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Left atrial appendage filling defect in exclusive early-phase scanning of dual-phase cardiac computed tomography: an indicator for elevated thromboembolic risk

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Abstract

Background: Dual-phase cardiac computed tomography (CCT) has been applied to detect left atrial appendage (LAA) thrombosis, which is characterized as the presence of left atrial appendage filling defects (LAADF) in both early- and delayed-phase scanning. However, the clinical implication of LAAFD in exclusive early-phase scanning (LAAFD-EEpS) of CCT in patients with atrial fibrillation (AF) is unclear.

Methods: The baseline clinical data and dual-phase CCT findings in 1183 AF patients (62.1 ± 11.6 years, 59.9% male) was collected and analyzed. A further analysis of CCT and transesophageal echocardiography (TEE) data (within 5 days) in a subgroup of 687 patients was performed. LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning of dual-phase CCT.

Results: A total of 133 (11.2%) patients were detected with LAAFD-EEpS. Patients with LAAFD-EEpS had a higher prevalence of ischemic stroke or transient ischemic attack (TIA)

($p < 0.001$) and a higher predefined thromboembolic risk ($p < 0.001$). In multivariate analysis, a history of ischemic stroke or TIA was independently associated with LAAFD-EEpS (odds ratio [OR] 11.412, 95% confidence interval [CI] 6.561–19.851, $p < 0.001$). When spontaneous echo contrast in TEE was used as the reference standard, the sensitivity, specificity, positive predictive value, and negative predictive value of LAAFD-EEpS was 77.0% (95% CI 66.5–87.6%), 89.0% (95% CI 86.5–91.4%), 40.5% (95% CI 31.6–49.5%), 97.5% (96.3–98.8%), respectively.

Conclusions: In AF patients, LAAFD-EEpS is not an uncommon finding in dual-phase CCT scanning, and is associated with elevated thromboembolic risk.

Key words: atrial fibrillation, atrial appendage, thromboembolism, radiology

Introduction

Left atrial appendage (LAA) is the major source of thrombus in patients with non-valvular atrial fibrillation (AF) due to its anatomic feature and circulatory stasis nature [1–3], and transesophageal echocardiography (TEE) has long been regarded as the golden standard for detecting LAA thrombus [4]. However, the procedure is semi-invasive and operator-dependent [5]. Recently, dual-phase cardiac computed tomography (CCT) has been demonstrated to be an alternative modality to detect LAA thrombus in AF patients, with high sensitivity and specificity [6–9]. In dual-phase CCT, the presence of LAA filling defects (LAAFD) in both early- and delayed-phase scanning is regarded as the manifestation of LAA thrombus [8], while the presence of LAAFD in exclusive early-phase scanning (LAAFD-EEpS) was assumed as the consequence of LAA circulatory stasis rather than thrombus [8, 10]. However, the clinical implication of LAAFD-EEpS remains unclear. Therefore, the present study was conducted to evaluate the prevalence of LAAFD-EEpS in dual-phase CCT and its association with thromboembolic risk in AF patients.

Methods

Study population

In the present retrospective single-center study, all in-hospital patients screened were diagnosed with AF in the present institution between September 2017 and June 2021, among

whom, dual-phase CCT data were available in 1,235 patients. The exclusion criteria were: i) history of LAA occlusion or ligation; ii) left atrial (LA)/LAA thrombosis identified in CCT. After the screening process, 1,183 patients were included in the analysis. Under further review of the TEE data of all patients, a subgroup which included 687 patients, in whom both CCT and TEE data (the interval < 5 days) were available (Fig. 1). The study protocol was reviewed and approved by the institutional review board. The study complies with the Declaration of Helsinki.

Demographic and medical data of all patients were collected. Valvular heart disease (VHD) was defined as moderate to severe mitral stenosis or mechanical prosthetic heart valve(s). Anti-platelet agent and anticoagulant intake within 7 days of administration was collected. The thromboembolic risk was predefined as low, moderate, and high according to the presence of VHD and the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years old (doubled), diabetes, stroke/transient ischemic attack [TIA]/thromboembolism [doubled], peripheral vascular disease/old myocardial infarction, age 65–74 years, female sex) (Table 1).

