JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12828

CT-criteria for left atrium appendage thrombus detection

Bauyrzhan Kaliyev[1], Raushan Rakhimzhanova[2], Tairkhan Dautov[1], Ayan Abdrakhmanov[3], Lyazzat Bastarbekova[1], Azhar Kabdullina[4], Zhanar Moldakhanova[1]

[1]*Department of Radiology, National Research Cardiac Surgery Center, Astana, Kazakhstan*
[2]*Department of Radiology No1, Astana Medical University, Astana, Kazakhstan*
[3]*Department of Interventional Arrhythmology, National Research Cardiac Surgery Center, Astana, Kazakhstan*
[4]*Department of Nuclear Medicine, Medical Centre Hospital of President's Affairs Administration of the Republic of Kazakhstan, Astana, Kazakhstan*

Received: 2022-02-28.
Accepted: 2022-12-16

J Clin Med Kaz 2023; 20(1):7-13

Corresponding author:
Bauyrzhan Kaliyev.
E-mail: baur233113@mail.ru;
ORCID: 0000-0003-4825-749X

Abstract

Objective: Atrial fibrillation is strongly associated with stroke and accounts for 60% of cardioembolic stroke. Assessing thromboembolic risk is important for patients with atrial fibrillation. Approximately 90% of all thrombus are localized in the left atrium appendage (LAA). This study aimed to determine the efficacy of cardiac computed tomography (CT) for LAA thrombus detection.

Material and methods: This retrospective study included 292 patients. LAA thrombus was confirmed or excluded by cardiac CT with the reference to transesophageal echocardiography (TEE). We excluded patients with allergic reactions to iodide, increased creatinine levels, thyroid disease (hyperthyroidism), pregnancy, and age <18 years.

Results: According to the cardiac CT, 103 of 292 people had LAA thrombus, while according to TEE, only 48 of patients had LAA thrombus. The sensitivity and specificity of CT were 97.7% and 77%, respectively. The sensitivity and specificity of the CT was higher in 2016–2020, when the delayed phase was added to the standard protocol, compared to 2012–2015 years. Older age, higher BMI, higher CHA_2DS_2-VASc and HAS-BLED scores, and larger LA and LVESV were significantly associated with LAA thrombus detection on cardiac CT. Higher LVESV and LVEDV indexes (LVESVI and LVEDVI) and lower LV ejection fraction measured by TEE were also predictors of LAA thrombus detection by cardiac CT.

Conclusion: Our findings show that cardiac CT has high sensitivity and specificity for excluding or confirming LAA thrombus, and can also be exclusively used to determine the presence or absence of a thrombus.

Key words: left atrium appendage thrombus, cardiac computed tomography, atrial fibrillation, cardioembolic stroke, transesophageal echocardiography

Introduction

Cardioembolism is one of the major causes of ischemic strokes and comprises 14–30% of all cerebral infarctions [1-2]. Atrial fibrillation (AF) accounts for up to 60% of cardioembolic strokes [3]. The mechanism of stroke development in patients with AF is well known. Once, a patient develops AF, the dysrhythmia causes contractile dysfunction and stasis, which further lead to thrombus formation and an increased risk of thromboembolism [4]. Approximately 90% of all thrombi are localized in the left atrium appendage (LAA) [5-8]. Current therapeutic strategies for AF are pharmacological and non-pharmacological [9]. The majority of patients with AF are treated with antiarrhythmic drugs and anticoagulation drugs, and only a minority with a persistent form of AF require different types of cardioversion [10]. Electrical cardioversion with radiofrequency pulmonary vein antral isolation is an effective approach in the treatment of persistent AF [11-12]. However, the presence of blood clots in the LAA is a contraindication to electric cardioversion [13-14]. After normalization of sinus rhythm, restoration of contractility and blood flow can lead to the detachment of a blood clot from the LAA and subsequent cardioembolic stroke. Assessing the risk of stroke in patients with AF is crucial. The gold standard for identifying an LAA thrombus is transesophageal echocardiography (TEE) [15-16]. However, TEE is a semi-invasive procedure with various complications [17]. Computed tomography (CT) is widely used in clinical practice, and recent technological improvements in cardiac CT have made the method more attractive because of its non-invasiveness, and it is a viable alternative to TEE. The development of CT-derived criteria for an increased risk of LAA thrombus can be an effective method for diagnosing thromboembolism. Studies in this area have been done before has shown that LAA thrombus detection with additional data collection tends to increase [18]. Despite this, the data obtained are mixed, and the reliability of the study differs sharply from each other in the results provided [19-20]. In this study, we analyzed the efficacy of cardiac CT for diagnosing LAA thrombus with reference to TEE data.

