Peer Review File

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Reviewer A:

The authors prospectively enrolled 131 patients with anterior STEMI treated with emergency PCI, and randomized the study population into ARNI and Enalapril. The use of ARNI lead to a rapid decline in the levels of NT-proBNP, and significant improvements in echocardiographic parameters, including LVEF, LVEDV, and LVESV. Although this study demonstrated important findings, I have several comments on it.

[Abstract]

1. The abstract is too lengthy. In the present form of manuscript, the total word count for the abstract is more than 360 words, which exceeded the journal's limit of word count for the abstract.

Response: We have revised the abstract to comply the word limit- approximately 360 words (see Page 3-5).

2. Please indicate "95% confidence interval (CI)" when explain the changes in NT-proBNP levels.

Response: We have carefully reanalyzed our primary outcomes and provided 95% confidence interval for changes in NT-proBNP (see Page 4, line 73-75).

3. The echocardiographic parameters at 24 weeks were described in the order of the values in the ARNI group and the values in the Enalapril group. And the p-values for these values were obtained from the comparison between ARNI group vs. Enalapril, rather than from the comparison between baseline and 24th week. Please indicate these information clearly in the Abstract.

Response: We re-compared the between-group difference in change (from baseline to each follow-up time point) in NT-proBNP and echocardiographic parameters, instead of only comparing the difference between the groups at each time point. We have revised the Abstract to make these information clearer (see Page 3-4, line 61-65, line 72-78).

4. For the standard deviations of the echocardiographic parameters and the percentages of secondary outcomes, it would e better to describe only to the first decimal place.

Response: We agree with the point and now keep the standard deviations of the echocardiographic parameters and the percentages of secondary outcomes to one digit after the decimal as suggested (see Page 4, line 83-84; Page 15-16, line 304-316; Table 3, Table 4).

5. In the conclusions of the Abstract, the authors stated that the benefits of ARNI were observed regardless of whether the patients exhibited symptoms or signs of HF when ARNI was initiated. However, I think the "regardless of the symptoms or signs of HF" cannot be supported by the results described in the Abstract (as well as in the main text). Thus, I recommend the authors to remove the phrase ("regardless of whether…").

Besides, I think the authors could not infer the benefits of ARNI were regardless of the symptoms or signs of HF, because they neither performed a subgroup analysis according to the HF symptoms or signs, nor adjusted the multivariable regression analysis with the symptoms or signs of HF.

Response: We were not sufficiently rigorous in our wording and thank the reviewer for pointing this out. As correctly pointed out by the reviewer, we have not provided any direct evidence that benefits of ARNI were regardless of the symptoms or signs of HF. This phrase has now been removed (see Page 5).

6. Many typo errors in the Abstract, especially for the distinction between uppercase and lower case letters, and for the description of abbreviations.
Response: We thanks the reviewer for pointing out our mistake, which has been fixed.

7. This clinical trial was registered on 1 February 2021 in the Chinese Clinical Trial Registry (ChiCTR21000429444). However, the actual patient enrollment was performed between February 17, 2019 and December 28, 2019. The authors indicated that the trial was "retrospectively registered" in the Chinese Clinical Trial Registry, while the approval by the ethics committee was obtained on January 2, 2019. Because this was a prospective randomized clinical trial, I think the authors should clarify this issue in the manuscript (probably in the Methods section). Also, I think the authors need to provide the approval document issued by the ethics committee, together with the original documents submitted to the ethics committee, including the study plan, case report form and informed consent form.
Response: As we did not realize the importance of clinical trial registration, we regret that we were not able to conduct research registration in time before the start of the study. We performed an online supplementary registration on the website of the China Clinical Trial Registry on 1 February 2021. The meaning of "retrospectively registered" here is the registration of clinical trials that have been initiated in the past. By browsing the registration webpage (https://www.chictr.org.cn/showproj.aspx?proj=121312) of this study, you can find that the study design is a randomized controlled study, and the recruitment time is from 2019-02-17 to 2019-12-28. We will also provide the original documents approved by the ethics committee (see attachment).

