Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Clinical Implications of CT-detected Hypoattenuation Thickening on Left Atrial Appendage Occlusion Devices

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Conflicts of interest are listed at the end of this article.

See also the editorial by Choe in this issue.

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Background: At follow-up CT after left atrial appendage occlusion (LAAO), hypoattenuation thickening (HAT) on the atrial aspect of the device is a common finding but the clinical implications require further study.

Purpose: To assess the association of HAT grade at follow-up CT with clinical characteristics and outcomes in patients who underwent LAAO.

Materials and Methods: This prospective study included consecutive participants with atrial fibrillation and who were at high risk for stroke (CHA_2DS_2-VASc score ≥4) who underwent LAAO and were administered pacifier or nonpacifier devices at two French medical centers between January 2012 and November 2020. Postprocedure CT images were evaluated by two radiologists in consensus and device-specific interpretation algorithms were applied to classify HAT as low grade (low suspicion of thrombosis) or high grade (high suspicion of thrombosis). The association between HAT grade and clinical characteristics was assessed using multinomial logistic regression, and variables associated with risk of stroke were assessed using a Cox proportional hazard model.

Results: This study included 412 participants (mean age, 76 years ± 8 [SD]; 284 male participants) who underwent follow-up CT at a mean of 4.2 months ± 1.7 after LAAO. Low-grade and high-grade HAT were depicted in 98 of 412 (23.8%) and 21 of 412 (5.1%) participants, respectively. High-grade HAT was associated with higher odds of antithrombotic drug discontinuation during follow-up (odds ratio, 9.5; 95% CI: 3.1, 29.1; $P < .001$), whereas low-grade HAT was associated with lower odds of persisting left atrial appendage patency (odds ratio, 0.46; 95% CI: 0.27, 0.79; $P = .005$). During a median follow-up of 17 months (IQR, 11–41 months), stroke occurred in 24 of 412 (5.8%) participants. High-grade HAT was associated with stroke (hazard ratio, 4.6; 95% CI: 1.5, 14.0; $P = .008$) and low-grade HAT ($P = .62$) was not.

Conclusion: Low-grade HAT was a more common finding at CT performed after LAAO CT (24%) than was high-grade HAT (5%), but it was associated with more favorable outcomes than high-grade HAT, which was associated with higher stroke risk.

Supplemental material is available for this article.

Atrial fibrillation is responsible for 15%–20% of all ischemic strokes (1). These events often result from thrombus formation in the left atrial appendage (LAA). This issue is commonly addressed with oral anticoagulation; however, this can lead to a risk of bleeding (2). Another approach to prevent thromboembolic complications in patients with atrial fibrillation is percutaneous LAA occlusion (LAAO) (3–5). This method uses implantable devices of various sizes and shapes to exclude the LAA from blood circulation. Current catheter-based devices for LAAO are based on two different principles: The pacifier principle (Amplatzer Cardiac Plug and Amulet; Abbott Laboratories) is based on a dual-seal technology with a self-expanding lobe connected by an articulated waist to an external disc that seals the ostium. The design is aimed at sealing the body and ostium of the LAA, respectively. The nonpacifier principle (plug device type; ie, Watchman 2.5 and Watchman FLX [Boston Scientific]) is based on a self-expanding device with a single lobe filling the LAA body and obstructing the neck of the LAA. The safety and efficacy of LAAO has been demonstrated and it is currently recommended as a class IIb indication in patients with atrial fibrillation and a contraindication to oral anticoagulation (6). However, a substantial number of patients may develop device-related thrombosis (DRT; ie, thrombus formation on the atrial aspect of the device), potentially leading to thromboembolic events (7).

Although CT has been shown to be sensitive to DRT, diagnosis of DRT remains challenging at CT because prominent device re-endothelialization may show as hypoattenuation thickening (HAT) on the atrial aspect of the device, and this may be confounded with thrombosis (8). Consensus regarding the evaluation and surveillance of DRT at postprocedural imaging is lacking. Standardized CT criteria have been introduced in pacifier devices to help characterize HAT (9). Indeed, patient outcomes

Abbreviations

DRT = device-related thrombosis, HAT = hypoattenuation thickening, LAA = left atrial appendage, LAAO = LAA occlusion

Summary

High-grade hypoattenuation thickening at CT after left atrial appendage occlusion is associated with higher stroke risk during follow-up.

Key Results

- In this prospective study of 412 participants referred for left atrial appendage (LAA) occlusion, low-grade and high-grade hypoattenuation thickening (HAT) were observed at 3–6 months postimplantation CT in 98 (24%) and 21 (5%) participants, respectively.
- High-grade HAT was associated with higher odds of antithrombotic drug discontinuation before CT scans acquired after implantation and higher risk of subsequent stroke (hazard ratio, 4.6; P = .008) during a median follow-up of 17 months (IQR, 11–41).
- Low-grade HAT was associated with lower odds of persisting LAA patency (odds ratio, 0.46; P = .005).

suggest that laminar thickening may reflect a potential healing process (10), and this concept is supported by human and animal histologic data (11–13). In nonpacifier devices, although standardized criteria are lacking, a specific CT-based algorithm was recently proposed for the Watchman FLX device (14).

The prognostic and therapeutic implications of these imaging findings remain largely unknown because of an absence of large prospective cohort studies with systematic CT imaging performed after LAAO. This study aimed to assess the association of HAT grade at follow-up CT with clinical characteristics and outcomes in patients who underwent LAAO.

