients have been established among all these centers. Although the administrative levels of these hospitals are not exactly the same, they are able to provide standard and timely PCI for the enrolled patients. In the revised manuscript, we added some detailed primary PCI information about the 30 hospitals (red mark, P4 L20-L27).

4. In study design, it is recommended to specify this is an 'open-label' study.

Thanks a lot for the reviewer’s good suggestion. We specify this is an 'open-label' study in the revised manuscript (P2 L11, and P4 L10).

5. The author has stated in the main text "We choose to enroll patients with AMI but not STEMI because a certain number of patients with left main coronary artery occlusion present non-ST-segment elevation myocardial infarction (NSTEMI) instead of STEMI". This sentence gives me an impression that this study will exclude patients with left main coronary artery occlusion present ST-segment elevation myocardial infarction (STEMI). If yes, the author should specify in the exclusion criteria. If not, please rephrase this sentence to avoid misunderstanding.

Thanks a lot for the reviewer’s good suggestion. This sentence has been rewritten to avoid misunderstanding. (P5 L3-6)
6. For the inclusion criteria, why to have an age upper limit of 80?

Thanks a lot for the reviewer’s comment. Because patients over 80 often have less life expectancy, more clinical complications and are less available for follow up. In consideration of the conditions of patients, we decided not to enroll patients over 80.

7. For the inclusion criteria, it will be better to have this as the forth one: "TIMI flow grade 3 achieved after pretreatment of thrombus aspiration or balloon dilatation"

Thanks a lot for the reviewer’s good suggestion. We have revised according to the recommendation. (Table 1)

8. For the exclusion criteria "life expectancy less than 1 year", how will the investigators judge one patient’s life expectancy?

Thanks a lot for the reviewer’s comment. This criterion is only suitable for patients with malignant tumor, end-stage organ failure or other terminal diseases whose life expectancy are known and have been assessed by specialists in their medical history. The investigators will refer to the medical history if available.

9. Will the author exclude those who are unable to sign the informed consent, like unconsciousness?

Thanks a lot for the reviewer’s comment. Yes, and we have added “Patients unable or unwilling to sign the informed consent” to the exclusion criteria. (Table 1)

10. When and who will conduct the informed consent?

Thanks a lot for the reviewer’s comment. The investigator of the specific hospital will conduct the informed consent. The details about informed consent of this study have been read by the investigators of the participating hospitals. (P5, L9)

11. I am confused about the timing and procedure for patients to sign the informed consent. Will patient sign the informed consent BEFORE the primary angiography (the eligibility of achieving TIMI 3 is not possible to be confirmed at this time)? Or will they sign the informed consent after achieving TIMI 3 DURING the primary angiography (it might be difficult for patients to sign
anything or make any decision when they are lying on an operational bed)? Therefore, it might be better for the author to specify the way to get the informed consent from patients.

Thanks a lot for the reviewer’s comment. The informed consent is signed before the primary angiography. Patients do not achieve TIMI 3 flow after primary PCI will NOT be included even if informed consent was signed. (P5, L9)

12. After one patient having been randomized to the deferred stenting group:

What will be done if the interventionalist think the patient unsuitable for deferred stenting due to some practical reasons or patient's clinical situation?

What will be done if the interventionalist think the stent implantation could be waived during the second PCI?

What will the author deal with these cases during statistical analysis?

Thanks a lot for the reviewer’s comment.

1) The deferred stenting will be canceled in this condition.

2) The deferred stenting will be waived if the infarct-related lesion is stable (<50% residue stenosis without significant thrombus burden or dissection).

According to the intention-to-treat principle, all these eligible patients who actually did not receive deferred stenting will still be included in the DS group in intention-to-treat analysis. By the way, a per-protocol analysis will also be conducted with patients not treated according to the allocated procedure being excluded from the DS group. (P6 L6-11)

13. For those randomized to deferred stenting group, will the second PCI be conducted within the same hospitalization period as the first PCI?

Thanks a lot for the reviewer’s comment. Yes, and we have added it to the clinical procedures part. (P8 L3-4)

14. For those randomized to deferred stenting group, please specify the treatments during the "deferred period"? As this will contribute to the effects on clinical outcomes.

Thanks a lot for the reviewer’s comment. Patients will be transferred to coronary care unit (CCU) after PCI procedure and intravenous glycoprotein IIb/IIIa inhibitor (tirofiban 0.15
ug/kg/min or other in equal dose consistency) will be administered for 18 hours. Dual-antiplatelet therapy will maintain during the deferred period. The usage and doses are in accordance with the 2017 ESC Guidelines for the management of AMI in patients presenting with STEMI. (P6 L12-18)

15. In the paragraph of sample size, please rephrase the first sentence. In addition, the author did not mention the α level for sample size calculation.

Thanks a lot for the reviewer’s good suggestion. We have rewritten the sentence and added the α level. (P6 L21-22, L27)

16. The author did not mention how they will collect data about the patient characteristics and procedure related variables.

Thanks a lot for the reviewer’s good suggestion. We have described the methods of data collection in Table 2 and first paragraph of Data collection and management. (Table 2, P7 L20-24)

17. For the primary endpoint, the author uses a composite outcome of cardiac death and recurrent myocardial infarction. It might be better to use "all-cause mortality" instead of the "cardiac death" because "all-cause mortality" reflect an intervention's net benefit.

Thanks a lot for the reviewer’s good suggestion. We have revised according to the recommendation. (P2, P7)

18. For the outcomes, it will be better to have a definition for all clinical events and who will adjudicate these clinical endpoints?

Thanks a lot for the reviewer’s good suggestion.

Definitions are listed in Supplementary Table 2.

Clinical events are adjudicated by an independent committee consists of 5 cardiologists not participating in this trial. (P7, L16-17)

19. The author should clearly specify the timeframe for each endpoint.
Thanks a lot for the reviewer’s comment. We have listed the timeframe of each endpoint in Table 2.

20. It will be better that the author gives detailed information on how to collect data on the primary and secondary outcomes, patients’ baseline characteristics, clinical events.

Thanks a lot for the reviewer’s comment.

Most of patients' baseline characteristics are collected using CRFs during hospitalization at least 24 hours after primary PCI by investigators of each center. However, angiographic data are recorded during the procedure.

For incidences of primary and secondary outcomes and clinical events, investigators will ask the patient to visit the hospital at specific time point to collect the data. Patients are required to undergo electrocardiogram, echocardiogram in each center according to the follow up plan. Details about data collection are in Table 2.

Angiographic and echocardiographic data are stored in CD-ROMs and sent to a core lab in Zhongshan Hospital, where the data are analyzed by specialists masked of random allocation.

(P7, P8)

Thank you and best regards.

Yours sincerely,

Junbo Ge on behalf of the authors.