[Introduction]
1. The introduction is also too lengthy. I recommend the authors summarize the current contents in the Introduction section, and also move some parts to the Discussion section.
Response: We have now revised the Introduction and think it is more streamlined (see Page 5-8).

2. In May 2021, the preliminary results of the PARADISE-MI trial were reported in the ACC.21.
- https://www.acc.org/latest-in-cardiology/clinical-trials/2021/05/14/01/22/paradise-mi
- https://www.acc.org/latest-in-cardiology/articles/2021/05/12/18/51/sat-9am-paradise-mi-acc-2021
- https://www.tctmd.com/news/paradise-mi-arni-doesnt-surpass-ace-inhibitor-after-acute-mi
Because the present study and the PARADISE-MI trial have many similarities in terms of study design and rationale, I think the authors should indicate the results of the PARADISE-MI trial in the Introduction section, and also should further discuss regarding the results of the PARADISE-MI trial, together with the similarities and differences with the present study, in the Discussion section.
Response: The result of the PARADISE-MI trial is an important new advance, and a brief description is given in the Introduction(see Page 7, line 41-44). We also compared and discussed the results of our study with PARADISE-MI trial (see Page 21-22, line 433-451).

[Methods]

1. The Methods section is written in the present tense, rather than the past tense. It seems that the Methods section has been copied from the study protocol. Please revise the entire Methods section with appropriate tense.

Response: Language editors suggest that it is better to write the Methods in the past tense, hence the tense in the Method is still the past tense.

2. It seems that the dose adjustment/escalation regimen for ARNI in the PIONEER-HF trial has been applied to the present study. The authors should cite the PIONEER-HF trial in the paragraph that explains the dose titration algorithm in the Methods section.

Response: The ARNI dose adjustment algorithm in this study did refer to the PIONEER-HF trial. We now reference this important paper in the revised version (see Page 10, line 204).

3. In the present study, 50 patients (38.2%) were on ACEi or ARB before the entry to the study protocol. The authors indicated that there was a wash-out period for these patients. I recommend the authors explain this issue in the Methods section of the main text.

Response: Regardless of what RAAS inhibitor the patient has received before, all emergency patients are given dual antiplatelet, statins, beta blockers, and enalapril after primary PCI according to our research protocol. In order to reduce the risk of angioedema, enalapril should be stopped for 36 hours before starting ARNI. We have added a brief description in the Method section (see Page 10, line 196-199).

4. The occurrence of "arrhythmia" was included in the composite secondary outcome. However, the type of arrhythmia has not been indicated. Did the authors included all forms of arrhythmia, or only the potentially fatal arrhythmia (such as VT and VF)?

Response: We are sorry that we didn't make a clear definition of arrhythmia in the original manuscript. Arrhythmia was defined as malignant arrhythmia that required defibrillator or cardioversion, including cardiac arrest, persistent ventricular tachycardia, and ventricular fibrillation. Thus, to avoid misunderstanding we used the term "malignant arrhythmia" instead of "arrhythmia" in the revised version (see Page 12, line 246-247).

5. The occurrence of "outpatient heart failure" was included in the composite secondary outcome. In the study protocol, the outpatient HF was defined as below:

Outpatient heart failure is defined as:

• An urgent/unscheduled visit to an ED, acute/urgent care facility or outpatient clinic or a non-urgent office/practice or study visit for a primary diagnosis of HF that does not require an overnight hospital stay.

• Patients must exhibit at least one documented new HF symptom with objective evidence of clinical HF consisting of at least 2 physical examination findings or one physical examination findings and at least one laboratory criterion.