Materials and Methods

Study Design and Participants

From January 2012 to November 2020, consecutive patients with atrial fibrillation and high stroke risk (CHA_2DS_2-VASc score ≥4) referred for LAAO in two French university hospitals were included in this prospective study. The inclusion criterion was an indication for LAAO according to the current European Society of Cardiology recommendations (6). Exclusion criteria were glomerular filtration rate less than 30 mL/min/1.73 m^2, allergy to iodine-enhanced CT and percutaneous LAAO, and failure to obtain participant consent. History of stroke, embolism, or bleeding and CHA_2DS_2-VASc and HAS-BLED scores were retrieved from the electronic medical records, along with body mass index, comorbidities, age, and sex. At inclusion, participants underwent contrast-enhanced cardiac CT. Percutaneous LAAO was performed within the week following inclusion. Details regarding LAAO procedures are described elsewhere (15,16). In each participant, a cardiac plug (Amplatzer cardiac plug; Abbott Laboratories) was implanted from 2012 to 2014, followed by Amulet (Abbott Laboratories) thereafter. Watchman 2.5 was implanted between 2014 and 2018, followed by Watchman FLX. Follow-up cardiac CT was performed between 3 and 6 months, based on institutional protocols, and imaging findings were related to participant outcomes at subsequent follow-up (Fig 1). The antithrombotic regimen after LAA occlusion was at the discretion of the cardiologist but consisted mostly of single antiplatelet therapy because this strategy was the consensus in our institutions (17). The study was approved by the institutional ethics committee, and all participants provided written informed consent.

CT Imaging Protocol

CT was performed before and after implantation using the same protocols on various CT systems (Somatom Definition and Somatom Force, Siemens Healthineers; Aquilion One, Canon Medical Systems), according to the international expert consensus regarding the use of cardiac CT for preprocedural LAAO. CT protocols consisted of electrocardiography-gated contrast-enhanced image acquisitions at the arterial phase after intravenous injection of an iodine contrast agent (iomeprol, 350 mg of iodine per milliliter; Iomeron, Bracco). Images were reconstructed in the transaxial plane with a section thickness of 0.6–0.75 mm and a section interval of 0.6 or 0.75 mm. No specific algorithm was used to reduce metal artifacts because these were shown to potentially generate false-positive results when diagnosing thrombosis in contact with metal implants (18). Mean dose-length product was 279 mGy · cm ± 129 (SD), and mean volume CT dose index was 19.8 mGy ± 9.1. Detailed CT protocols are in Appendix S1.

Image Analysis

The analysis of cardiac CT images was performed by two cardiac imaging specialists in consensus (H.C. and X.I., with 20 and 10 years of experience in cardiac CT, respectively). Arterial-enhanced CT images were interpreted based on a device type–specific algorithm and the readers were blinded to the history and outcomes of participants. For pacifier devices, the classification was similar to that proposed by Korsholm et al (8), where laminar defects smaller than 1-mm thick covering the atrial aspect were considered a normal finding suggestive of neoendothelialization (11). Defects that were at least 1-mm thick were categorized as low-grade HAT if 1–3-mm thick and regular or high-grade HAT if larger than 3 mm and/or irregular.

For nonpacifier devices, intradevice hypoattenuation inside the nitinol frame of the device and flat sessile hypoattenuation smaller than 1 mm on the external side of the nitinol frame around the screw hub were considered to be normal findings. Sessile defects at least 1 mm and staying below device shoulder level were categorized as low-grade HAT; this finding was considered to be highly suggestive of subfabric thrombosis. In addition, healing and re-endothelialization can also occur on the atrial aspect of the fabric in nonpacifier devices, as previously shown in canines (11). Therefore, flat sessile HAT at least 3 mm in continuity with the left atrium wall was also considered low-grade HAT. Protruding sessile defects extending beyond device shoulder level (>3 mm) and pedunculated defects were categorized as high-grade HAT, suggestive of DRT. Interpretation algorithms for the analysis of HAT in pacifier and nonpacifier devices are illustrated in Figure 2. In addition to HAT, persisting LAA patency was documented, defined on arterial-enhanced images as an LAA attenuation at least 100 HU or at least 25% of that in the left atrium (19). The absence of persisting LAA patency was interpreted as an effective LAA sealing.

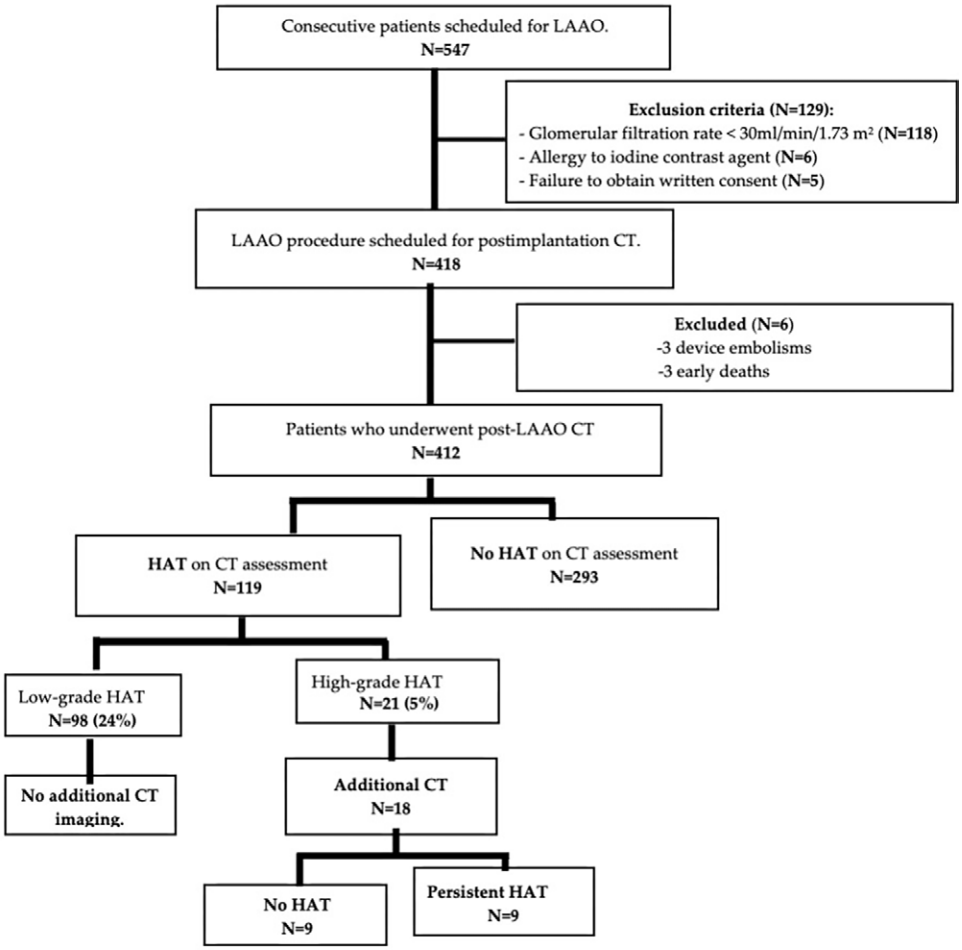


Figure 1: Flowchart of study participant selection and exclusion. HAT = hypoattenuation thickening, LAAO = left atrial appendage occlusion.