Material and methods

We retrospectively analyzed the data of 292 patients diagnosed with AF, who were admitted to our institution from February 2012 to September 2020. All patients underwent both TEE and cardiac CT. The exclusion criteria for CT were allergic reactions to iodide, increased creatinine levels, thyroid disease (hyperthyroidism), pregnancy, and age <18 years. The institutional ethics committee approved the study following the Declaration of Helsinki. In addition, the patients signed consent to the study.

Transesophageal echocardiography

TEE was performed using a Phillips IE33 device. The study included the assessment of left ventricular (LV) function (LV ejection fraction), valve apparatus, and left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV).

Computed tomography

CT scanning was performed with a Siemens Somatom Definition 64 device with retrospective cardiosynchronization and reconstruction with a slice thickness of 0.6 mm and pitch of 0.2 mm. We used the standard patient position (supine), with intravenous contrast bolus injection using an automatic bolus-free CT injector (Ohio Tandem; speed 5 mL/s), followed by the introduction of saline solution (50 mL). The scan was performed with "bolus tracking" at the ascending aorta at 170 units. At the starting level of the scan at the tracheal bifurcation, the delay after the introduction of contrast was 10 seconds. Patients were scanned employing electrocardiographic synchronization. The dose of the contrast agent was calculated based on the patient's weight.

The study was carried out within the limits of the LAA in order to reduce the exposure of the patient to the minimum possible. When a hypodense area was detected with contrast filling of the LAA, a 60-second scan was brought into the arterial phase. Two experienced cardiologists, who were blinded to the CT results, analyzed the TEE.

The analysis of the CT angiography data was performed by two experienced radiologists. Uniform filling of the LAA was regarded as normal. A defect in the filling of the LAA was regarded as a blood clot. The volume of the left atrium (LA) was measured on a Syngo Via workstation using the volume application along the inner contour of the LA, including the LA ear manually on each slice. Figure 1 shows an image of the LA volume calculation. Figure 2 illustrates the detection of the LAA thrombus by CT and TEE.

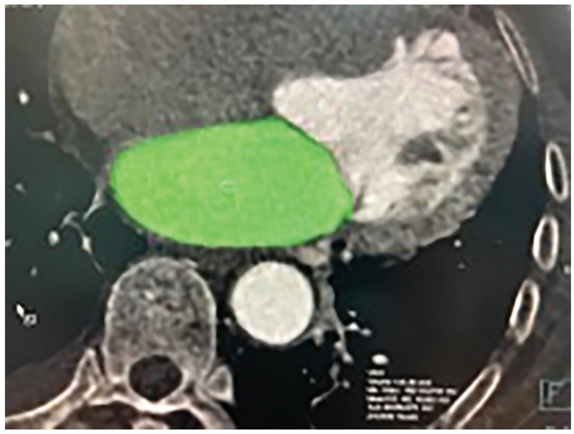

Figure 1 - A calculation of the volume of the left atrium.