• The event requires initiation or intensification of treatment specifically for HF. Such treatment can include administration of intravenous agent (e.g., diuretic, vasodilator, vasopressor, or inotrope) or mechanical or circulatory intervention for HF, OR initiation of oral loop diuretic treatment, or intensification of oral maintenance loop diuretics for the diagnosis of HF, over a sustained period (i.e.,

initiation or doubling of total daily dose through a period of ≥ 4 weeks), which is confirmed at a subsequent outpatient visit.

However, I could not find the specific criterion/criteria for the diagnosis of HF. Please provide detailed criteria (physician examination findings and laboratory findings) for the diagnosis of HF.
Response: We are sorry that we did not provide this important information. We have added to the Methods sections detailing the criterion for the diagnosis of HF (see Page 11-12, line 229-242).

6. According to the study protocol, the authors calculated the necessary sample size as 142 patients, considering the loss to follow-up rate of 10%. However, in the manuscript, the authors stated that the sample size for each group to be 64 cases (without considering the loss to follow-up rate). And then, in the Results section, it is shown that 131 patients (not "142 patients" as calculated in the study protocol) were randomized. Please clarify these discrepancies.
Response: We initially planned to recruit at least 142 patients according to the study protocol. However, due to limited time and personnel resources, we had to stop the recruitment after recruiting 131 patients. To make up for the insufficient sample size, we have carefully managed the follow-up of patients. Reassuringly, only very few patients lost to follow-up. The number of patients who completed all follow-ups was exactly equal to the minimum sample size required for this study. Therefore, in order to avoid misunderstandings, we did not mention the loss to follow-up rate in the statistics section.

7. Were the study outcomes assessed using the intention-to-treat (ITT) analysis or the per-protocol (PP) analysis? Please indicate the statistical approach used in the study (for each outcome).
Response: Analysis of the primary and secondary outcomes was performed based on the per-protocol (PP) population. We have added a brief description in the Statistical Analysis section (see Page 13, line 254-255).

[Results]
1. Most of the difference in the composite secondary outcome was derived from the difference in the occurrence of "outpatient HF or HF hospitalization". This would be relevant finding, considering the pharmacological effects of ARNI. However, I have concerns regarding the specific endpoint, the "outpatient HF". This endpoint is not as serious as the other endpoints consisting the composite secondary outcome. Also, the specific diagnostic criteria of "outpatient HF" was not provided in the manuscript. I recommend the authors clarify this issue, and also provide the number of patients who experienced "outpatient HF" and that of patients who experienced "HF hospitalization", separately. Same concerns for the endpoint of "arrhythmia".
Response: Outpatient heart failure is an end-point event that deserves attention. Different from ward patients, more than half of outpatients with HF were in New York Heart Association NYHA functional class Ⅰ or Ⅱ [1]. The symptom of patients with NYHA functional class Ⅱ are often considered to stable or unapparent. However, the REVERSE trial showed that the heart of patients with NYHA class Ⅱ has already undergone remodeling [2]. The risk of HF hospitalization and sudden death in these patients was close to that of NYHA class III patients [3-4]. This reminds us that in addition to hospitalization, we need to pay more attention to the long-term management of heart failure patients outside the hospital. Therefore, it is very important to observe the impact of

ARNI on outpatient HF.

We have added detailed diagnostic criteria for HF in the method section, and thus explained the diagnostic criteria for outpatient HF (see Page 11-12, line 229-245). We have also provided the specific number of outpatient HF and hospitalizations for heart failure, respectively (see Page 16, line 319-322). we used the term "malignant arrhythmia" instead of "arrhythmia" and provided a clear definition in the revised version (see Page 12, line 246-247).

References:

1. **Ferreira JP, Metra M, Mordi I, et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(1):112-120.**
2. **St John Sutton M, Cerkvenik J, Borlaug BA, et al. Effects of Cardiac Resynchronization Therapy on Cardiac Remodeling and Contractile Function: Results From Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE). J Am Heart Assoc. 2015;4(9):e002054.**
3. **Mogensen UM, Gong J, Jhund PS, et al. Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2018;20(4):760-768.**
4. **Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015;36(30):1990-1997.**

[Discussion]

1. Please discuss regarding the preliminary findings of the PARADISE-MI trial.

Response: We have added the discussion of preliminary findings of the PARADISE-MI trial in the Discussion part (see Page 21-22, line 433-452).

