Author’s response to reviews

Title: Global peak left atrial longitudinal strain assessed by transthoracic echocardiography is a good predictor of left atrial appendage thrombus in patients in sinus rhythm with heart failure and very low ejection fraction - an observational study

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Author’s response to reviews:

Reviewer #1: I appreciate the authors for the work that they have done to improve this manuscript.

There is only one issue that has not been resolved in the revised manuscript.

Is the absolute difference in global peak left atrial longitudinal strain (PALS) clinically relevant?

How does the difference in global PALS values between groups compare to inter-observer and intra-observer variability for this index?

If the mean global PALS in patients with left atrial appendage thrombus was (LAAT) was 7.2% and the mean global PALS in those without LAAT was 9.7%, is this difference (2.5%) greater than the variability in global PALS measurements?

To address this issue, measures of absolute reliability, such as root mean square error and limits of agreement, are recommended to be used, in conjunction with measures of relative reliability, such as intraclass correlation coefficient, which was provided by the authors.
Following the Reviewer suggestion we have decided to assess reliability and reproducibility of PALS measurements based on the echocardiographic data from the current study. We included the methodology and the results in the revised manuscript. The analysis showed very good intra-observer variability and moderately good inter-observer agreement. We believe that the global PALS assessment by TDI is reproducible but an echocardiographist should have some experience with this method to produce more reliable measurements.

Reviewer #2: The consideration of the initial review comments is appreciated. Many of the initial points have been addressed. However, there remain substantial concerns with the manuscript as it currently stands, as detailed below:

1. Because echocardiographic findings and measurements which were done in this study were essential for both the primary and the secondary objectives of the study, the process of performing echocardiographic examinations including measurements of various parameters was very important. In particular, the reproducibility of left atrial strain parameters and the diagnosis of the presence of left atrial appendage thrombus were critical. I have concerns regarding the reproducibility of echocardiographic findings in this study because all TTE measurements including left atrial strain analysis were performed by one echocardiographic expert. Also, there is no information in the Methods to clarify whether left atrial appendage thrombus was diagnosed by one expert but it seems to be done in the same way as other echocardiographic measurements. In addition, the authors did not consider this fact as one of the most important limitations of this study. In my opinion, echocardiographic analysis should be done at least by two independent experts or, as a minimum, the manuscript should include a description of limitations associated with the analysis by one expert only.

We fully agree that the reliability and reproducibility of PALS measurements are very important in the context of this study. Thus, we have decided to assess reliability and reproducibility of PALS measurements based on the echocardiographic data from the current study. We included the methodology and the results in the revised manuscript. The analysis showed very good intra-observer variability and moderately good inter-observer agreement. We believe that the global PALS assessment by TDI is reproducible but an echocardiographist should have some experience with this method to produce more reliable measurements.

Left atrial appendage thrombus was diagnosed by one expert – we have clarified this in the manuscript, as suggested.
2. The authors defined the study population as the population with heart failure in some places, i.e., the title of the manuscript, in the Background, Methods and the Conclusions of the Abstract as well as the beginning of the Discussion section and in the Conclusions section of the study. However, the precise definition of study population is missing in the Methods section. Importantly, the authors missed heart failure among inclusion criteria for study enrollment. Consequently, they did not provide information on how heart failure was defined for the purposes of this study. Also, they did not provide data regarding the indications for the index hospitalization in the study population. So, the readers cannot know if the study population was the population with low LVEF only or if the patients had both low LVEF and heart failure, and if they had heart failure, there is no data on HF severity. It is important because discrepancies are known to exist between imaging parameters and symptoms and clinical outcome. The difference in mean LVEF between asymptomatic and symptomatic HF patients enrolled in large clinical trials was small, and also many prospective studies have demonstrated a strong relationship between the functional NYHA class and mortality. I suggest improvements of the Methods section to address these issues.

Thank you for this very important remark. All patients had heart failure diagnosis made before entering the study. It was documented in their medical history. We have added this information in the Methods section. We also check medical records for NYHA class assessment during index hospitalization and included this information in our analyses. There were no asymptomatic patients in this group and the majority of subjects were in NYHA III class.