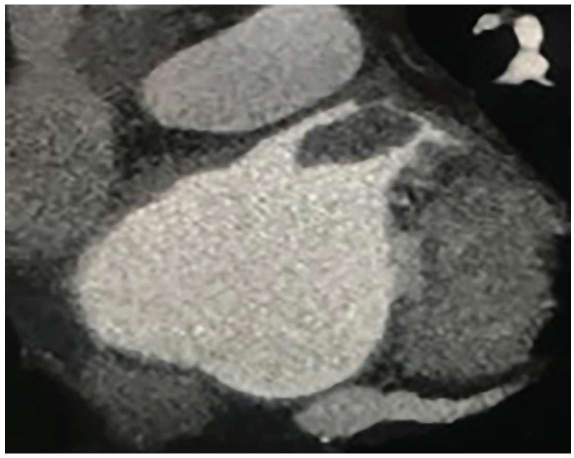

Figure 2A - LAA thrombus detected by CT

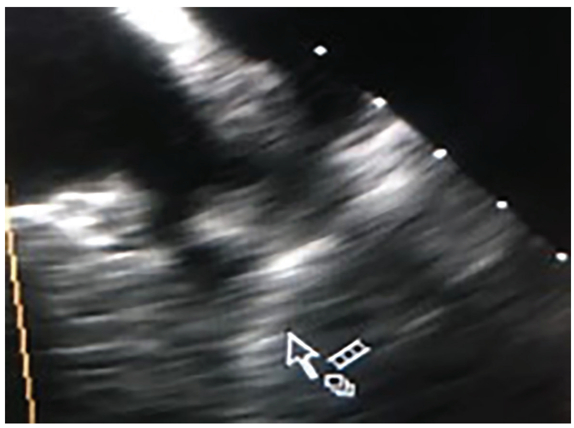

Figure 2B - LAA thrombus confirmed by TEE in the same patient

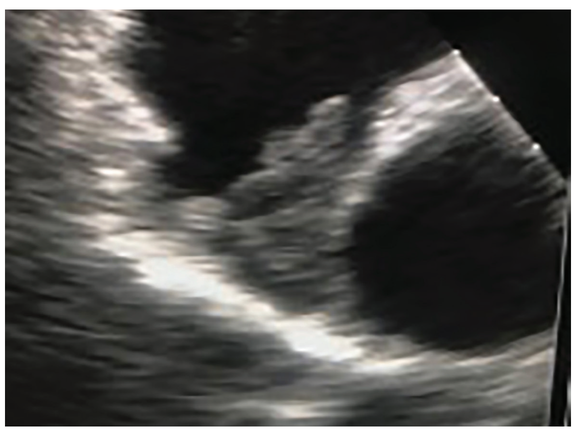

Figure 2C - LAA thrombus confirmed by TEE in the same patient

Statistical analysis

As TEE is considered a gold standard for determining the presence or absence of thrombi, CT was evaluated for sensitivity and specificity with respect to TEE. Quantitative variables are reported as means and standard deviations. Categorical variables are presented as numbers and percentages in each respective class. Each variable underwent bivariate analysis with respect to the primary outcome to determine their statistical significance. For continuous data, the Student t-test was used to determine the differences between means of variables in the groups. For qualitative data, Pearson's chi-square and Fisher's exact tests were used to determine a significant association with the outcome in two groups. The significance level was set at α = 0.05. All statistical analyses were performed using STATA 14.0 software.

Results

The mean age of the 292 patients was 57.1 years (range 19–86), 62.3% were men, and the mean body mass index (BMI) was 29.2 kg/m^2. The mean CHA_2DS_2-VASc score was 1.99 (range 0–6), the mean HAS-BLED score was 1.45 (range 0–5); 67.5% of patients had a history hypertension, and the average LA volume measured by cardiac CT was 127.4 cm^3. The Table 1 shows the identified clinical and demographic features. According to cardiac CT and TEE, 103 (Table 2) and 48 (Table 3) patients, respectively, of the 292 patients had LAA thrombus.

Older age, higher BMI, higher CHA_2DS_2-VASc and HAS-BLED scores, and larger LA and LVESV were significantly associated with LAA thrombus detection on cardiac CT (p=0.012, <0.001, 0.001, <0.001, <0.001, and 0.004, respectively) (Table 2).

Higher LVESV and LVEDV indexes (LVESVI and

Table 1 Demographic and medical characteristics of the patients (N=292)

	Mean or n	SD or %
Age, years	57.1	±11.4
Sex		
Female	110	37.7%
Male	182	62.3%
Body mass index, kg/m2	29.2	±5.1
CHA2DS2-VASc score	1.99	±1.45
HAS-BLED score	1.45	±1.2
Weight, kg	83.8	±17.1
Hypertension		
Yes	197	67.5%
No	95	32.5%
PT, sec	15.9	±6.2
INR, sec	1.34	±0.6
Fibrinogen, g/L	3.41	±3.3
APTT, sec	40.7	±13.2
TEE		
ESD, cm	3.5	±0.7
EDD, cm	4.8	±0.7
ESV, mL	48.4	±27.7
EDV, mL	105.7	±34.7
IVS, cm	1.06	±0.24
Cardiac CT		
LA volume, cm3	127.4	±46.7