Participant Follow-up

Follow-up visits were scheduled at 1, 3, and 12 months and every 6 months afterward, and adverse events were recorded (20). Patients with neurologic signs during follow-up were referred to a stroke center where stroke was diagnosed at MRI. Brain MRI protocols were not standardized across sites, but always included both an axial fluid-attenuated inversion recovery sequence (typical parameters: section thickness, 5 mm; repetition time msec/echo time msec, 9000/104; inversion time, 2500 msec; flip angle, 150°; matrix, 416 × 512) and an axial diffusion-weighted sequence (typical parameters: section thickness, 5 mm; 4600/19 and 5500/119; flip angle, 90°; matrix, 128 × 128). In the event of death in between visits, the cause of death was investigated by a clinical research assistant, with telephone calls made to the family or the referring general practitioner. Apart from stroke, death causes were not specifically analyzed. The primary end point was the occurrence of stroke during follow-up. Death was also analyzed as a secondary end point. The cases of all participants with high-grade HAT suggestive of DRT were discussed with the referring physician to evaluate the risk-to-benefit ratio of upgrading or not upgrading the antithrombotic therapy after implantation (ranging from no treatment to anticoagulant therapy with aspirin) given the participant's clinical profile. Clinical and imaging follow-up were performed according to local protocols.

Statistical Analysis

Continuous variables are presented as means ± SDs when following a normal distribution and as medians with IQRs otherwise. Categorical variables are presented as proportions and percentages. Continuous variables were compared using independent-sample parametric (unpaired Student *t* test) or nonparametric (Mann-Whitney test) tests depending on data normality. Categorical variables were compared using Fisher exact or χ^2 tests, as appropriate. Occurrence of HAT was analyzed with a multinomial logistic regression (21) because the dependent variable HAT is categorical with three outcomes (ie, no HAT, low-grade HAT, and high-grade HAT). The subset of features was selected from a complete model. We kept all features with $P < .2$ in the final model. Determinants of adverse outcomes at follow-up (stroke and death) were analyzed with regression analysis using the Cox proportional hazard model. Survival curves (ie, time to event) for stroke and death were generated according to the HAT grade using the Kaplan-Meier method. Stepwise backward regression based on the Akaike information criterion was performed by following the procedure described by Moore (22)