2. Page 14, first paragraph, "patients with heart failure and full ejection fraction"

- Does it mean a full range of ejection fraction?

Response: Yes. However, due to major changes to the Discussion section, this sentence has been removed.

[Conclusion]

1. In order to state that the benefits of ARNI were "regardless of whether the patients exhibited symptoms or signs of HF", the authors need to provide relevant subgroup analyses, or at least, should adjust the primary and secondary outcomes with the symptoms and signs of HF. I think the authors should remove this sentence.

Response: This sentence has now been removed.

[Footnote]

Data Sharing Statement is not provided.

Response: We have provided a Data Sharing Statement.

[Figures and Tables]

1. Please provide relevant captions to each figure.

Response: We have provided relevant captions to each figure (see Page 35-36, line 728-749).

2. Figure 1 – "120<SBP >=100" The direction of the inequality sign is weird.
Response: we have modified this Figure as advised (see Figure 1).

3. Figure 3 and Figure 4 – Please provide the p-values in the figure. Use of footnotes (*, †, ‡, §, etc) would be helpful.
Response: We have added the footnotes as advised (see Figure 3).

4. Figure 5 – Please provide the numbers at risk, at the bottom of the survival curves.
Response: We have added the numbers of patients at risk at the bottom of the survival curves as advised.

5. In the Tables 3A, 3B, and 3C, I think the first decimal place would be enough for the echocardiographic parameters.
Response: We have modified this as suggested in the Tables (see Table 3).

[Others]
There are many typo errors as indicated in the parentheses below. Please note that I could not find all of the typo errors, and below are just typical examples.

Page 6 [Introduction] … Previous clinical trials (were) confirmed that …
Page 8 [Methods] … diuretics and inotropes ( ) according to the patient's condition.
Page 8 [Methods] Use the MS-Fast^TM NT-proBNP … --> The structure of this sentence is incomplete.
The "heart failure (HF)" has been described as an abbreviated form (HF) or as a full name (heart failure) without any rules. Please revise them.
Page 12 [Results] outpatient HF or HF hospitalization occurred in 6 patients… ◊ The "outpatient" should be started with a capital letter.
Page 13 [Discussion] In the first paragraph of the page 13, left ventricular ejection fraction, left ventricular end-diastolic volume and left ventricular end-systolic volume can be provided as abbreviations.
Page 14 [Discussion] acute myocardial infarction --> AMI
Page 15 [Discussion] In addition, Daniel pfau et al. --> Daniel Pfau et al.
Page 16 [Discussion] "which may be due to the follow-up time was not long enough or the sample size was not large enough" \ Please check the grammar.
Page 17 [Discussion] eGFR --> Please provide the full name.
Page 17 limitation --> Limitation
Response: We are very grateful to the reviewer for pointing out the above error and feel very sorry for it. We have now corrected the above-mentioned errors.

Reviewer B:
The authors report that ARNI decreased NT-proBNP, improved LV function, and reduced recurrent HF events in patients with anterior wall STEMI undergoing primary PCI. It is an interesting topic. Early use of ARNI in STEMI patients can be crucial. However, I have several comments, and I hope these

concerns help to improve the study protocol and manuscript.

1. There are numerous sentences with ambiguous meanings throughout the manuscript. Please proofread the whole manuscript.

Response: We apologize that our language was not clear. we have improved the language using the AME language editing service (Order ID: AESE20210451, see Editorial certificate).

2. Primary and secondary endpoints are confusing. Endpoints must be "the change of values" from the baseline to the pre-specified time point, and the authors descript the definitions as "the change of values" However, the investigators compared just values at each time point. Do not compare 279 vs. 671, and please consider comparing (1168 – 279) vs. (1033 – 671) in all kinds of laboratory or echocardiographic endpoints, except clinical outcomes. Please add detailed definitions of endpoints in the method, and please modify the results and tables.