Dual-phase CCT

Prospective electrocardiogram-gated dual-phase CCT was performed using 128-slice spiral scanners (SOMATOM Definition AS 128; SOMATOM Definition Flash, Siemens Medical Solutions). The imaging protocol complied with conventional clinical procedures. Collimation was 128 × 0.625 mm and the gantry rotation time was 330 ms. The tube voltage was 100–120 kV and the tube current 300–350 mA. A bolus of contrast media (50–60 mL) was injected via the antecubital vein with an infusion rate of 5 mL/s. Bolus tracking technique was used to properly time the onset of image acquisition: early-phase scanning started 6 s after the threshold of 100 HU reached in LAA; delayed-phase scanning began 60 s after the end of early-phase scanning. No beta-blocker was used for the regulation of heart rate, because CCT was performed to evaluate the intracardiac structures rather than the coronary arteries. After contrast injection, the imaging was acquired covering the region from the bottom of the aortic arch to the apex of the left ventricle so that the entire LA (including LAA) was scanned. The estimated radiation dose was 4–7 mSv.

TEE

Transesophageal echocardiography was performed after standard clinical preparation with a 5.0-mHZ, 128-element, multiplane probe (Phillips). Imaging acquisition of the LAA was performed by rotating the imaging sector from 0° to 180° to optimize the visualization of the entire LAA.

Image analysis

All of the imaging was independently reviewed by two experienced readers in a blind manner. In cases of disagreement, a consensus was achieved by a joint reading. In CCT, LAAFD was defined as a triangular, oval or irregular shape in LAA with homogeneous attenuation. A thrombus was defined as LAAFD present in both early- and delayed-phase scanning, while LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning (Fig. 2). In TEE, a thrombus was defined as a uniformly consistent, echo-reflective mass that distinguished itself from the surrounding LA or LAA wall. Spontaneous echo contrast (SEC) was characterized by dynamic clouds of echoes curling slowly in a circular or spiral shape within the LAA cavity.

Statistical analysis

Continuous variables were described as the mean ± standard deviation for normally distributed data and median (25% to 75% quartile) for non-normally distributed data. Comparisons between groups were performed with the Student t test (normally distributed data) or the Kruskal–Wallis test (non-normally distributed data). Categorical variables were described as counts (percentage) and compared by chi-square analysis. Binominal logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the presence of LAAFD-EEpS. Variables selected for testing in the multivariate analysis were those with $p < 0.05$ in the univariate model. With SEC in TEE as the reference standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated, including the 95% CI based on a binomial distribution. All tests were two-tailed, and a statistical significance was established at $p < 0.05$. All analyses were performed using SPSS software (version 22.0; SPSS, Inc.).

Results

Baseline characteristics of the study population

A total of 1,183 patients were included in the study. Mean age was 62.1 ± 11.6 years, and 709 (59.9%) were male. LAAFD-EEpS was detected in 133 (11.2%) patients with dual-phase CCT. The number of patients with low, moderate and high thromboembolic risk was 262 (22.1%), 307 (26.0%), 614 (51.1%), respectively. The baseline characteristics of the patients with or without LAAFD-EEpS were shown in Table 2. Patients with LAAFD-EEpS were older ($p < 0.001$), had a higher prevalence of non-paroxysmal AF ($p < 0.001$), chronic heart failure (CHF) ($p < 0.001$), diabetes mellitus ($p = 0.016$), ischemic stroke or TIA ($p < 0.001$), VHD ($p < 0.001$), antiplatelet agent prescription ($p = 0.017$); and had higher CHA_2DS_2-VASc scores ($p < 0.001$). In transthoracic echocardiogram (TTE), patients with LAAFD-EEpS had significantly larger left atrial diameter (LAD) ($p < 0.001$), left ventricular end-diastolic diameter (LVEDD) ($p < 0.001$), and lower left ventricular ejection fraction (LVEF) ($p < 0.001$).

LAAFD-EEpS and thromboembolic risk

The association of LAAFD-EEpS and thromboembolic events is shown in Figure 3A. In patients with LAAFD-EEpS, 47 (35.3%), 23 (17.3%), 4 (3.0%) had a history of ischemic stroke, TIA, and peripheral embolism, respectively, while in patients without LAAFD-EEP, the number was 86 (8.2%), 14 (1.3%), and 2 (0.2%), respectively (overall $p < 0.001$). In addition, the percentage of patients who were at high, moderate, low risk of thromboembolic events in LAAFD-EEpS group was 93.6%, 5.6%, 0.8%, respectively, while that in patients without LAA LAAFD-EEpS was 47.0%, 28.3%, 24.7%, respectively (overall $p < 0.001$) (Fig. 3B).

Risk factors for LAAFD-EEpS

In multivariate analysis, older age (OR 1.048; 95% CI 1.020–1.076; $p = 0.001$), non-paroxysmal AF (OR 7.657; 95% CI 3.635–16.125; $p < 0.001$), a history of CHF (OR 2.140; 95% CI 1.123–4.081; $p < 0.021$), VHD (OR 3.435; 95% CI 1.446–8.160; $p = 0.005$), ischemic stroke or TIA (OR 11.412; 95% CI 6.561–19.851; $p < 0.001$), antiplatelet agent prescription (OR 2.416; 95% CI 1.232–4.737; $p = 0.010$), larger LAD (OR 1.099; 95% CI 1.059–1.141; p

< 0.001) and lower LVEF (OR 0.949; 95% CI 0.921–0.978; p = 0.001) were independent predictors of the presence of LAAFD-EEpS (Table 3). After adjustment for confounding factors, a history of ischemic stroke or TIA increased more than tenfold risk for the presence of LAAFD-EEpS.

LAAFD-EEpS in CCT and SEC in TEE

A total of 687 patients with available CCT and TEE data (the interval < 5 days) were analyzed, in whom 319 (46.4%) were at high thromboembolic risk, while 368 (53.6%) were at low to moderate thromboembolic risk. The median interval of CCT and TEE were 1.7 (0.7–3.0) days. In TEE, none of the patients were detected with LAA thrombus, and 61 (8.9%) patients were detected with SEC. In CCT scanning, 116 (16.9%) patients were identified with LAAFD-EEpS. Figure 4 shows the image of CCT and TEE of a patient with both LAAFD-EEpS and SEC.

The concordance between LAAFD-EEpS and SEC were moderate, with the overall kappa value of 0.572. When SEC in TEE was used as the reference standard, the sensitivity, specificity, PPV, and NPV of LAAFD-EEpS was 90.2% (95% CI 82.7–97.6%), 90.3% (95% CI 87.9–92.6%), 47.4% (95% CI 38.3–56.5%), 98.9% (98.1–99.8%), respectively. In patients with high thromboembolic risk, the values were 87.9% (76.7–99.0%), 89.8% (86.4–93.4%), 50.0% (37.1–62.9%), 98.5% (97.0–100.0%), respectively; while in patients with low to moderate thromboembolic risk, the values were 92.9% (83.3–100.0%), 90.6% (87.5–93.7%), 44.8% (32.0–57.6%), 99.4% (98.5–100.0%), respectively (Table 4).

Discussion

The major findings of the present study are: i) LAAFD-EEpS occurs in 11.2% of AF patients; ii) the predefined thromboembolic risk is remarkably elevated in patients with LAAFD-EEpS; iii) patients with a history of ischemic stroke or TIA are tenfold more likely to be detected with LAAFD-EEpS; iv) LAAFD-EEpS has a high sensitivity and specificity to predict SEC in TEE. According to available research, this study is the first report focusing on the clinical relevance of LAAFD-EEpS in dual-phase CCT.

The findings in the present study underline the clinical relevance of LAAFD-EEpS.

Firstly, it was found that the presence of LAAFD-EEpS was significantly associated with the history of ischemic stroke/TIA as well as the predefined thromboembolic risk. Secondly, LAAFD-EEpS had a high sensitivity and specificity to predict the presence of SEC in TEE which was indicative of LAA circulatory stasis and even erythrocytes aggregation [11, 12]. Thirdly, in multivariate analysis, non-paroxysmal AF, CHF, VHD, LAD, LVEF were all independent predictors for LAAFD-EEpS other than ischemic stroke/TIA history were found. It was believed that all of these predictors predispose LA/LAA to a circulatory stasis status by their subsequent hemodynamic effect of elevated LA pressure. Therefore, LAAFD-EEpS may serve as a strong clue of LAA circulatory stasis and should be emphasized in clinical practice. Notably, in the present study, there were 3.8% of patients with low thromboembolic risk who were detected with LAAFD-EEpS. Although the evidence of LAA circulatory stasis is not an established indication for anticoagulation according to the current AF management guidelines [13], it deserves further investigation whether anticoagulation could benefit the patients with low CHA_2DS_2-VASc score but LAAFD-EEpS in CCT.

Cardiac computed tomography has been shown to be an alternative method to detect the presence of LAA thrombus in numerous studies [14–16], with various parameters proposed to improve the diagnostic accuracy [17–19]. Recent studies with dual-phase CCT demonstrated that LAAFD in early-phase scanning was of limited value for identification of LAA thrombus, whereas LAAFD in delayed-phase scanning could largely improve the diagnostic accuracy [6, 9]. According to a meta-analysis including 2,540 patients, the pooled sensitivity and specificity could be as high as 99.1% and 98.9%, respectively, when using delayed-phase scanning [6]. In previous studies, few data on the accurate prevalence of LAAFD-EEpS in AF patients was reported. In the present study, CCT imaging was screened in 1,183 in-hospital AF patients and it was found that LAAFD-EEpS could be identified in 11.2% of the patients, which was correlated with a higher thromboembolic risk. Therefore, it was believed herein, that the value of early-phase scanning has been underestimated over the past decade, and that dual-phase CCT could be an ideal modality not only for detecting LAA thrombus, but also for reflecting the presence of LAA circulatory stasis.

Spontaneous echo contrast in TEE has been demonstrated to be associated with increased

thromboembolic risk in both AF and normal sinus rhythm patients [11, 12]. Previous studies assessed the relationship between LAAFD-EEpS in CCT and SEC in TEE. Kim et al. [10] prospectively performed CCT and TEE in 314 patients with suspected embolic stroke and found that if using LAAFD-EEpS to predict the presence of SEC, the sensitivity, specificity, PPV and NPV were 84.6%, 99.1%, 97.8%, 92.9%, respectively. The PPV in the present study is remarkably lower, which may be due to the different study population. Previous studies showed that the mechanism of SEC is a rouleau formation of erythrocytes [11, 12, 20]. Although this condition is closely correlated with circulatory stasis, it is a more advanced stage towards the final stage of clot formation. Theoretically, in patients with LAA circulatory stasis but no obvious erythrocyte aggregation, the LAAFD-EEpS can be observed but no SEC, which leads to false-positive cases. This could explain the lower specificity and PPV of LAAFD-EEpS to predict SEC.

Limitations of the study

The main limitation of the present study is that it is retrospective nature, thus some quantitative parameters such as grade of SEC, blood velocity in LAA, Hounsfield unit values of LAA are not available. However, the clinical data were prospectively recorded in the medical system. In addition, the percentage of anticoagulant use in the study is relatively low, which could possibly explain why anticoagulant use is not associated with LAAFD-EEpS. Finally, the present study employs dual-phase CCT for detection of LAA circulatory stasis, which may potentially increase the radiation exposure to patients.

Conclusions

In conclusion, LAAFD-EEpS is not an uncommon finding in AF patients, which is associated with a history of thromboembolic events and elevated thromboembolic risk. Furthermore, LAAFD-EEpS has a high sensitivity and specificity to predict SEC in TEE. These observations underline the role of early-phase scanning in CCT. The prognostic value of LAAFD-EEpS is to be investigated in future research.

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Conflict of interest: None declared

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Table 1. Predefined thromboembolic risk.

Thromboembolic risk	**VHD**	**CHA_2SD_2-VASc score**	
		Male	**Female**
Low	No	0	0 - 1
Moderate	No	1	2
High	Yes	NA	NA
	No	≥ 2	≥ 3

VHD — valvular heart disease; NA — not applicable

Table 2. Baseline characteristics of the study population.

Variables	**LAAFD-EEpS**		**Total (n = 1,183)**	**P value**
	Absent (n = 1,050)	**Present (n = 133)**		
Demographic characteristics				

Age [years]	**61.5 ± 11.6**	**66.9 ± 10.1**	**62.1 ± 11.6**	**< 0.001**
Male sex	629 (60.0%)	80 (60.2%)	709 (59.9%)	0.957
Body mass index [kg/m^2]	24.3 ± 3.4	24.2 ± 3.6	24.3 ± 3.4	0.696
Clinical characteristics				
Non-paroxysmal AF	**389 (37.0%)**	**122 (91.7%)**	**511 (43.2%)**	**< 0.001**
Hypertension	588 (56.0%)	86 (64.7%)	674 (57.0%)	0.057
Diabetes mellitus	**159 (15.1%)**	**31 (23.3%)**	**190 (16.1%)**	**0.016**
Chronic heart failure	**55 (5.2%)**	**41 (30.8%)**	**96 (8.1%)**	**< 0.001**
Coronary artery disease	160 (15.2%)	28 (21.1%)	188 (15.9%)	0.084
Ischemic stroke or TIA	**100 (9.5%)**	**60 (45.1%)**	**160 (13.5%)**	**< 0.001**
Valvular heart disease	**35 (3.3%)**	**20 (15.0%)**	**55 (4.6%)**	**< 0.001**
CHA_2DS_2-VASc score	**2 (1, 3)**	**3 (2, 5)**	**2 (1, 3)**	**< 0.001**
Antithrombotic therapy:				
Antiplatelet	**109 (10.4%)**	**23 (17.3%)**	**132 (11.2%)**	**0.017**
Anticoagulant	75 (7.1%)	13 (9.8%)	88 (7.4%)	0.276
Transthoracic echocardiography:				
LAD [mm]	**38.0 ± 7.1**	**46.9 ± 9.1**	**39.0 ± 7.8**	**< 0.001**
LVEDD [mm]	**46.5 ± 5.5**	**48.8 ± 8.1**	**46.8 ± 5.9**	**< 0.001**
LVEF [%]	**62.9 ± 7.8**	**56.2 ± 11.1**	**62.2 ± 8.5**	**< 0.001**

AF — atrial fibrillation; LAD — left atrial diameter; LAAFD-EEpS — left atrial appendage filling defects in exclusive early-phase scanning; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack

Table 3. Univariate and multivariate analysis of left atrial appendage filling defects in exclusive early-phase scanning (LAAFD-EEpS).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	**1.046 (1.028–1.064)**	**< 0.001**	**1.048 (1.020–1.076)**	**0.001**
Male sex	0.990 (0.685–1.431)	0.957		
Body mass index	0.989 (0.937–1.044)	0.696		
Non-paroxysmal AF	**18.846 (10.041–35.371)**	**< 0.001**	**7.657 (3.635–16.125)**	**< 0.001**
Hypertension	1.438 (0.987–2.094)	0.058		
Diabetes mellitus	**1.703 (1.101–2.634)**	**0.017**	1.433 (0.788–2.605)	0.239
Chronic heart failure	**8.062 (5.103–12.737)**	**< 0.001**	**2.140 (1.123–4.081)**	**0.021**
Coronary artery disease	1.483 (0.946–2.325)	0.086		
Ischemic stroke or TIA	**7.808 (5.240–11.635)**	**< 0.001**	**11.412 (6.561–19.851)**	**< 0.001**
Valvular heart disease	**5.133 (2.866–9.193)**	**< 0.001**	**3.435 (1.446–8.160)**	**0.005**
Antiplatelet	**1.805 (1.105–2.950)**	**0.018**	**2.416 (1.232–4.737)**	**0.010**
Anticoagulant	1.408 (0.759–2.614)	0.278		
LAD	**1.145 (1.114–1.178)**	**< 0.001**	**1.099 (1.059–1.141)**	**< 0.001**
LVEDD	**1.059 (1.030–1.089)**	**< 0.001**	0.974 (0.932–1.018)	0.240
LVEF	**0.931 (0.914–0.948)**	**< 0.001**	**0.949 (0.921–0.978)**	**0.001**

AF — atrial fibrillation; CI — confidence interval; LAD — left atrial diameter; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; OR — odds ratio; TIA — transient ischemic attack

Table 4. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of left atrial appendage filling defects in exclusive early-phase scanning.

Variables	High risk (n = 319)	Low/moderate risk (n = 368)	Total (n = 687)
Sensitivity (95% CI)	87.9% (99.0–76.7)	92.9% (83.3–100.0)	90.2% (82.7–97.6)
Specificity (95% CI)	89.9% (86.4–93.4)	90.6% (87.5–93.7)	90.3% (87.9–92.6)
PPV (95% CI)	50.0% (37.1–62.9)	44.8% (32.0–57.6)	47.4% (38.3–56.5)
NPV (95% CI)	98.5% (97.0–100.0)	99.4% (98.5–100.0)	98.9% (98.1–99.8)

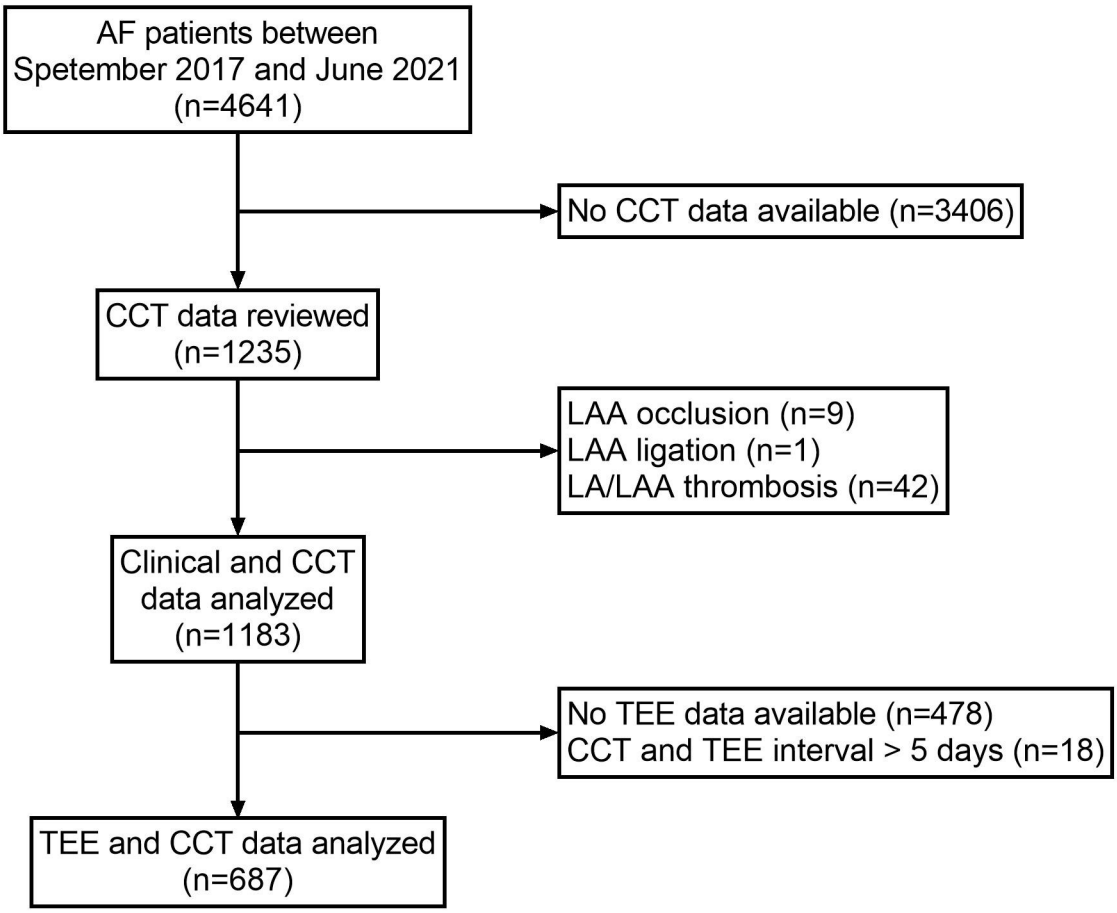
CI — confidence interval

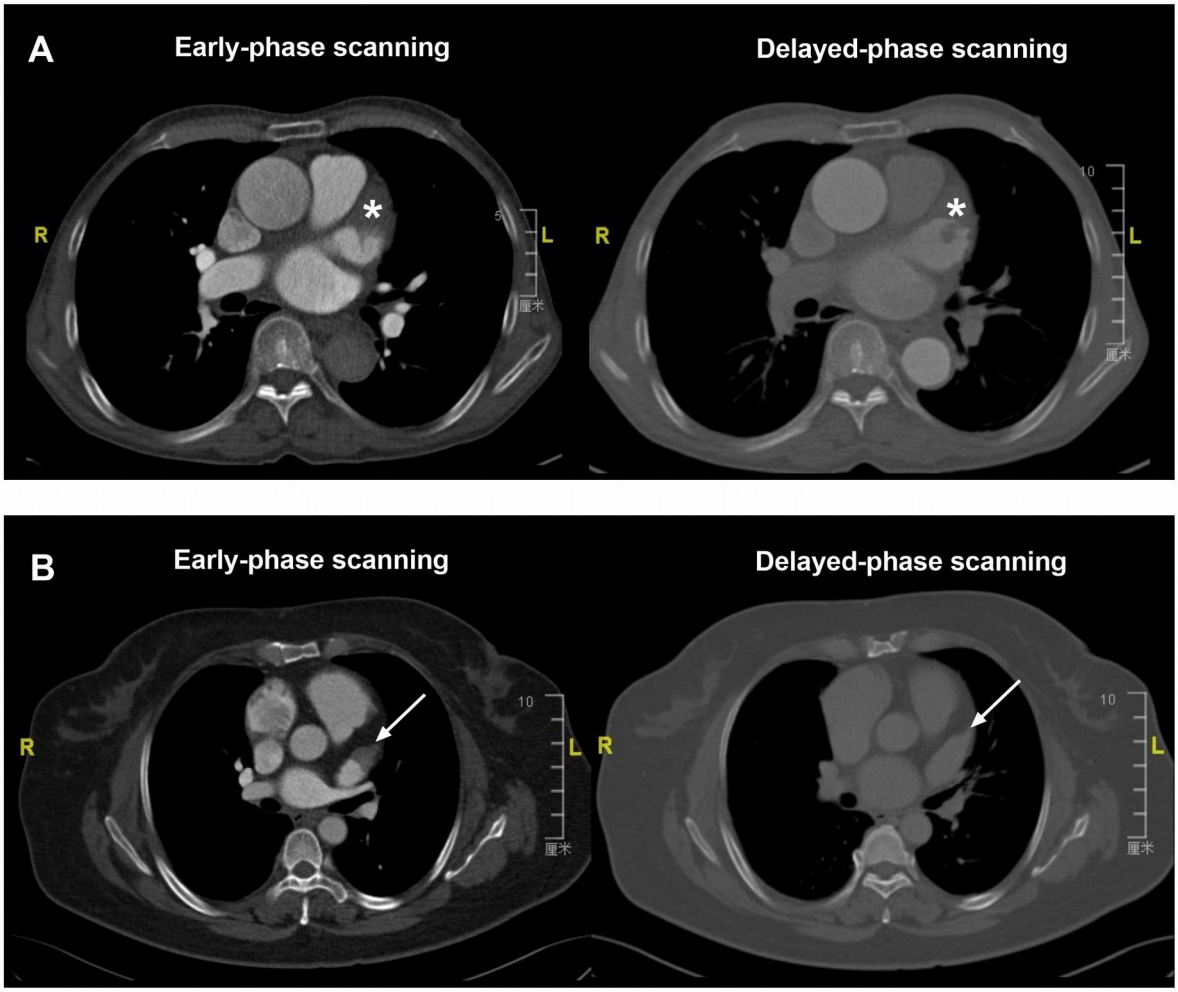
Figure 1. Flow chart of the study population; AF — atrial fibrillation; CCT — cardiac computed tomography; LA — left atrium; LAA — left atrial appendage; TEE — transesophageal echocardiography.

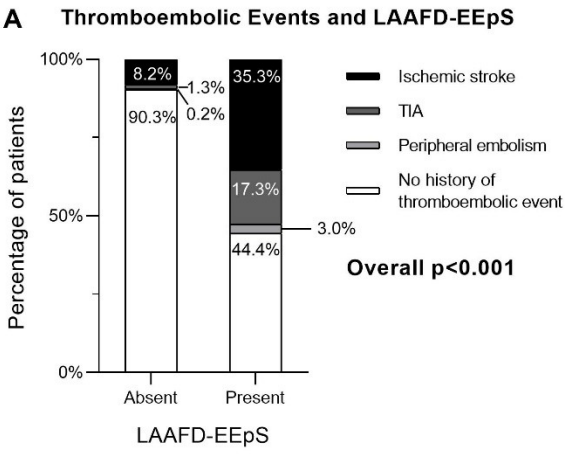
Figure 2. The definition of thrombus and left atrial appendage filling defects in exclusive early-phase scanning (LAAFD-EEpS) in dual-phase CCT; **A.** Left atrial appendage (LAA) thrombus was defined as LAAFD present in both early- and delayed-phase scanning (asterisk); **B.** LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning (arrow).

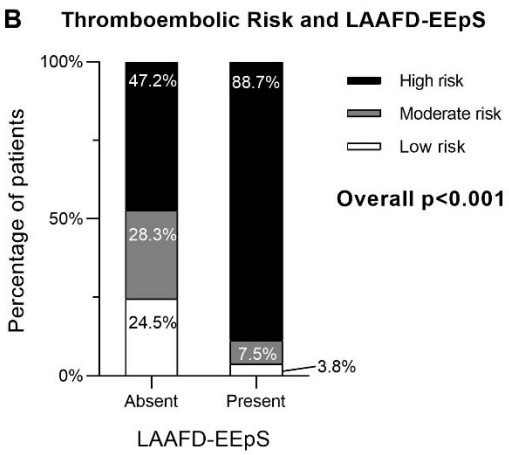
Figure 3. Association between left atrial appendage filling defects in exclusive early-phase scanning (LAAFD-EEpS) and thromboembolic risk; **A.** Percentage of patients who had a history of ischemic stroke, transient ischemic attack (TIA), peripheral embolism, and no history of thromboembolic events in patients with or without LAAFD-EEpS; **B.** Percentage of patients who were at high, moderate, and low risk of thromboembolic events in patients with or without LAAFD-EEpS.

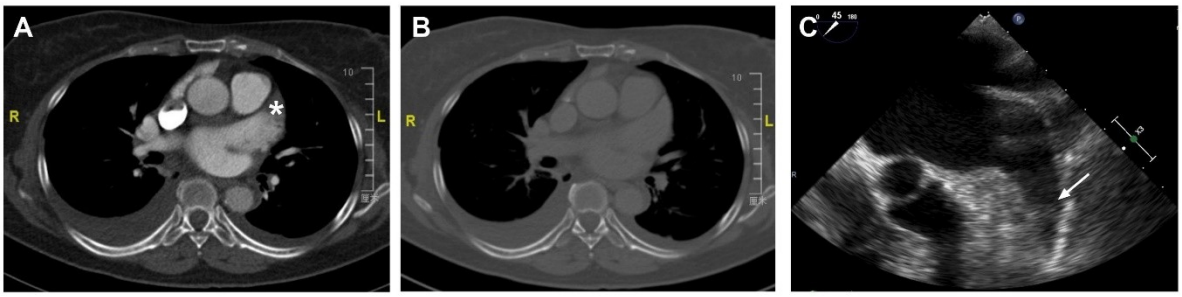
Figure 4. The image of CCT and TEE of a patient. A, Early-phase scanning of CCT shows LAAFD (asterisk). B, Delayed-phase scanning of CCT shows normal filling in LAA. C, TEE shows SEC in LAA (arrow).


AF patients between Spetember 2017 and June 2021 (n=4641)
No CCT data available (n=3406)
CCT data reviewed (n=1235)
LAA occlusion (n=9)
LAA ligation (n=1)
LA/LAA thrombosis (n=42)
Clinical and CCT data analyzed (n=1183)
No TEE data available (n=478)
CCT and TEE interval > 5 days (n=18)
TEE and CCT data analyzed (n=687)


A
Early-phase scanning
Delayed-phase scanning
R
L
B
Early-phase scanning
Delayed-phase scanning
R
L


A
Thromboembolic Events and LAAFD-EEpS
Percentage of patients
100%
50%
0%
8.2%
1.3%
90.3%
0.2%
35.3%
17.3%
3.0%
44.4%
Absent
Present
LAAFD-EEpS
Ischemic stroke
TIA
Peripheral embolism
No history of thromboembolic event
Overall p<0.001


B
Thromboembolic Risk and LAAFD-EEpS
Percentage of patients
100%
50%
0%
47.2%
28.3%
24.5%
88.7%
7.5%
3.8%
Absent
Present
LAAFD-EEpS
High risk
Moderate risk
Low risk
Overall p<0.001


A
R
L
B
R
L
C