Author's response to reviews

Title: The value of diastolic function parameters in the prediction of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation

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Author's response to reviews: see over
Dear Drs. Picano and Sicari:

Thank you very much for giving us the opportunity to revise our manuscript. The following is a point-by-point response to reviewers’ comments. For your convenience we provided two versions of the revised manuscript: a “clean” version and one, with highlighted changes and marked deletions.

**Reviewer#1:**

**General comments**
The topic of the manuscript is interesting, the methodology of the study is well conducted and the paper is well written. However, I have some remarks should be considered by the authors in any revision.

**Major comments**
The sample size is small and the prevalence of LAAT is low to be conclusive. Even though the findings of the study indicate that echocardiographic diastolic parameters are associated with LAAT independently of clinical, LVEF and left atrium, however in the several logistic model analyzed the OR of E:e’ ranges from 1.0 to 1.1. Thus the clinical effect in terms of risk of LAAT in presence of high filling pressure is modest.

• **Response:** We agree. We addressed this issue in this limitation section. We would like to point out that E:e’ odds ratio of 1.1 is for every one point change of E:e’ prime. Given the wide spectrum of E:e’ value (ranging from 5 to more than 20), the impact of E/e’ can be substantial.

In the limitation section of the revised manuscript we explicitly stated:

“**The authors are cognizant of the small sample size and infrequent LAAT events, which impaired our ability to analyze many covariates within a single regression model**”.

“**the small sample size and limited number of events is another limitation**” and

“**the findings of this hypothesis-generating study are not applicable clinically at this time, as they demand prospective validation**”.

Some strong statements in the discussion should be avoided since not supported by the data. In particular, in page 10, last paragraph “We suggest that E:e’, e’ velocity, and other simple echocardiographic parameters may be useful in predicting systemic thromboembolism in nonvalvular AF as a complement or a replacement to the CHADS2 score”. And in page 11, first paragraph: “Therefore, if validated, the main strength of this parameter could potentially obviate the need for a TEE before restoration of sinus rhythm in lower risk individuals”.

• **Response:** We deleted the aforementioned statement.

Fourth, the discussion is too long and should be shortened.
• **Response**: We shortened the discussion section.

If we read the mean values of pulmonary pressure in the 2 groups, we noted that the mean values in both groups are < 30 mmhg, ovvero into the normal range. This aspect should be better specify.

• **Response**: Not quite sure what the reviewer is referring to in this comment. There is no mention of the pulmonary pressure anywhere in the manuscript. We suspect that this comment was entered in error. Otherwise, please specify the location of the problem (page/section).

Minor comments
Page 3 "pure atrial flutter". This definition is not correct, the most correct one is typical atrial flutter.

• **Response**: Thank you very much for pointing out this source of confusion. What we meant by “pure atrial flutter” is atrial flutter without intervening episodes of atrial fibrillation. As the reviewers are well aware, occasionally patients may alternate between atrial flutter and fibrillation. Thus, we sought to eliminate patients who have atrial flutter only.

To address this concern, we corrected the statement as follows: “Patients with atrial flutter, without intervening episodes with atrial fibrillation, were not included”.

In page 4 is reported the figure 2, whereas this figure corresponds to figure 1.

• **Response**: Thank you for pointing out this error. Correction was made.

**Reviewer#2**
The manuscript written by Doukky and coauthors showed that the diastolic dysfunction as assessed by the ratio e / e 'is associated with increased incidence of left atrial appendage thrombus, independently of other clinical predictors. Even if the study is retrospective was well written and the data was showed in a clear manner.

I have only one minor concern:

Is it corrected the value of interquartile range 91 days between TTE and TEE examination (pag 6)?

• **Response**: The interquartile range represents the difference between the 25th and 75th percentile of the values (in this case the time interval between TTE and TEE). The percentiles involved were calculated using the standard weighted average method. For added clarity, in the revised manuscript, we reported the “raw” 25th and 75th percentile rather than the difference. We did the same thing in table 1 (duration since first AF episode).