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; PT, prothrombin time; TEE, transesophageal echocardiography

Table 2 Demographic and medical characteristics of patients with and without LAA thrombus according to CT (N=292)

	No LAA thrombus		
(n=189)	LAA thrombus		
(n=103)	p-value		
Age	55.9 ± 11.6	59.4 ± 10.8	0.012
Sex			
Female	69 (62.7)	41 (37.3)	0.578
Male	120 (65.9)	62 (34.1)	
Body mass index, kg/m2	28.2 ± 4.6	31.1 ± 5.4	<0.001
CHA2DS2-VASc score	1.75 ± 1.4	2.43 ± 1.5	<0.001
HAS-BLED score	1.16 ± 1.03	1.96 ± 1.3	<0.001
Weight, kg	83.4 ± 18.3	84.7 ± 14.6	0.517
Hypertension			
Yes	123 (62.4)	74 (37.6)	0.238
No	66 (69.5)	29 (30.5)	
PT, sec	15.6 ± 6.3	16.6 ± 5.9	0.203
INR, sec	1.32 ± 0.61	1.4 ± 0.7	0.283
Fibrinogen, g/L	3.32 ± 3.3	3.56 ± 3.3	0.549
APTT, sec	40.9 ± 14.1	40.3 ± 11.5	0.684
TEE			
ESD, cm	3.5 ± 0.7	3.6 ± 0.8	0.044
EDD, cm	4.75 ± 0.7	4.95 ± 0.7	0.017
ESV, mL	45 ± 18.6	54.7 ± 38.6	0.004
EDV, mL	102.8 ± 32.4	111 ± 38.1	0.051
IVS, cm	1.04 ± 0.2	1.09 ± 0.3	0.066
Cardiac CT			
LA volume, cm3	116.7 ± 42.2	147.3 ± 48.3	<0.001

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; LAA, left atrial appendage; PT, prothrombin time; TEE, transesophageal echocardiography

Table 3 Demographic and medical characteristics of patients with and without LAA thrombus according to TEE (N=292)

	No LAA thrombus (244)	LAA thrombus (48)	p-value
Age	56.9 ± 11.2	58.2 ± 12.5	0.505
Sex			
Female	89 (80.9%)	21 (19.1%)	0.342
Male	155 (85.2%)	27 (14.8%)	
Body mass index, kg/m2	29.1 ± 5.1	30.2 ± 4.9	0.158
CHA2DS2-VASc score	1.96 ± 1.4	2.17 ± 1.6	0.365
HAS-BLED score	1.37 ± 1.2	1.8 ± 1.2	0.017
Weight, kg	84.3 ± 17.6	81.7 ± 13.9	0.353
Hypertension			
Yes	165 (83.8%)	32 (16.2%)	0.897
No	79 (83.2%)	16 (16.4%)	
PT, sec	15.7 ± 5.9	17.4 ± 7.1	0.076
INR, sec	1.32 ± 0.6	1.5 ± 0.8	0.112
Fibrinogen, g/L	3.3 ± 2.95	4.1 ± 4.8	0.118
APTT, sec	40.7 ± 13.6	40.6 ± 11.4	0.956
TEE			
ESD, cm	3.5 ± 0.7	3.7 ± 0.9	0.086
EDD, cm	4.8 ± 0.7	3.9 ± 0.8	0.616
ESV, mL	47.3 ± 26.6	54.2 ± 32.2	0.113
EDV, mL	104.3 ± 31.9	112.7 ± 46.1	0.125
IVS, cm	1.04 ± 0.22	1.14 ± 0.32	0.008
Cardiac CT			
LA volume, cm3	123.04 ± 44.5	127.5 ± 51.3	<0.001

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; LAA, left atrial appendage; PT, prothrombin time; TEE, transesophageal echocardiography

Table 4 Comparison of volume measurements between patients with and without LAA thrombus according to CT (N=292)