Response: We have added detailed definitions of outcomes in the Method. We re-compared the between-group difference in change (from baseline to each follow-up time point) in NT-proBNP and echocardiographic parameters, instead of only comparing the difference between the groups at each time point. We have modified the results and tables.

3. In addition, please define the definitions of HF. There are so many cases of HF. Although this trial included only ant. wall MI, I think the higher incidence of HF despite successful primary PCI and other preventive medications. Please explain it.

Response: During the past few decades, with the advancement of new drugs and emergency PCI, more and more patients suffering from AMI have received timely treatment. However, the incidence of heart failure post-MI has remained persistently high. The CHINA PEACE study showed that the incidence of HF in patients with AMI was as high as 13% during hospitalization [1]. Another retrospective cohort study found that the incidence of HF in patients with non-STEMI and STEMI within 1 year was as high as 23.4% and 25.4%, respectively [2]. Therefore, we think the incidence of HF hospitalization (ARNI group and enalapril group were 6/64 and 9/64) in this study does not seem high compared to the studies mentioned above. In addition to, we have provided a clear definition of HF in the revised version (see Page 11-12, line 229-242).

References:

1. **Li J, Li X, Wang Q, et al. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. Lancet. 2015;385(9966):441-451.**
2. **Tang X, Liu P, Li R, et al. Milrinone for the Treatment of Acute Heart Failure After Acute Myocardial Infarction: A Systematic Review and Meta-Analysis. Basic Clin Pharmacol Toxicol. 2015;117(3):186-194.**

4. Practical guidance recommends 3 day-stop of ACEi before starting ARNI. In this trial, all candidates received enalapril for the first time after PCI. However, there is no description of the transition from enalapril to ARNI.

Response: We are sorry that we did not provide this important information. We have added a brief description in the Method section (see Page 10, line 96-99).

5. Please modify the conclusion. Please consider showing detailed secondary endpoints. By contrast, I am curious what this sentence "regardless of whether the patients exhibited symptoms or signs of heart failure when sacubitril/valsartan was initiated" is meaning.

Response: We were not sufficiently rigorous in our wording and thank the reviewer for pointing this out. This sentence has now been removed.

6. In the introduction, Line 111, is ARNI a new single-molecule? What does mean "a single"?

Response: we have modified our text (see Page 7, line 128-130).

7. In the introduction, it seems to be not appropriate to demonstrate the results of the PARALLAX trial because it is not published, and the PARAGON trial has already been published for patients with HFpEF. Please consider modifying and adding about why research for patients with MI is needed.

Response: We have deleted the description of the PARALLAX study and revised much of the Introduction accordingly (see Page 7-8).

8. Please demonstrate systolic and diastolic BP, serum creatinine concentration, and potassium level throughout the follow-up period.

Response: Please see the table below:

Table Change in blood pressure, serum creatinine and serum Potassium from baseline to 12 and 24weeks

Variables	ARNI	Enalapril	*P* value
Systolic Blood pressure, mm Hg			
baseline	111.63 (9.91)	109.70 (8.90)	0.242
12 weeks	106.28 (8.73)	107.50 (8.55)	0.426
24 weeks	104.53 (6.85)	106.69 (7.66)	0.096
Diastolic Blood pressure, mm Hg			
baseline	69.14 (6.93)	68.52 (6.32)	0.591
12 weeks	66.31 (6.21)	65.22 (6.51)	0.332
24 weeks	64.66 (5.61)	64.16 (6.36)	0.638
Serum creatinine, μmol/l			
baseline	85.19 (28.23)	91.78 (26.86	0.173
12 weeks	88.47 (30.11)	96.05 (36.56	0.203
24 weeks	87.53 (30.78)	97.36 (43.06	0.14
Serum Potassium, mmol/l			
baseline	4.09 (0.42)	4.05 (0.38)	0.518
12 weeks	4.13 (0.43)	4.15 (0.41)	0.774
24 weeks	4.18 (0.48)	4.22 (0.45)	0.615

Data are presented as Mean (SD)

9. Please consider merging Fig 3 and 4 (Not mandatory)

Response: We have merged Fig 3 and Fig 4 as suggested (see Figure 3).

10. In the discussion, please add the 1st paragraph that summarizes the results, especially the contents

that will be discussed in the discussion section. In addition, if possible, please rearrange all paragraphs in the discussion according to the contents of the new 1st paragraph.

Response: We have added the 1st paragraph that summarizes the results and other paragraphs has also been modified accordingly (see Page 17-23).

11. Please clarify some terminology such as emergent PCI versus primary PCI (did all patients receive primary PCI, right?) or acute ST-elevation anterior wall MI versus acute anterior STEMI. Please find the most appropriate terms.

Response: We apologize for the inaccurate term we use, and have corrected this in the revised manuscript. In this present study, all patients received primary PCI for STEMI. We now use the terms: "primary PCI" and "acute anterior STEMI".

12. Please clarify and rearrange the abbreviations throughout the whole text, tables, and figures. For example, does NPs mean natriuretic peptides or natriuretic peptide system? Or please avoid abbreviations usually not used, such as WRF in the table.

Response: All abbreviations are carefully checked to make sure that all abbreviations are written fully the first time and afterwards left out. The NPs always refer to natriuretic peptides. We have also revised the expression "WFR" to "worsening renal function" (see Table 5).

Second Round of Review

Editorial office review based on the CONSORT statement.

1. Please also identify the trial as a 'parallel" design on line 114 and in the abstract.

Response: This study is a prospective, randomized, double-blind, parallel-group trial. We have revised the Abstract and Methods (see Page 3, line 49; Page 6, line 118).

2. Please add the dosage of the medicines, on lines 136-146.

Response: We have added the dosage of the medicines (see Page 8, line 151-153).

3. Please specify "software-based random functions." On line 137.

Response: The randomization sequence was generated by the statistical software R. Now we have modified it (see Page 7, line 141).

4. The information given on lines 141-143 is about blinding, not about the allocation concealment. The difference between allocation concealment and blinding is that the former focuses on the phase before implementation while the latter one focuses on the phase during the execution of the protocol. Please fulfill the allocation concealment information. For example, did you use sequentially numbered containers or other ways to conceal the allocation?

Response: We are sorry that we did not provide this important information. We have added a brief description in the Method section (see Page 8, line 147-148).

5. We failed to find required information of item 10 on lines 140-141. Please add this information in the manuscript.

Response: We have added the relevant information in the revised manuscript (see Page 6, line 122-123; Page 7, line 145-146).

6. The potential harms data should be reported in the abstract too.

Response: We have added the safety analysis in Abstract section (see Page 3, line 58-60; Page 4, line 70-71).

Other concerns

The authors applied per protocol analysis instead of intention-to-treat way. In the discussion, please compare the difference between the data using the two methods. Also, explain the findings after considering such an influence caused by the per protocol strategy.

Response: We used a per-protocol analysis and therefore only data from patients with complete follow-up were analyzed. In literature it is argued that an intention-to-treat analysis is preferable for a randomized trial [1]. However, an intention-to-treat analysis would reduce our intervention's effect if patients assigned to the intervention group were lost to follow-up after randomization [2]. Therefore, we decided to use a per-protocol analysis beforehand. With regard to follow-up, we do not expect a large difference in outcomes between a per-protocol analysis and an intention-to-treat analysis because of the number of patients lost to follow-up was low in our study. Furthermore, the sample size was not significantly reduced and therefore there was no reduction in study power. We explained the reasons for using per-protocol analysis in the Discussion section (see Page 17, line 346-351).

1. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res. 2011;2(3):109-112.

2. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017;377(14):1391-1398.