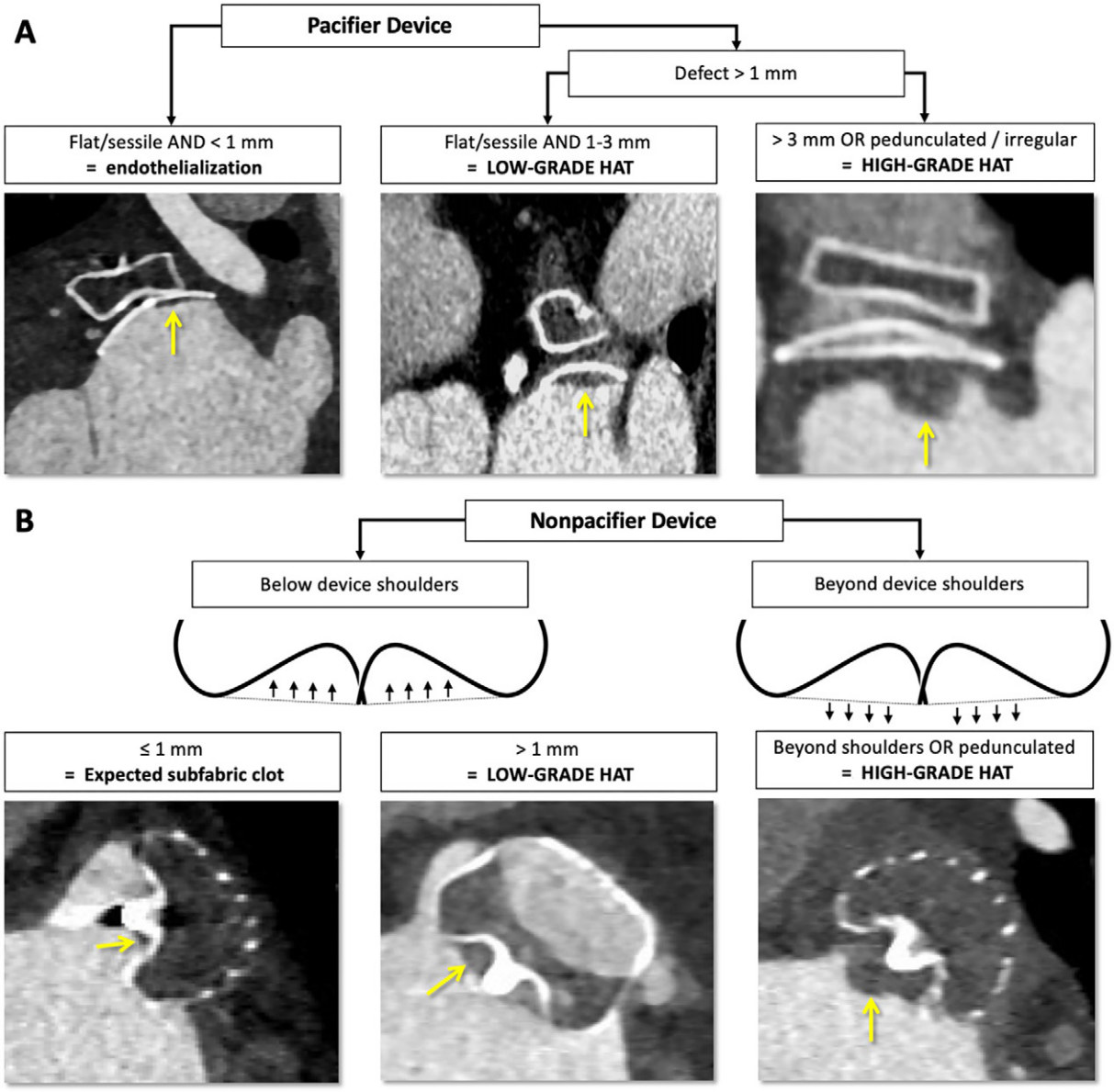


Figure 2: CT interpretation algorithms for the analysis of hypoattenuation thickening (HAT; arrows). **(A)** Interpretation algorithm applicable to pacifier devices. **(B)** Interpretation algorithm applicable to nonpacifier devices.

and Zuur et al (23). Model assumptions were checked. If needed, continuous features were transformed into categorical features as recommended by Moore (22). All odds ratios are provided with 95% CIs. We used the data from Fauchier et al (24) for sample size calculation. They reported a hazard ratio of 4.4 between DRT and stroke, an incidence of DRT after LAAO of 7.2%, and an incidence of stroke after LAAO of 15.4% per year in the DRT group versus 3.2% per year in patients with no DRT (24). With a two-sided significance of .05 and a power of 0.8, and anticipating a maximum dropout rate of 20%, a total of 512 patient-years was required. Because of a lack of convergence, baseline and follow-up treatments were not added as variables within the survival models. Instead, the association between treatment and HAT, stroke, and death was analyzed using the Fisher exact or χ^2 tests. $P <$ .05 was considered to indicate statistical significance. The survival and multinomial analyses were performed by using, respectively, survival and Nnet R packages in R version 4.1.2 (The R Foundation). Statistical analyses were performed by an author (X.P.B., with 10 years of experience in statistical analysis).

Results

Participant Characteristics

A total of 547 consecutive participants underwent LAAO procedures at both centers during the study period. We excluded 129 participants (118 because of renal failure, six because of iodine contrast allergy, and five because of failure to obtain written consent). Therefore, 418 participants were scheduled to undergo CT after undergoing LAAO (Fig 1). Periprocedural complications included three device embolisms (two

Table 1: Study Participant Characteristics

Characteristic	Participant Data (n = 412)
Mean age (y)*	76 ± 8 (49–95)
No. of male participants	284 (69)
No. of female participants	128 (31)
Mean height (cm)	168 ± 9
Mean weight (kg)	76 ± 16
Mean BMI (kg/m^2)	26.7 ± 4.9
Mean GFR (mL/min)	69 ± 25
Diabetes	110 (27)
Hypertension	356 (86)
Dyslipidemia	248 (60)
History of stroke or embolism	161 (39)
Mean LVEF (%)	57 ± 7
Atrial fibrillation or flutter	227 (55)
Mean CHA_2DS_2-VASc score	4.4 ± 1.3
Mean HAS-BLED score	3.1 ± 0.8
History of relevant bleeding	378 (92)
Intracranial	285 (69)
Intracranial amyloid angiopathy	95 (23)
Gastrointestinal	79 (19)
Hematuria	6 (1)
Epistaxis	8 (2)
Implanted devices	
Pacifier device	237 (57)
Mean pacifier device size (mm)	22.4 ± 3.8
Nonpacifier device	175 (43)
Mean nonpacifier device size (mm)	24.9 ± 3.0
Antithrombotic drugs at discharge	
None	0 (0)
Single antiplatelet	366 (88)
Dual antiplatelet	6 (1)
Single anticoagulant	34 (8)
Single antiplatelet plus anticoagulant	6 (1)

Note.—Categorical variables are numbers of participants; except where otherwise indicated, data in parentheses are percentages. Mean data are ±SDs. BMI = body mass index, GFR = glomerular filtration rate, LVEF = left ventricular ejection fraction.

* Data in parentheses are ranges.

Table 2: Participant Characteristics at Follow-up CT

Characteristic	Participant Data (n = 412)
Mean delay between LAAO and follow-up CT (mo)	4.2 ± 1.7
Antithrombotic drugs at follow-up CT	
None	25 (6)
Single antiplatelet	377 (92)
Dual antiplatelet	4 (1)
Single anticoagulant	6 (1)
Single antiplatelet plus anticoagulant	0 (0)
LAA patency	185 (45)
No HAT	293 (71)
Total low-grade HAT	98 (24)
Pacifier-type low-grade HAT	43 (18)
Nonpacifier-type low-grade HAT	55 (31)
Total high-grade HAT	21 (5)
Pacifier-type high-grade HAT	10 (4.1)
Nonpacifier-type high-grade HAT	11 (6.3)

Note.—Categorical variables are numbers of participants; data in parentheses are percentages. Mean data are ±SDs. HAT = hypoattenuation thickening, LAA = left atrial appendage, LAAO = LAA occlusion.

requiring surgery and one percutaneous recapture), seven pericardial effusions (four requiring pericardiocentesis), and three late deaths, all related to postprocedural open chest surgery (two embolisms and one pericardiocentesis). Our study cohort was composed of 412 participants (mean age, 76 years ± 8; 284 male participants). Participant baseline and periprocedural characteristics are shown in Table 1. Atrial fibrillation or flutter manifested in 227 of 412 participants (55.1%). A history of stroke or embolism was present in 161 of 412 participants (39.1%). A history of bleeding was present in 378 of 412 (91.7%). The mean CHA_2DS_2-VASc score was 4.4 ± 1.3 and the mean HAS-BLED score was 3.1 ± 0.8. LAAO procedures were performed using pacifier devices in 57% (235 of 412) and nonpacifier devices in 43% (177 of 412) of participants. All participants were discharged under antithrombotic drug therapy, which consisted of single antiplatelet therapy in the vast majority (88%). The other therapies after implantation are detailed in Table 1.

Participant characteristics at the time of follow-up CT are shown in Table 2. The mean interval between the LAAO procedure and follow-up CT was 4.2 months ± 1.7. In a subset of 6.1% (25 of 412), antithrombotic drugs had to be discontinued during the weeks following the LAAO procedure because of episodes of repeated bleeding.

Image Analysis

At follow-up CT, low-grade and high-grade HAT were depicted in 23.8% (98 of 412) and 5.1% (21 of 412) of participants, respectively. The median hypoattenuation thickness was 3 mm (IQR, 2–5 mm), and the HAT shape was flat or sessile in 82.4% (98 of 119). Examples of low-grade and high-grade HAT are shown in Figure 3. In addition to HAT, follow-up CT showed persisting LAA patency in 185 of 412 participants (44.9%).

Determinants of HAT

Univariable analyses of high-grade HAT correlates are provided in Table S1. Compared with participants without high-grade HAT (ie, those with no HAT or low-grade HAT), those with high-grade HAT were older (mean age with high-grade HAT, 81 years; mean age with low-grade HAT, 76 years; mean age with no HAT, 75 years; P = .003), had higher HAS-BLED scores (mean score with high-grade HAT, 3.6; mean score with low-grade HAT, 3.1; mean score with no HAT, 3.1; P = .004), and were more likely to have interrupted antithrombotic drugs at the time of follow-up CT (33% [seven of 21] with high-grade HAT, 5% [five of 98] with low-grade HAT, and 4.4% [13 of 293] with no HAT; P < .001). Compared with participants with no HAT, those with low-grade

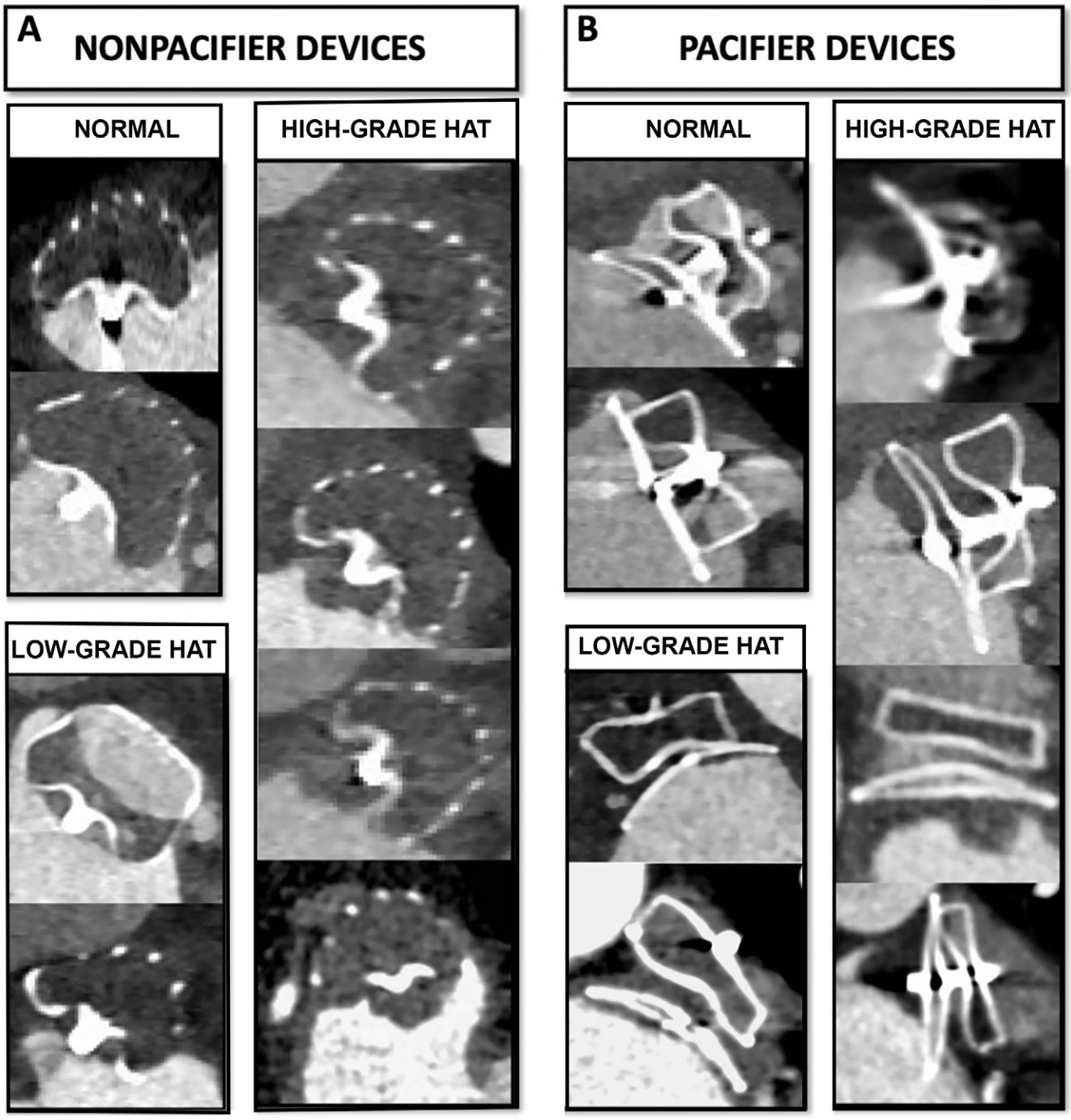


Figure 3: Examples of CT findings after left atrial appendage occlusion (LAAO). Contrast-enhanced CT images acquired in 16 participants (mean age, 77 years ± 8 (SD); 11 men, five women) after undergoing LAAO are shown. Images are reformatted along the device axis. Normal findings, low-grade hypoattenuated thickening (HAT), and high-grade HAT are shown in participants implanted with **(A)** nonpacifier and **(B)** pacifier devices.

HAT were more likely to undergo implantation with nonpacifier devices (P = .001) and with smaller devices (P = .02) and were less likely to show LAA patency at follow-up CT (30% with low-grade HAT [29 of 98], 50.5% with no HAT [148 of 293]; P < .001) or to present with atrial fibrillation or flutter (63% with low-grade HAT [62 of 98], 39.9% with no HAT [117 of 293]; P < .001), as shown in Table 3. The results from multinomial logistic regression analyses to identify the determinants of high-grade and low-grade HAT are shown in Table 3. High-grade HAT was associated with higher odds of antithrombotic drug discontinuation during follow-up (odds ratio, 9.5; 95% CI: 3.1, 29.1; P < .001) and with age (P = .003) but was not related to any other characteristics, including device type (P = .42) or device size (P = .81). Low-grade HAT was positively related to height (P = .001) and nonpacifier device type (P = .003) and inversely related to persisting LAA patency (P = .005) and the presence of atrial fibrillation or flutter (P = .003).

Table 3: Determinants of High-Grade and Low-Grade HAT

	Low-Grade HAT		High-Grade HAT	
Characteristic	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Height	1.06 (1.02, 1.10)	.001*	1.01 (0.97, 1.05)	.59
Weight	0.98 (0.96, 1.00)	.09	1.02 (0.98, 1.05)	.36
Atrial fibrillation or flutter	0.47 (0.28, 0.78)	.003*	1.46 (0.51, 4.15)	.48
Age	0.99 (0.95, 1.02)	.40	1.10 (1.03, 1.17)	.003*
Nonpacifier device	2.20 (1.31, 3.70)	.003*	1.49 (0.56, 3.97)	.42
Device size	0.94 (0.87, 1.01)	.10	1.02 (0.88, 1.18)	.81
LAA patency	0.46 (0.27, 0.79)	.005*	0.65 (0.24, 1.76)	.34
No antithrombotic drug at follow-up CT	0.87 (0.28, 2.73)	.81	9.47 (3.08, 29.14)	<.001*

Note.—Odds ratio for determinants of high-grade and low-grade hypoattenuation thickening (HAT) from the generalized logistic model. Data in parentheses are 95% CIs. LAA = left atrial appendage.

* Indicates statistical significance.

Table 4: Antithrombotic Therapy Used for the 21 Participants with High-Grade HAT

Therapeutic Option	Post-LAAO Procedure	At Follow-up CT	After HAT Diagnosis
No antithrombotic drug	0 (0)	7 (33)	3 (13)
Single antiplatelet	16 (76)	13 (62)	8 (38)
Dual antiplatelet	0 (0)	0 (0)	1 (5)
Single anticoagulant	5 (24)*	1 (5)†	8 (38)‡
Single antiplatelet with anticoagulant	0 (0)	0 (0)	1 (5)

Note.—Data are numbers of participants, with percentages in parentheses. Participants treated with single antiplatelet received aspirin; those treated with dual antiplatelet received aspirin and clopidogrel; those treated with a single anticoagulant received dabigatran, coumadin, or apixaban; those treated with single antiplatelet with anticoagulant received coumadin and aspirin. HAT = hypoattenuation thickening, LAAO = left atrial appendage occlusion.

* One participant was treated with dabigatran, one with apixaban, and three with coumadin.

† The participant was treated with dabigatran.

‡ One participant was treated with coumadin and seven with apixaban.

Table 5: Hazard Ratios for the Incidence of Stroke and Death Among the 412 Participants according to the Grade of HAT

Parameter	Hazard Ratio	*P* Value
Predictors of stroke		
Low-grade HAT (*n* = 98)	0.75 (0.25, 2.28)	.62
High-grade HAT (*n* = 21)	4.57 (1.49, 13.97)	.008*
Nonpacifier device (*n* = 175)	0.62 (0.24, 1.60)	.33
Body mass index (*n* = 412)	0.90 (0.82, 0.99)	.035*
Diabetes (*n* = 110)	0.13 (0.02, 0.95)	.045*
Predictors of death		
Low-grade HAT (*n* = 98)	1.24 (0.69, 2.30)	.48
High-grade HAT (*n* = 21)	1.28 (0.39, 4.2)	.68
Nonpacifier device (*n* = 175)	1.19 (0.68, 2.1)	.543
Age (*n* = 412)	1.05 (1.01, 1.10)	.008*

Note.—Data in parentheses are 95% CIs. Follow-up duration ranged from 24 to 100 months. Average follow-up duration was 27.2 months (median, 17.8 months) for death and 25.6 months (median, 15.6 months) for stroke. Hazard ratios in low-grade and high-grade HAT were computed using the no-HAT population as reference. Hazard ratio for nonpacifier device were computed using the pacifier device population as reference. HAT = hypoattenuation thickening.

* Indicates statistical significance.

Treatment of Participants with High-Grade HAT

The distribution of treatment regimens in participants with high-grade HAT before and after depiction at CT is shown in Table 4. After high-grade HAT depiction at CT, 38% (eight of 21) were treated with single antiplatelet therapy, 5% (one of 21) with dual antiplatelet therapy, 38% (eight of 21) with single anticoagulant therapy, and 5% (one of 21) with single anticoagulant therapy and aspirin; 14% (three of 21) were not treated. Imaging follow-up after high-grade HAT depiction was available in 86% (18 of 21) participants (three early deaths after the first postimplanation CT). HAT regression was observed in 50% (nine of 18) after a mean of 84 days ± 22 after depiction at CT; the other participants showed residual HAT. None of these participants experienced bleeding episodes during follow-up.