3. In the revised version of manuscript, the investigators provided some data on treatment that was applied in patients of both subgroups during the study period. However, the authors did not provide data about antithrombotic treatment which was applied in the patients with left atrial appendage thrombus that was diagnosed in TEE. Specifically, they did not provide data on the type of anticoagulant medications (VKAs, NOACs). There is no information about the adherence to the anticoagulant therapy (including the information about the results of monitoring of anticoagulant intensity such as the INR when receiving VKAs) during the long-term follow-up. As a result of such approach, oral antithrombotic treatment (especially effective OAT) was not considered by the authors as a potential factor in the regression models for the prediction of composite clinical endpoint. It would be important to have these data in order to assess the usefulness of left atrial strain analysis for the long-term clinical outcomes in the patients with left atrial appendage thrombus, especially that there was no significant difference in the occurrence of death and ischemic stroke in the long-term follow-up between the groups of patients with and without left atrial appendage thrombus. The lack of OAT in these models seems to be important, especially that the authors indicated CHA2DS2-VASc score as the best predictor of the composite endpoint of death and ischemic stroke. Also, this issue is one of the weaknesses of the Discussion and has not been addressed as important limitation of this study. I suggest to include data about anticoagulant medications such as the percentage of patients that received VKAs or
NOACs. In addition, it would be useful to include data about the adherence and monitoring of OAT or, as a minimum, to address the lack of such data in the section describing the limitations of the study.

Patients with a confirmed diagnosis of LAAT were discharged and prescribed the following anticoagulants: 2 patients on acenocoumarol, 4 on warfarin, 8 on low molecular weight heparin, 3 on rivaroxaban, 2 on dabigatran, and 1 on apixaban. We added this information in the manuscript.

Unfortunately, we do not have any follow-up data on the adherence to the anticoagulant therapy, effective OAT nor information if the medications recommended at discharge were later changed or withdrawn. We fully agree with the reviewer that the lack of this data affects the secondary endpoint interpretation and we have added this information as limitation of this study as suggested.

4. As I indicated in my first review, data on univariate analysis and multivariate analysis should be provided and presented separately for both study endpoints in both Results section and tables. However, both multivariate regression model for the prediction of left atrial appendage thrombus and univariate regression model for the prediction of composite endpoint are missing. This makes reading and understanding of the results of the study difficult, especially because the authors often refer to the results of multivariate analysis (with regard to left atrial appendage prediction; p. 10, p. 12) and univariate analysis (composite endpoint prediction; p. 10, p. 14). In addition, the authors did not provide the factors which were included in the univariate model for the prediction of the composite endpoint (p. 9, p. 10).

Following the Reviewer’s suggestion we have added a separate table with the results of the univariate analyses for the secondary endpoint.

The approach used for the multivariate model building was a stepwise forward selection. We have not added a separate table for the multivariate analysis for the primary endpoint because there was only one variable left in the final model (global PALS) – none of other variables added one after one to the model could significantly improve it. Presenting step-by-step model building would require another very large table and we believe it would not provide further relevant information. If the Reviewer feels these data still should appear with this paper we could add them as supplementary files.
5. The Methods and the Results sections still need further improvement. The description of methods is poorly organized. The precise definitions of primary and secondary objectives at the Study design subsection are still lacking. In addition, the data from the Study population subsection should be moved to the Results section. Some comments in the Results section about the results in groups of patients with and without left atrial appendage thrombus with regard to the baseline clinical data (no differences including history of stroke), baseline echocardiographic data (significant differences in LAVI, global PALS, global PACS) and follow-up data (no significant differences but more ischemic strokes in the patients with left atrial appendage thrombus) are needed. The data about composite clinical endpoint in the Table 1 should be separated from the baseline data.

Thank you for these valuable comments. Following the Reviewer suggestions, the precise definitions of primary and secondary objectives have been moved to the Study design subsection and the data from the Study population subsection have been moved to the Results section. Several comments in the Results section about the results in groups of patients with and without left atrial appendage thrombus (regarding their baseline clinical and echocardiographic data as well as follow-up data) have been added to the Results section, as suggested. The data about composite clinical endpoint in the Table 1 have been separated from the baseline data, as suggested.

6. Although the scientific writing was improved, it still requires further attention and some improvements, especially with regard to logical flow. Also, the problem with inconsistent use of abbreviations has not been rectified (for example, the abbreviation “LAA” was used for left atrial appendage (p. 7, p. 11) or left atrium area (p. 7). Explanations of several abbreviations (such as E/A, e’ or sometimes E’) are lacking.

The inconsistency in the use of the abbreviations LAA and e’/E’ has been corrected. The explanations of E/A and e’ have been added. The manuscript has been edited by professional English editors with special attention to logical flow. We enclose the Certificate of English editing.

7. The primary and secondary objectives of the study are not precisely defined in the Abstract. The conclusions should be consistent with these objectives.

The primary and secondary objectives have been precisely defined in the abstract, as suggested by the Reviewer.