Author's response to reviews

Title: Motion of left atrial appendage as a determinant of thrombus formation in patients with a low CHADS2 score receiving warfarin for persistent nonvalvular atrial fibrillation

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Author's response to reviews: see over
1. Introduction section: the statement: “However, it is well known that some AF patients that have PT-INR within the therapeutic range or a low CHADS2 score still suffer from thromboembolism” is not supported by references. Please give at least one reference.

   We added reference #6 to support that statement.

2. “The average of the two PT-INR measurements was used for analysis”. This is a little bit problematic, since one subject could have a „low” INR one month prior the echo examination, and „high” INR at the time of echo exam, and the calculation will be obtained with an „optimal” (averaged) INR value. Hypothetically, during the first period, this patient could develop a thrombus in the LAA. Can you comment this small laxity?

   We agree with you. We added the following sentences to the “Study limitation” section. (Page 11, line 7)

   “We measured the PT-INR levels one month before and at the time of TTE and TEE and averaged the two measurements. However, we recognized that there could be disparity between the measurements, and average value may not provide an accurate index of blood coagulability during this one-month period. In general, accurate evaluation of the blood coagulability was not possible.”

   Thank you for your helpful comment.

3. In the methods section the Authors explained, that the LAA volumes were determined using a Simpson’s method and that “although an autopsy study reported that the LAA is usually a multilobed structure (17), three-dimensional TEE revealed that the LAA was round in vivo (18),.. However, reference 18 is a case report. Recently, DiBiase et al (J Am Coll Cardiol. 2012;60:531-8) evaluated a large series of AF patients with MRI and CT and categorized the findings in at least 4 different LAA morphologies. Please, discuss.
We cited the suggested report and added the following sentence to the “Methods” section. (Page 5, line 17)

“Cardiac computed tomography or magnetic resonance tomography revealed that in 97% of patients, the LAA in vivo was shaped like a cactus (30%), chicken wing (48%) or windsock (19%).”

4. Results: despite the anticoagulation, surprisingly high percentage of the patients had thrombus in the LAA. Please, explain! The target INR is achieved only in the 2/3 of the patients. Did this influence the data?

We added the following sentences to the “Discussion” section. (Page 9, line 14)

“Among all of the patients, LAA thrombus was found in 16.5%. This may be due to the fact that target PT-INR level was achieved only in the two thirds of the patients. However, this high rate of LAA thrombus in the present study was concordant with that in a previous study (15.6%) (24).”

5. I would advise the Authors to skip the separate analysis of the CHADS-VASC group, since in this group only 5 patients had a thrombosis and the statistics is underpowered.

We deleted the results regarding CHADS2-VAsc score throughout the manuscript.

Thank you for your helpful comment.

6. Please, give an explanation for the creation of the 3 models for the multivariate analysis? In model clinical variables were included, but only INR and the duration of the AF were mentioned. What about the other important clinical variables which could affect the development of thrombi in the LAA?

We corrected the results and added the following sentences to the “Methods”
“Multivariate logistic regression analysis was performed using clinical variables with a p value $\leq 0.10$ in univariate analysis to determine the independent predictors of LAA thrombus.”

However, the CHADS2 score was excluded because the CHADS2 score already includes the information on the presence or absence of hypertension and prior stroke.

Thank you for your helpful comment.

7. The Discussion section is a little bit rough-and-ready. The first part of the second paragraph on page 10. is superfluous (TEE is known as the most sensitive…

We agree with you. We deleted the suggested sentence from the “Discussion” section.

8. In the same paragraph: “Performing TEE in patients with a low CHADS2 score is controversial.” Why?

We think that TEE is not a non-invasive method but semi-invasive method. Therefore, performing TEE in patients with a low CHADS2 score is not necessarily essential.

9. The section “LAA thrombus in patients with a low CHA2DS2-VASc score” is more a description than an explanation of the findings.

We agree with you. We deleted the suggested sentences from the “Discussion” section.

10. Please add to the discussion the paper by Ayirala et al. Echocardiographic
predictors of left atrial appendage thrombus formation. JASE. 2011;24:499-505

We cited the suggested report and added the following comment. (Page 10, line 7)
“A recent TEE study demonstrated that increased LA volume and lower LV ejection fraction were significant predictors of LAA thrombus (24). However, LAA motion was not considered in this recent study.”

Thank you for your helpful comment.

11. There are numerous grammatical and typographical errors throughout the manuscript.

We revised the manuscript and corrected the grammatical and typographical errors throughout the manuscript.