	Overall	No LAA thrombus		
(n=189)	LAA thrombus			
(n=103)	p-value			
LVESVI, mL/m2	24.8 ± 13.9	23.1 ± 8.9	28.04 ± 19.9	0.004
LVEDVI, mL/m2	54.2 ± 16.9	52.7 ± 15.1	56.9 ± 19.7	0.045
LVEF, %	55.9 ± 8.9	56.8 ± 7.3	54.1 ± 11.2	0.015

Values are presented as mean ± SD
Abbreviations: LAA, left atrial appendage; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index

Table 5 Multivariate analysis of predictors of left atrial appendage thrombus according to CT (N=292)

	OR	95% CI	p-value
Age	1.01	0.98 – 1.04	0.579
BMI, kg/m2	1.14	1.07 – 1.23	0.000
CHA2DS2-VASc score	1.11	0.89 – 1.38	0.359
HAS-BLED SCORE	1.88	1.42 – 2.48	<0.001
ESD, cm	0.99	0.62 – 1.56	0.951
EDD, cm	0.93	0.87 – 0.99	0.023
LA volume, cm3	1.014	1.01 – 1.02	<0.001
LVESVI, mL/m2	1.19	1.04 – 1.35	0.010

Abbreviations: BMI, body mass index; CT, computed tomography; EDD, end-diastolic dimension; ESD, end-systolic dimension; LA, left atrium; LVESVI, left ventricular end-systolic volume index

Table 6 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2012–2020

cardiac CT

		negative	positive
†GS	negative	188	56
	positive	1	47

†Echocardiography results are taken as the gold standard (GS)

Sensitivity = TP/(TP+FN) = 47/(47+1) = 97.9%
Specificity = TN/(TN+FP) = 188/(188+56) = 77%

CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 7 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2012–2015

cardiac CT

		negative	positive
†GS	negative	48	17
	positive	1	34

Sensitivity = TP/(TP+FN) = 34/(34+1) = 97.1%
Specificity = TN/(TN+FP) = 48/(48+17) = 73.85%

Positive predictive value = TP/(TP+FP) = 34/(34+17)=66.7%
Negative predictive value = TN/(TN+FN) = 48/(48+1)=98%
Accuracy = (TP+TN)/ (TP+TN+FP+FN)=(34+48)/(34+48+17+1)=82%

CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 8 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2016–2020

cardiac CT

		negative	positive
†GS	negative	140	39
	positive	0	13

Sensitivity = TP/(TP+FN) = 13/(13+0) = 100%
Specificity = TN/(TN+FP) = 140/(140+39) = 78.2%

Positive predictive value = TP/(TP+FP) = 13/(13+39)=25%
Negative predictive value = TN/(TN+FN) = 140/(140+0)=100%
Accuracy = (TP+TN)/ (TP+TN+FP+FN)=(13+140)/(13+140+39+0)=79,6%
CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 9 Comparison of volume measurements between patients with and without LAA thrombus according to transesophageal echocardiography (N=292)

	Overall	No LAA thrombus		
(244)	LAA thrombus			
(48)	p-value			
LVESVI, mL/m2	24.8 ± 13.9	24.2 ± 13.04	28.1 ± 17.6	0.089
LVEDVI, mL/m2	54.2 ± 16.9	53.3 ± 14.9	58.9 ± 24.9	0.041
LVEF, %	55.9 ± 8.9	56.2 ± 8.4	54.2 ± 11.4	0.166

Values are presented as mean ± SD
Abbreviations: LAA, left atrial appendage; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index

Table 10 Multivariate analysis of predictors of left atrial appendage thrombus according to transesophageal echocardiography (N=292)

	Odds ratio	95% CI	p-value
HAS-BLED score	1.31	1 – 1.71	0.046
Interventricular septum, cm	3.2	0.95 – 10.6	0.060
Left atrial volume, cm3	1.01	1 – 1.01	0.003

LVEDVI) and lower LV ejection fraction measured by TEE were also predictors of LAA thrombus detection by cardiac CT (Table 4). After adjustment for age, CHA_2DS_2-VASc score, and LV end-systolic dimension, multivariate logistic regression showed that an increase in BMI by 1 kg/m^2 increased the risk of LAA thrombus by 14% (p<0.001). Higher HAS-BLED score and LVESVI were significantly associated with LAA thrombus detection on cardiac CT. An increase in LVESVI by 1 mL/m2 increased the possibility of blood clot formation by 19% (Table 5). Although LA volume was significantly related to the disease, the increase in risk was not notable (odds ratio [OR]=1.014, p<0.001).

The sensitivity and specificity of CT were 97.7% and 77%, respectively (Table 6).

The sensitivity and specificity of the CT was higher in 2016–2020, when the delayed phase was added to the standard protocol, compared to 2012–2015 years. The positive predictive and negative predictive values of CT detection of true thrombus were 66.7% and 98% respectively for first-pass scans, and 25% and 100% for the delayed scans, respectively (Tables 7 and 8).

A higher HAS-BLED score, larger interventricular septum, larger LA volume, and higher LVEDVI were significantly associated with LAA thrombus detection on TEE (p = 0.017, 0.008, <0.001, and 0.041, respectively) (Tables 3 and 9). Multivariate logistic regression model showed that only a higher HAS-BLED score was significantly associated with LAA thrombus detection on TEE (OR=1.31, p=0.046) (Table 10).

Discussion

Cardiac CT can provide important clinical data necessary for the assessment and treatment of arrhythmias by ablation, such as the anatomy and size of vessels carrying blood to the left atrium, atherosclerotic changes and features of the anatomy of the coronary arteries, the presence of a LAA thrombus with high accuracy. In a recent publication by Lazoura et al. [21], a CT scan of the heart performed on 122 patients undergoing surgery for arrhythmias showed a 100% predictive value using a delayed scan and confirmed by TEE, which was approved when we found an arterial phase sensitivity and specificity of 97.1 % and 73.8%, and with the addition of a delayed scan, the data corresponding to 100% and 78.2%. Filling the LAA with contrast takes additional time due to anatomical and physiological features; that is why delayed scanning improves the diagnostic value of the study and reduces the number of false-positive results. In this clinical experience, we found that 1-min delayed phase is appropriate to differentiate thrombus of LAA.

CT sensitivity and negative predictive value are enhanced by a two-phase technique that includes delayed imaging. Cardiac computed tomography, especially when delayed imaging is used, is a viable alternative to TEE for the diagnosis of LA/LAA thrombi/clot, avoiding the inconvenience and hazards of TEE. A non-invasive approach equivalent to TEE for diagnosing intracardiac thrombus with high reliability and precision would have great clinical use. CT is a well-established yet underutilized imaging method for cardiac thrombus. CT is capable of detecting intracardiac thrombus with good diagnostic sensitivity [22, 23 24]. A recent meta-analysis indicated that the high overall accuracy of cardiac CT, relative to TEE, may be utilized to identify LA or LAA thrombus in patients with AF. The researchers included 19 trials with a total of 2955 patients and determined that the weighted mean sensitivity and specificity were 96% (95% CI: 92–100%) and 92% (95% CI: 91–93%), respectively, while the positive and negative predictive values were 41% (95% CI: 37–44%) and 99% (95% CI: 99–100%) [25]. The results of studies presented by Romero et al. showed that biphasic delayed-scan greatly improved the specificity and diagnostic accuracy of imaging to 91% than conventional angiography, which is equal to 41% [25]. This is due to the fact that a pseudo-filling defect, such as flow standstill, may also generate an apparent filling defect on CT scans, simulating a thrombus. Due to the fact that CT detects a cardiac thrombus based on its anatomical appearance, it might be difficult to distinguish between thrombus and flow stagnation.

It is revealed that TEE data as high left atrial volume, LVESV, and LVEDV were independently associated with evidence of thrombus in the LAA in patients with confirmed AF and treating with anticoagulant therapy. Furthermore, the same result was received even BMI and CHA_2DS_2-VASc score correction. LV ejection fraction and patient gender were not significantly associated with the presence of a LAA thrombus, which is associated with a low number of patients with heart failure. Increased LVEDVI remained a significant predictor of LAA thrombus detection on TEE. A previous report showed that increased LA systolic and diastolic volume indexes were independently associated with LAA thrombosis in patients with AF [26]. An increase in the volume of the left atrium is associated with coronary atherosclerosis, which can be the cause of coronary artery disease and ischemic stroke, making it an independent risk factor. [27-28]. An increase in LA volume is often associated with a relapse of AF after radiofrequency ablation [29]. We found that the CHA_2DS_2-VASc score showed a statistically significant association with the detection of LAA thrombosis detected by cardiac CT unlike for TEE.

The association between AF and obesity has been studied in patients with cardiac pathology. Several epidemiological studies have found a strong association between obesity and AF [30]. In our study, an increased BMI was associated with the risk of LAA thrombus.

An increase in LA volume measured by CT and an increase in LVESV and LVEDV were independently associated with the presence of an LAA thrombus. These data suggest that patients who have an increased LA volume, BMI, and end-systolic volume have a high risk for thromboembolism and should therefore be carefully monitored.

Conclusion

Our findings show that cardiac CT has high sensitivity and specificity and cannot only be used to exclude or confirm the presence of LAA thrombus, it can also be exclusively used to determine the presence or absence of thrombus. These results are consistent with previous studies. We propose the use of cardiac CT, which is non-invasive, as an initial step in diagnosis, with TEE only being employed for the confirmation of an LAA thrombus. This can reduce the various complications that occur after TEE, which is a semi-invasive procedure. Moreover, this approach seems economically beneficial for the government and patients.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

References

1. Murtagh B, Smalling RW. Cardioembolic stroke. *Curr Atheroscler Rep.* 2006;8:310-316. https://doi.org/10.1007/s11883-006-0009-9
2. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev.* 2010;6:150-161. https://doi.org/10.2174/157340310791658730
3. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol.* 2003;2:177-188 https://doi.org/10.1016/s1474-4422(03)00324-7
4. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. 2016;47:895-900. https://doi.org/10.1161/STROKEAHA.115.0120044
5. Kong B, Liu Y, Huang H, Jiang H, Huang C. Left atrial appendage closure for thromboembolism prevention in patients with atrial fibrillation: advances and perspectives. *J Thorac Dis.* 2015;7:199-203. https://doi.org/10.3978/j.issn.2072-1439.2015.01.20
6. Syed FF, DeSimone CV, Friedman PA, Asirvatham SJ. Left atrial appendage exclusion for atrial fibrillation. *Cardiol Clin*. 2014;32:601-625. https://doi.org/10.1016/j.ccl.2014.07.006
7. Hart RG, Pearce LA, Miller VT, Anderson DC, Rothrock JF, Albers GW, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovasc Dis.* 2000;10:39-43. https://doi.org/10.1016/0003-4975(95)00887-X
8. Mahajan R, Brooks AG, Sullivan T, Lim HS, Alasady M, Abed HS, et al. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. *Heart*. 2012;98:1120-1126. https://doi.org/10.1136/heartjnl-2012-301799
9. Xu J, Luc JG, Phan K. Atrial fibrillation: review of current treatment strategies. *J Thorac Dis*. 2016;8:E886-E900. https://doi.org/10.21037/jtd.2016.09.13
10. Bond R, Olshansky B, Kirchhof P. Recent advances in rhythm control for atrial fibrillation. *F1000Res.* 2017;6:1796. https://doi.org/10.12688/f1000research.11061.1
11. Brandes A, Crijns HJGM, Rienstra M, Kirchhof P, Grove EL, Pedersen KB, et al. Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure. *Europace*. 2020;22:1149-1161. https://doi.org/10.1093/europace/euaa057
12. Kojodjojo P, O'Neill MD, Lim PB, Malcolm-Lawes L, Whinnett ZI, Salukhe TV, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. *Heart*. 2010;96:1379-1384. https://doi.org/10.1136/hrt.2009.192419
13. Squara F, Bres M, Scarlatti D, Moceri P, Ferrari E. Clinical outcomes after AF cardioversion in patients presenting left atrial sludge in trans-esophageal echocardiography. *J Interv Card Electrophysiol.* 2020;57:149-156. https://doi.org/10.1007/s10840-019-00561-8
14. Melillo E, Palmiero G, Ferro A, Mocavero PE, Monda V, Ascione L. Diagnosis and management of left atrium appendage thrombosis in atrial fibrillation patients undergoing cardioversion. *Medicina. (Kaunas)* 2019;55:E511. https://doi.org/10.3390/medicina55090511
15. Acar J, Cormier B, Grimberg D, Kawthekar G, Iung B, Scheuer B, et al. Diagnosis of left atrial thrombi in mitral stenosis-usefulness of ultrasound techniques compared with other methods. *Eur Heart J*. 1991;12 Suppl B:70-76. https://doi.org/10.1093/eurheartj/12.suppl_B.70
16. Manning WJ, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med.* 1995;123:817-822. https://doi.org/10.7326/0003-4819-123-11-199512010-00001
17. Purza R, Ghosh S, Walker C, Hiebert B, Koley L, Mackenzie GS, et al. Transesophageal echocardiography complications in adult cardiac surgery: a retrospective cohort study. *Ann Thorac Surg.* 2017;103:795-802. https://doi.org/10.1016/j.athoracsur.2016.06.073
18. Hur J, Kim YJ, Lee H-J, et al. Left atrial appendage thrombi in stroke patients: detection with two-phase cardiac CT angiography versus transesophageal echocardiography. *Radiology*. 2009;251:683–690. https://doi.org/10.1148/radiol.2513090794
19. Budoff MJ, Shittu A, Hacioglu Y, et al. Comparison of transesophageal echocardiography versus computed tomography for detection of left atrial appendage filling defect (thrombus) Am J Cardiol. 2014;113:173–177. https://doi.org/10.1016/j.amjcard.2013.09.037
20. 20. Choi BH, Ko SM, Hwang HK, et al. Detection of left atrial thrombus in patients with mitral stenosis and atrial fibrillation: retrospective comparison of two-phase computed tomography, transoesophageal echocardiography and surgical findings. *Eur Radiol.* 2013;23:2944–2953. https://doi.org/10.1007/s00330-013-2944-5
21. Lazoura O, Ismail TF, Pavitt C et al (2015) A low-dose, dual-phase cardiovascular CT protocol to assess left atrial appendage anatomy and exclude thrombus prior to left atrial intervention. *Int J Cardiovasc Imaging*. https://doi.org/10.1007/s10554-015-0776-x
22. Shapiro MD, Neilan TG, Jassal DS, et al. Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr.* 2007;31(6):905-909. https://doi.org/10.1097/rct.0b013e31803c55e3
23. Kim YY, Klein AL, Halliburton SS, et al. Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J.* 2007;154(6):1199-1205. https://doi.org/10.1016/j.ahj.2007.08.004
24. Hur J, Kim YJ, Nam JE, et al. Thrombus in the left atrial appendage in stroke patients: detection with cardiac CT angiography--a preliminary report. *Radiology*. 2008;249(1):81-87. https://doi.org/10.1148/radiol.2491071544
25. Romero J, Husain SA, Kelesidis I, Sanz J, Medina HM, Garcia MJ. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. *Circ Cardiovasc Imaging*. 2013;6(2):185-194. https://doi.org/10.1161/CIRCIMAGING.112.000153
26. Osawa K, Nakanishi R, Ceponiene I, Nezarat N, French WJ, Budoff MJ. Predicting left atrial appendage thrombus from left atrial volume and confirmation by computed tomography with delayed enhancement. *Tex Heart Inst J.* 2020;47:78-85. https://doi.org/10.14503/THIJ-17-6290
27. Facchini E, Degiovanni A, Marino PN. Left atrium function in patients with coronary artery disease. *Curr Opin Cardiol*. 2014;29:423-429. https://doi.org/10.1097/HCO.0000000000000085
28. Xu Y, Zhao L, Zhang L, Han Y, Wang P, Yu S. Left atrial enlargement and the risk of stroke: a meta-analysis of prospective cohort studies. *Front Neurol.* 2020;11:26. https://doi.org/10.3389/fneur.2020.00026

29. Kim YG, Shim J, Oh SK, Park HS, Lee KN, Hwang SH, et al. Different responses of left atrium and left atrial appendage to radiofrequency catheter ablation of atrial fibrillation: A follow up MRI study. *Sci Rep* 2018;8:7871. https://doi.org/10.1038/s41598-018-26212-y
30. Vyas V, Lambiase P. Obesity and atrial fibrillation: epidemiology, pathophysiology and novel therapeutic opportunities. *Arrhythm Electrophysiol Rev.* 2019;8:28-36. https://doi.org/10.15420/aer.2018.76.2