Participant Outcomes

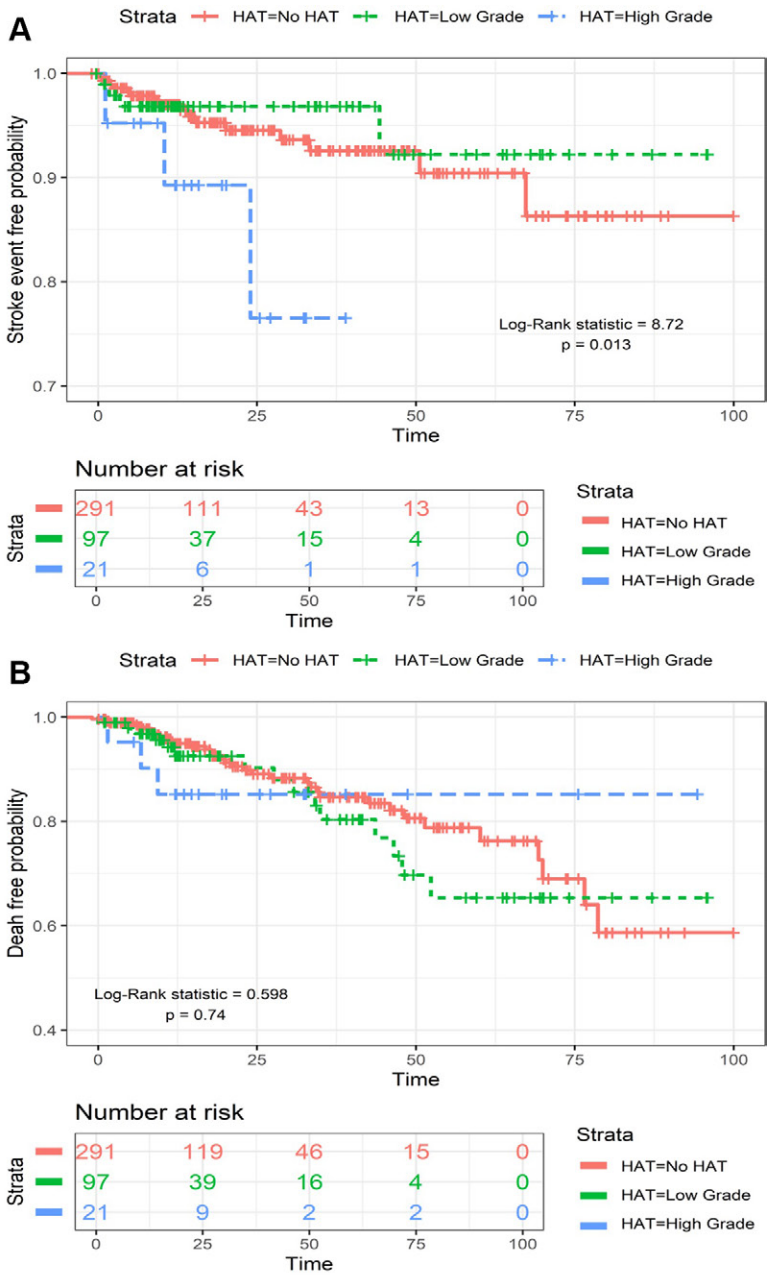
During a median follow-up of 17 months (IQR, 11–41 months), stroke occurred in 5.8% of participants (24 of 412) at a median interval of 10 months (IQR, 3–25 months) after the LAAO procedure. Death occurred in 13.1% (54 of 412) at a median interval of 20 months (IQR, 9–35 months) after the LAAO procedure. Stroke was not related to the use of antithrombotic drugs at baseline ($P > .99$) or during follow-up ($P = .38$). The results from Cox regression analyses are shown

in Table 5. High-grade HAT was found to be associated with the occurrence of stroke (hazard ratio, 4.6; 95% CI: 1.5, 14.0; P = .008), but low-grade HAT was not associated with occurrence of stroke (hazard ratio, 0.94; 95% CI: 0.3, 2.6; P = .90). Stroke occurred in 19% of participants (four of 21) with high-grade HAT versus 4% of participants (four of 98) with low-grade HAT and 5.5% of participants (16 of 293) with no HAT. No stroke was observed among the patients with antithrombotic drug discontinuation during follow-up. Occurrence of stroke and death according to the presence and grade of HAT is available in Table S2. Device type was also not related to stroke risk (nonpacifier hazard ratio, 0.6; 95% CI: 0.2, 1.6; P = .33). High body mass index was associated with a lower risk of stroke (hazard ratio, 0.90; 95% CI: 0.82, 0.99; P = .04); diabetes was also associated with a lower risk of stroke (hazard ratio, 0.13; 95% CI: 0.02, 0.95; P = .04). At survival analysis, death was related only to age (hazard ratio, 1.0; 95% CI: 1.0, 1.1; P = .008) and was not found to be associated with HAT of any grade (low-grade HAT hazard ratio, 1.2 [95% CI: 0.7, 2.3; P = .48]; high-grade HAT hazard ratio, 1.3 [95% CI: 0.4, 4.2; P = .68]) or device type (nonpacifier hazard ratio 1.2; 95% CI: 0.7, 2.1; P = .52). The results of survival analyses stratified by presence of HAT and HAT grades are shown in Figure 4. The clinical relevance of HAT interpretation is in Figure 5.

Discussion

Hypoattenuated thickening (HAT) in the atrial aspect of a left atrial appendage occlusion (LAAO) device is a frequent finding at follow-up CT, with equivocal prognostic clinical significance in the absence of large prospective cohorts with systematic follow-up CT. By following up 412 participants who underwent systematic follow-up CT after LAAO and by using a device-specific algorithm for HAT interpretation, our study detected low-grade HAT in 24% of participants and high-grade HAT in 5%. High-grade HAT was associated with higher odds of discontinuation of antithrombotic drugs during follow-up (P < .001), whereas low-grade HAT was associated with lower odds of persistent left atrial appendage patency (P = .005). Unlike low-grade HAT, high-grade HAT was associated with higher stroke risk during follow-up (hazard ratio, 4.57; 95% CI: 1.5, 14.0; P = .008).

