Reviewer’s report

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

Version: 1 Date: 13 Oct 2019

Reviewer: Iwona Swiatkiewicz

Reviewer's report:

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.

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.

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.

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).

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.

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.

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

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal