

Peer Review File

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Reviewer A

Comment1.1

General remarks:

Please state explicitly that the sample size was not calculated beforehand and that this was a convenience sample.

Reply 1.1

Thanks for your advice.

We have modified our text as advised.

Changes in the text:

We enrolled patients with NVAF who underwent TEE examination at the First Affiliated Hospital of Suzhou University between October 2019 and July 2022. The sample size was not calculated beforehand and that this was a convenience sample. (see page 5 line 134-136)

Specific remarks:

Comment1.2

Page 1

Line 20: Should be Female gender instead of just female

Line 38: Should be Clinical practise instead of clinic

Reply 1.2

Many thanks for your advice.

We have modified our text as advised.

Changes in the text:

Female gender, LVEF, LAEF can be used to predict left atrial appendage dense spontaneous echo contrast or left atrial appendage thrombus. (page 2 line 36)

Atrial fibrillation (AF) is one of the most frequently encountered arrhythmias in clinic clinical practise, with stroke triggered by detachment of left atrial appendage thrombus (LAAT) after AF being its most critical complication. (page 2 line 54)

Comment1.3

Page 6

Line 187 the sign „_“ should be deleted

Reply 1.3

Many thanks for your advice.

We have modified our text as advised.

Changes in the text:

The consistency statistic (C statistic) was computed to evaluate the predictive capability of the nomogram. (page 6 line 203)

Comment1.4

Page 11

Line 310 Should be Studying not studied

Line 321 Should be „a common“

Reply 1.4

Many thanks for your advice.

We have modified our text as advised.

Changes in the text:

developed a clinical prediction model using 433 patients with NVAf as the studying population and found that ECG variables, particularly LAD, LVEF, and pulmonary artery systolic pressure, were independent predictors of LAA SEC/LAAT (22). (page 12 line328)

The nomogram has emerged as a common prediction method in the field of medical research in recent years due to its ability to convert the contribution of each variable into a score and then calculate the probability of events, making it more intuitive (26) (page12 line 345)

Reviewer B

The title should reflect the development and validation of the nomogram and its comparison with the CHADS2 and CHA2DS2-VASc models. The abstract requires enhancement. The background lacks details on the clinical necessity for this predictive model and the existing knowledge gaps. The methods section should detail subject inclusion criteria, predictor assessment, and diagnostic criteria for LAASEC/LAAT. Results should concisely outline the clinical characteristics of participants. Given the absence of external validation samples and the use of cross-sectional data, the authors should temper their current conclusion. In the introduction, authors should furnish supportive data on the limited predictive accuracy of CHADS2 and CHA2DS2-VASc. They should also analyze how the current data address prior study limitations. Concerning the methodology, a critical issue is that predictors were not measured at baseline but simultaneously with the diagnosis of LAASEC/LAAT, contradicting typical prediction model practices. This study lacks external validation samples. Authors should justify why they did not divide the sample into training and validation sets. Finally, please cite a potentially related paper: Liu XW, Tian X, Hu J, Ma GJ, Gao

BL, Li CY. Factors associated with left atrial appendage filling defects on early-phase cardiac computed tomography in patients with nonvalvular atrial fibrillation: a case-control study. *Quant Imaging Med Surg* 2023;13(2):720-734. doi: 10.21037/qims-22-146.

Comment2.1

The title should reflect the development and validation of the nomogram and its comparison with the CHADS2 and CHA2DS2-VASc models.

Reply 2.1

Many thanks for your advice.

We have modified our text as advised.

Changes in the text:

Development and validation of a nomogram superior to CHADS2 and CHA2DS2-VASc models for predicting left atrial appendage dense spontaneous echo contrast/left atrial appendage thrombus (page1 line 1-5)

Comment2.2

The abstract requires enhancement.

Reply 2.2

Many thanks for your comment.

We have modified our text as advised.

Atrial fibrillation (AF) is one of the most frequently encountered arrhythmias in clinic clinical practice, with stroke triggered by detachment of left atrial appendage thrombus (LAAT) after AF being its most critical complication. (page 2 line 53-55)

Comment2.3

The background lacks details on the clinical necessity for this predictive model and the existing knowledge gaps.

Reply 2.3

Many thanks for your comment.

Individualized treatment of atrial fibrillation according to embolic risk classification is of great importance. Previous prediction models have limited predictive value, possibly because they do not include left atrial functional parameters. Our nomogram include left atrial functional parameters, especially left atrial strain rate indicators, which are of greater application value than other models. We have described this in my paper.(page 4 line 92-107,page5,124-130).

Comment2.4

The methods section should detail subject inclusion criteria, predictor assessment, and diagnostic criteria for LAASEC/LAAT.

Reply 2.4

Many thanks for your comment.

inclusion criteria, predictor assessment, and diagnostic criteria for LAASEC/LAAT has been described in my paper (page 5 line 138-142; page6 line 144-173; page7 line 175-180)

Comment2.5

Results should concisely outline the clinical characteristics of participants.

Reply 2.5

Many thanks for your comment.

We have modified our paper as advised

Changes in the text:

Among them, 55 patients were female and the median age was 67.0 (62.0, 72.0) years old. (page8 line223-224)

Comment2.6

Given the absence of external validation samples and the use of cross-sectional data, the authors should temper their current conclusion.

Reply 2.6

Many thanks for your comment.

We have modified our paper as advised

Changes in the text:

This may make it possible to predict LAASEC/LAAT through non-invasive examination, accurately identify high-risk stroke populations in AF patients, and then implement personalized anticoagulation.

Comment2.7

In the introduction, authors should furnish supportive data on the limited predictive accuracy of CHADS2 and CHA2DS2-VASc. They should also analyze how the current data address prior study limitations.

Reply 2.7

Many thanks for your comment.

In the introduction we have presented the supportive data on the limited predictive accuracy of CHADS2 and CHA2DS2-VASc and attached references. (page4 line102-103)

We also analyze how the current data address prior study limitations. (page4 line105-107)

Comment2.8

Concerning the methodology, a critical issue is that predictors were not measured at baseline but simultaneously with the diagnosis of LAASEC/LAAT, contradicting typical prediction model practices.

Reply 2.8

Many thanks for your comment.

All laboratory tests were conducted by taking peripheral venous blood in the morning on an empty stomach. Fasting for at least 6 hours before TEE, ECG and TEE were performed at the same time. The measurements of predictors were not described in the article, and we have supplemented and marked them in red. Therefore, all predictors were measured at baseline.

Changes in the text:

All laboratory tests were conducted by taking peripheral venous blood in the morning on an empty stomach. (page6 line151-152)

Fasting for at least 6 hours before TEE, ECG and TEE were performed at the same time.(page6 line 172)

Comment2.9

This study lacks external validation samples. Authors should justify why they did not divide the sample into training and validation sets.

Reply 2.9

The sample size of this study was relatively small, so we adopted the internal verification method of bootstrap. If the sample size of the training set is too small according to the splitting method, the model may be overfitting.

Comment2.10

Finally, please cite a potentially related paper: Liu XW, Tian X, Hu J, Ma GJ, Gao BL, Li CY. Factors associated with left atrial appendage filling defects on early-phase cardiac computed tomography in patients with nonvalvular atrial fibrillation: a case-control study. *Quant Imaging Med Surg* 2023;13(2):720-734. doi: 10.21037/qims-22-146.

Reply 2.10:

Changes in the text:

Many thanks for your comment.

We have cited relevant paper in our manuscript (references No.29).

29. Liu XW, Tian X, Hu J, et al. Factors associated with left atrial appendage filling defects on early-phase cardiac computed tomography in patients with nonvalvular atrial fibrillation: a case-control study. *Quant Imaging Med Surg* 2023;13(2):720-734.

Reviewer C

1. When using **abbreviations** in table/figure or table/figure description, please mention the entire expression in a footnote below the corresponding table/figure.

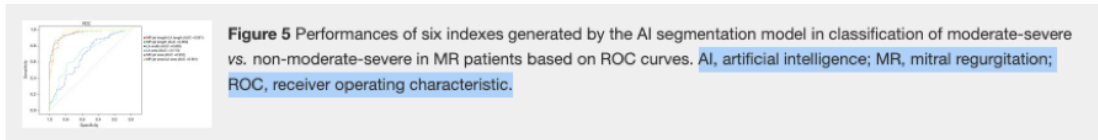
Please check and revise. Such as:

NVAF, TEE, SEC, LAAT, LAA, LASSO, AUC, DCA, NRI, IDI (figure 1);

SEC, LAAT, NVAF (figure 4);

SEC, LAAT, NVAF, ROC, DCA (figure 6); etc.

Here is an example:



Reply

Many thanks for your comment.

The paper has been revised as requested and marked it in red.

NVAF, nonvalvular atrial fibrillation; TEE, SEC, transesophageal echocardiography; LAAT, left atrial appendage thrombus; LAA, left atrial appendage; LASSO, least absolute shrinkage and selection operator; AUC, area under the curve; DCA, decision curve analysis; NRI, net reclassification index; IDI, the integrated discrimination improvement (figure 1);

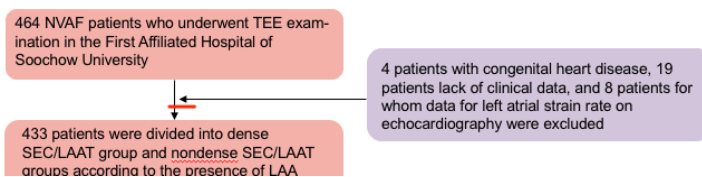
SEC, spontaneous echo contrast; LAAT, left atrial appendage thrombus; NVAF, nonvalvular atrial fibrillation (figure 4);

SEC, spontaneous echo contrast; LAAT, left atrial appendage thrombus; NVAF, nonvalvular atrial fibrillation; ROC, receiver operating characteristic curve; DCA, decision curve analysis (figure 6);

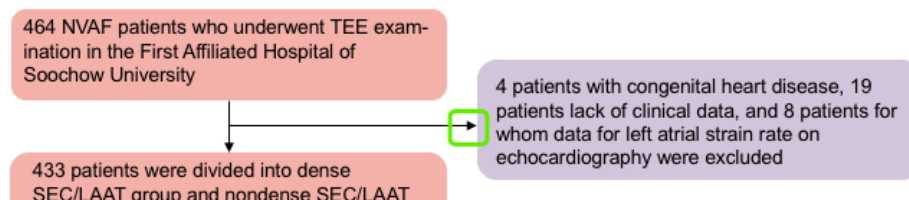
2. Figure 1

Please revise the arrow.

Before:



After:



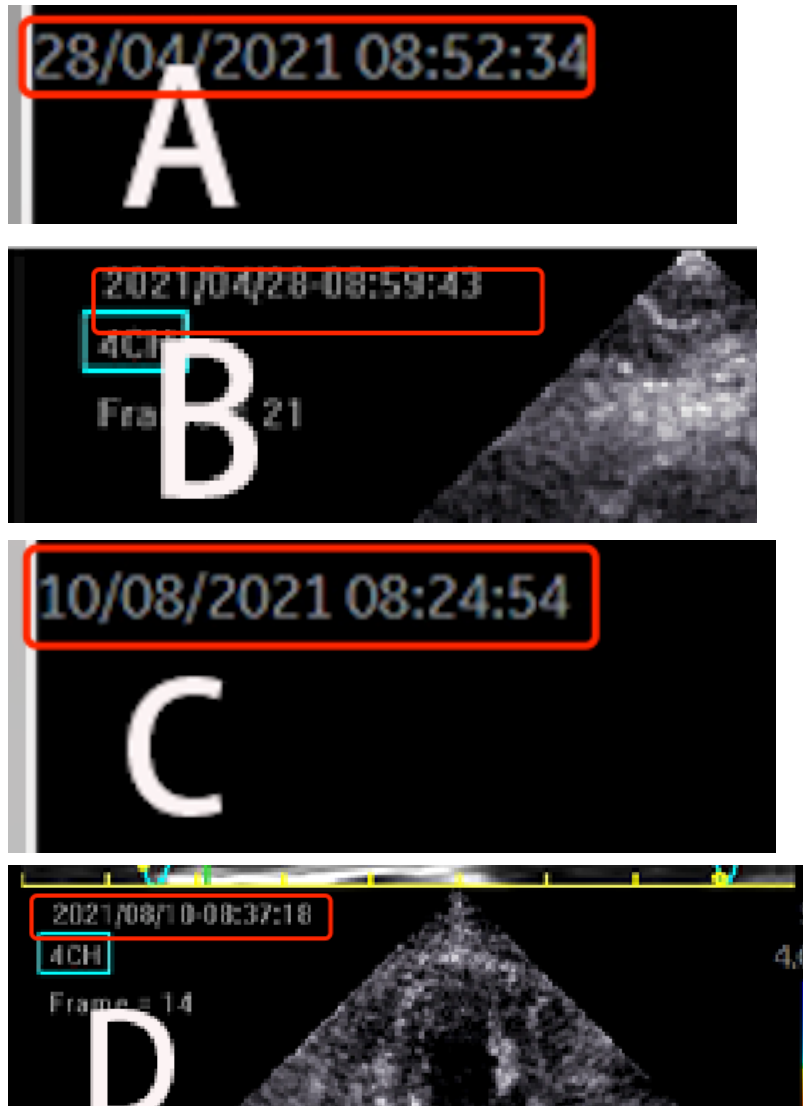
Reply

Many thanks for your comment.

Thanks for your help.

3. Figure 2

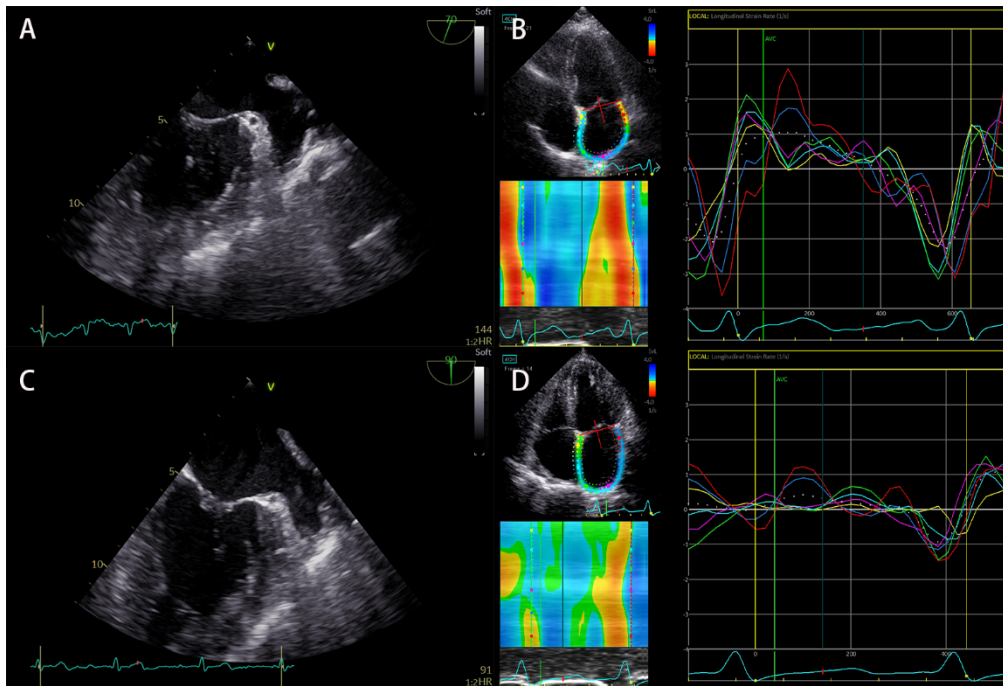
The patient ID and timepoint should be hidden/removed to prevent human subjects from being recognized.



Reply

Many thanks for your comment.

We have revised the image and placed the revised image below. We have also revised it in our manuscript.



4. Figure 4

The first letter should be capitalized: **F**emale.

Points

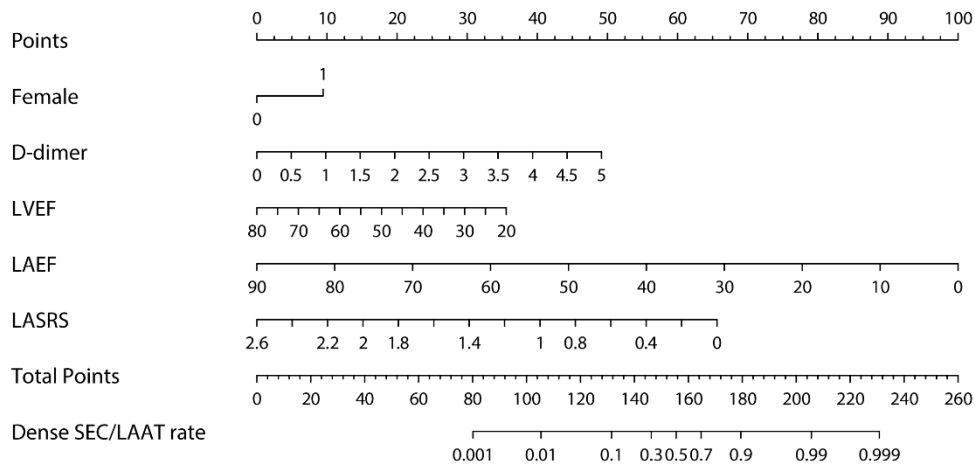
female

D-dimer

Reply

Many thanks for your comment.

We have revised the image and placed the revised image below. We have also revised it in our manuscript.



5. Figure 5

Please confirm if the accuracy of data.

d Probability

Mean absolute error = 0.018 n=433

274 the calibration curve of this nomogram (Figure 5). Given the relatively small amount of data
 275 in this study, we conducted internal validation through 500 repetitions of bootstrapping. In the
 276 calibration curve results, the calibration curve of this nomogram was very close to 45°,
 277 indicating good calibration of the predictive model. Meanwhile, the bootstrap C-statistic value
 278 was 0.903, with a bias of -0.018.

Reply

Many thanks for your comment.

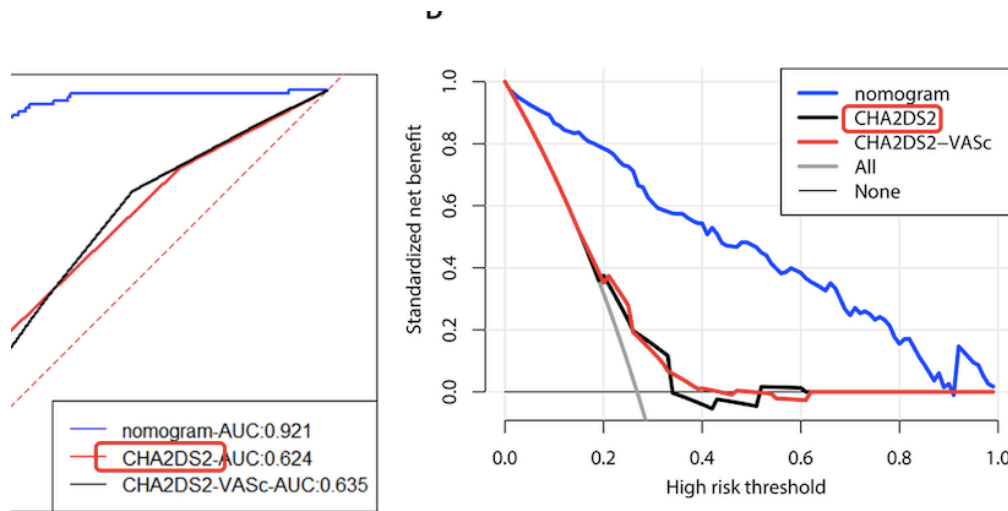
Thank you very much for pointing out our mistake. We have revised it in my paper and marked it in red.

Meanwhile, the bootstrap C-statistic value was 0.903, with a bias of 0.018.

6. Figure 6

Please unify: CHADS₂ or CHA₂DS₂

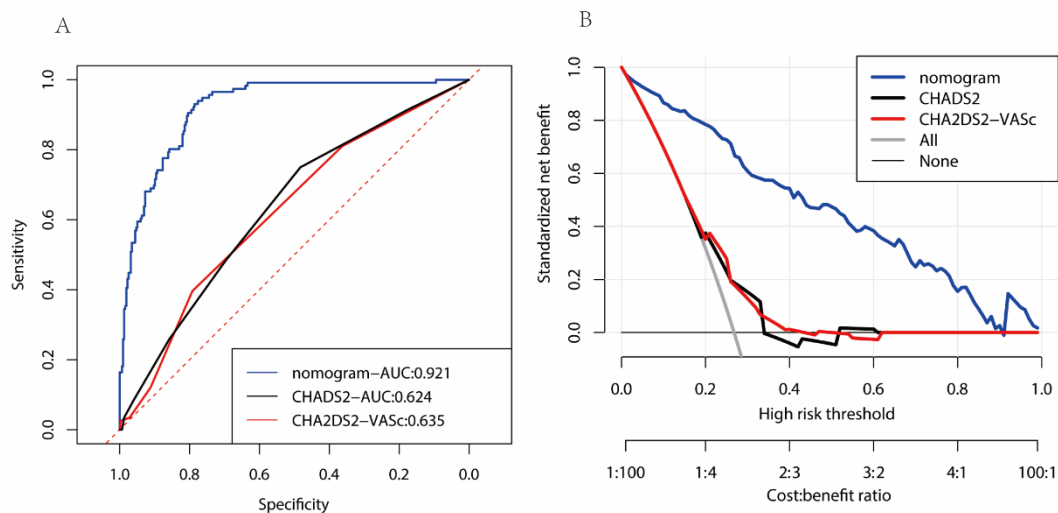
85 (CHADS₂ and CHA₂DS₂-VASc) in their predictive performance for dense SEC/LAAT, we
 86 plotted the ROC curves of three prediction models (Figure 6A). Accordingly, the AUC value
 87 and 95% confidence interval of nomogram was the highest, equal to 0.921 (0.785, 0.931),
 88 while that of CHADS₂ and CHA₂DS₂-VASc was 0.624 (0.397, 0.792) and 0.635 (0.483,
 89 0.750), respectively. Therefore, the nomogram better predicted dense SEC/LAAT.
 90 Furthermore, corresponding DCA curves were drawn (Figure 6B). A higher net benefit was



Reply

Many thanks for your comment.

We have revised Figure 6, the revised figure 6 was as follows, and we have also revised it in the manuscript



7. Please confirm if 'Table 2A' should be 'Table 2' or 'Figure 3A'.

245 **##Screening of variables for the predictive model**

246 We conducted LASSO regression on 22 variables with statistical significance (Figure 3).

247 The model had the minimum classification error at the level of $\lambda=0.015$ and the least number

248 of variables at the level of $\lambda=0.038$ (female gender, D-dimer, CHF, LVEF, E/e', LAEF,

249 LASVI, LASRS) (Table 2A) these eight variables exhibited good predictive value for dense

250 SEC/LAAT, with corresponding coefficients of 0.146, 0.187, 0.314, -0.025, 0.023, -0.050,

251 0.018, and -0.819, respectively.

252

253

254 To further simplify the model, the aforementioned eight variables were subjected to

255 stepwise regression analysis. The stepwise regression data in Table 2 indicated that female

Reply

Many thanks for your comment.

It should be Table 2. We have revised it in the manuscript and highlighted it in red.

8. Please check the accuracy of data.

Variable	LASSO regression	Stepwise regression analysis		
	Coefficient	OR	95%CI	P
Gender (female)	0.146	2.811	1.445, 5.469	0.002
D-dimer ($\mu\text{g/ml}$)	0.187	2.460	1.230, 4.921	0.011
CHF (%)	0.314	-	-	-
LVEF (%)	-0.025	0.961	0.927, 0.996	0.03
E/e'	0.023	-	-	-
LAEF (%)	-0.050	0.950	0.932, 0.967	<0.01

4 To further simplify the model, the aforementioned eight variables were subjected to

5 stepwise regression analysis. The stepwise regression data in Table 2 indicated that female

6 gender, high D-dimer level, low LVEF, low LAEF, and low LASRS were independent markers

7 for predicting SEC/LAAT ($P<0.05$), with odds ratios (OR) values and 95% confidence intervals

8 of 2.811 (1.445, 5.469), 2.46 (1.230, 4.921), 2.663 (0.976, 7.265), 0.95 (0.932, 0.967), and

9 0.173 (0.035, 0.848).

Reply

Many thanks for your comment.

Thank you very much for pointing out our miswriting. We have revised it in my paper and marked it in red.

9. Reference/citation

a. Reference 4 was missing. Please revise. Please note that references should be cited consecutively and consistently according to the order in which they first appear in the text.

86 be as high as 50 million (1). In patients with AF, orderly atrial contractions are transited into
87 rapid and disordered AF, and in addition to that of palpitations, the incidences of stroke and
88 heart failure in patients with AF are also markedly higher (2). In particular, AF-associated
89 stroke has garnered widespread attention owing to its high fatality and disability rates (3).[←]

90 It has been reported that patients with AF have a four to five-fold increased risk of stroke
91 (5). Therefore, the prevention of stroke is a key concern in AF treatment (6). At present, the
92 major preventive measure against AF-associated stroke is anticoagulant therapy, yet the

Reply

Many thanks for your comment.

Thank you very much for pointing out our mistake. We have revised it in my paper and marked it in red.

Atrial fibrillation (AF) is clinically one of the most frequently occurring arrhythmias, and due to the aging population of the planet, is increasing in incidence annually on a global scale. It has been reported that by 2020, the total number of patients with AF worldwide may be as high as 50 million (1,2). In patients with AF, orderly atrial contractions are transited into rapid and disordered AF, and in addition to that of palpitations, the incidences of stroke and heart failure in patients with AF are also markedly higher (3). In particular, AF-associated stroke has garnered widespread attention owing to its high fatality and disability rates (4).

b. Please indicate the citation of ‘Cetin et al.’ in this sentence.

Similar conto the study of Cetin et al., we found that LVEF was an independent predictor of LAA SEC/LAAT, but mean pulmonary artery pressure and LAD, which reflects left atrial size, were not.

Reply

Many thanks for your comment.

Thank you very much for pointing out our mistake. We have revised it in my paper and marked it in red.

Similar conto the study of Cetin et al. (22),

c. The authors mentioned “**studies...**”, while only one reference was cited. Change “Studies” to “A study” or add more citations. Please revise. Please number references

consecutively in the order in which they are first mentioned in the text.

Related studies have shown that extensive left atrial strain rate can be used for left atrial function assessment and that left atrial strain can be used to predict SEC and LAAT in clinical practise (14).

Nevertheless, clinical studies based on large sample sizes have shown a relatively limited value of CHA2DS2-VASc score in identifying high-risk stroke populations, with a C-statistic less than 0.7, which is only 0.004 higher than that of the CHADS2 score (21).

Other studies (23) have substantiated that LAV and LAVI, which better reflect left atrial structure, have limited predictive value for LAA SEC/LAAT.

Related studies have shown that extensive left atrial strain rate can be used for left atrial function assessment and that left atrial strain can be used to predict SEC and LAAT in clinic clinical practise (14).

Reply

Many thanks for your comment.

Thank you very much for pointing out our mistake. We have revised it in my paper and marked it in red.

A related study has shown that extensive left atrial strain rate can be used for left atrial function assessment and that left atrial strain can be used to predict SEC and LAAT in clinical practise (14).

However, the study is limited to examining the relationship between ECG variables and LAA dense SEC or LAAT, with other clinical data rarely being included.

Nevertheless, clinical study based on large sample sizes have shown a relatively limited value of CHA2DS2-VASc score in identifying high-risk stroke populations, with a C-statistic less than 0.7, which is only 0.004 higher than that of the CHADS2 score (21).

Due to the limited application value of previous prediction models, a recent study has used the presence of LAA dense SEC/LAAT as an alternative indicator for those at high risk of stroke to construct prediction models for patients with AF.

a study (23) has substantiated that LAV and LAVI, which better reflect left atrial structure, have limited predictive value for LAA SEC/LAAT.

d. Authors' names of reference 7 are missing. If there are more than three authors, name only the first three and then use “et al” and names of journals should be abbreviated in the style used in PubMed.

Reply

Many thanks for your comment.

Thank you very much for pointing out our mistake. We have revised it in my paper and marked it in red.

7. **Silverio A, Di Maio M, Prota C, et al.** Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients. *Eur Heart J Cardiovasc Pharmacother* 2021;7:f20-9.

10. Should it be “similar to”? Please check.

401 enrolled indicators that could better reflect left atrial structure and left atrial function. **Similar**
402 **cont**to the study of **Cetin et al.**(22), we found that LVEF was an independent predictor of LAA

Reply

Many thanks for your comment.

We have revised my paper as required and marked it in red in the text.

Similar to the study of Cetin et al. (22),

11. Table 1

There seems to be no “**ECG**” in Table 1, while it was explained in the legend. Please check and revise.

Reply

Many thanks for your comment.

We have revised my paper and deleted the related content.

12. Table 2

1) There seems to be no “**EDT**” and “**LASRE**” in Table 2, while it was explained in the legend. Please check and revise.

Reply

Many thanks for your comment.

We have revised my paper and deleted the related content.

2) **CI**, **LASRS** should be indicated the full expression in the legend.

Reply

Many thanks for your comment.

We have revised my paper as required, and marked it in red in the text.