The characteristics of the study cohort and the rates of procedure-related complications and stroke during follow-up are consistent with those in previous studies (25,26). The only specificity of our management protocol was the use of single antiplatelet therapy after LAAO in most participants, which is the current protocol in patients with a high risk of



C

Determinants of adverse outcomes at follow-up			
	Hazard ratio	95% CI	p.value
Predictors of stroke			
HAT low grade (N=98)	0.75	0.25 -2.28	0.616
HAT high grade (N=21)	**4.57**	**1.49 - 13.97**	**0.008**
Watchman device (N=175)	0.62	0.24 - 1.60	0.326
BMI (N=412)	**0.90**	**0.82 - 0.99**	**0.035**
Diabetes (N=110)	**0.13**	**0.02 - 0.95**	**0.045**
Predictors of death			
HAT low grade (N=98)	1.24	0.68 - 2.30	0.484
HAT high grade (N=21)	1.28	0.39 - 4.2	0.683
Watchman device (N=175)	1.19	0.68 - 2.1	0.543
Age (N=412)	**1.05**	**1.01 - 1.10**	**0.008**

Figure 4: Kaplan-Meier curves show **(A)** stroke-free and **(B)** death-free survival according to hypoattenuated thickening (HAT) grade. **(C)** Summary shows statistics from both analyses. BMI = body mass index.

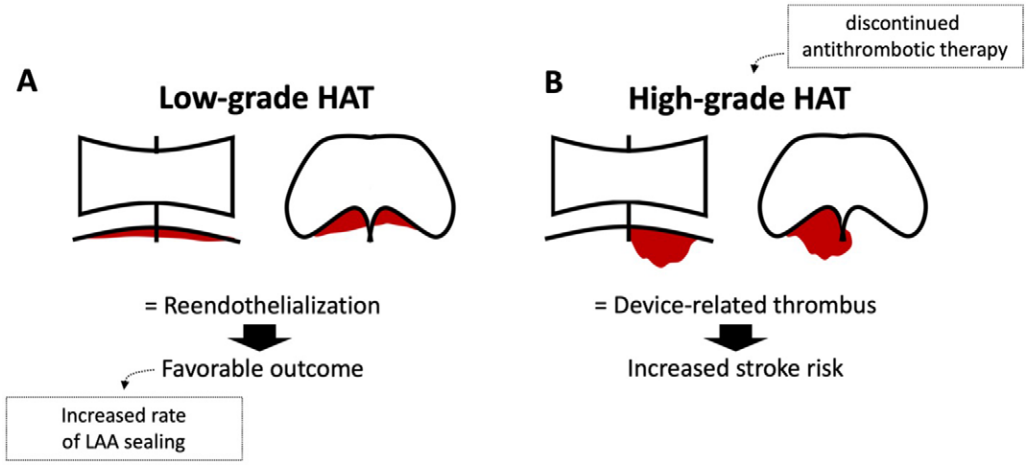


Figure 5: Diagrams show clinical relevance of hypoattenuated thickening (HAT) grades at CT after left atrial appendage (LAA) occlusion for pacifier device (left) and nonpacifier device (right). **(A)** CT features corresponding to low-grade HAT (red) and associated with favorable outcome. **(B)** CT features corresponding to high-grade HAT (red) and associated with adverse outcome.

bleeding in both institutions. One may argue that the high prevalence of thrombosis in our cohort is because of the use of single antiplatelet therapy. This strategy was initially based on a consensus with our referral neurologists and on favorable safety and efficacy data (17,27–29), with DRT rates similar to those reported in previous large LAAO studies (25,30).

Our results demonstrated that high-grade HAT is closely related to discontinuation of antithrombotic therapies during follow-up, which has not been reported in previous studies (13). Ongoing administration of antiplatelet drugs in patients experiencing repeated bleeding episodes while undergoing treatment is a long-standing challenge in clinical management after LAAO. To prevent the recurrence of life-threatening bleeding episodes, all antithrombotic drugs had to be discontinued in 25 (6.1%) participants in our study. Our results showed that this decision increases the risk of developing high-grade HAT. In a recent study by Kramer et al (14), low-grade HAT was found to have different clinical correlates than high-grade HAT, which may suggest a different mechanism. The inverse relationship between low-grade HAT and LAA patency, in agreement with a previous study (10), supports the concept of low-grade HAT as a sign of intradevice thrombosis and/or reendothelialization participating in effective LAA sealing (11). Thus, distinguishing between low-grade and high-grade HAT seems clinically relevant because the former is associated with a favorable risk profile whereas the latter exposes patients to higher risks that should cause the initiation of preventive measures.

The association between high-grade HAT at CT and higher stroke risk at follow-up is one of the main results of our study. This association had been suggested in previous studies (31,32) that had mainly used transesophageal echocardiography to depict DRT. Our study prospectively confirmed the prognostic implications of DRT and demonstrated that CT can help predict noninvasively such adverse outcomes. Future research should clarify how this information from CT may be used to adapt antithrombotic drug therapies and identify the best timing for CT follow-up, considering that delayed thrombus formation may also occur (31).

Our study had several limitations. First, functional characteristics were not included in the analysis of HAT correlates, which could be valuable in elucidating the mechanisms leading to DRT (33,34). Second, a specific analysis of device position was not performed, although device position has been found to have a role in formation of DRT (31). Third, there was a variable delay between the LAAO procedure and follow-up CT and systematic serial CT evaluations were not performed. Fourth, although all participants with high-grade HAT were followed up, those with low-grade HAT were not. This was due to institutional constraints in the two hospitals and may have resulted in the underdetection of late-occurring DRTs (31,32). Future research should clarify the optimal times for follow-up CT. Fifth, HAT diagnosis relied on a consensus between two experienced readers. The interreader agreement in HAT diagnosis and classification should be addressed in future studies. Finally, for practical reasons, brain MRI was only performed if stroke or transient ischemic attack was clinically suspected, and the generalization of our results to silent cerebral events would require further study.

In conclusion, 4 months after left atrial appendage occlusion (LAAO), 24% of participants showed low-grade hypoattenuation thickening (HAT), which was associated with favorable outcomes potentially corresponding to prominent re-endothelialization, effectively sealing the left atrial appendage. However, high-grade HAT, which is highly suggestive of thrombosis, was rare (5%), was more frequently observed in participants in whom antithrombotic therapy was discontinued, and was associated with higher stroke risks. These findings support the introduction of unequivocal standardized CT criteria for HAT grading, with important implications for treatment regimen optimization after implantation. Future research should be conducted to better define the optimal times for follow-up CT after LAAO, and the optimal therapeutic options in patients showing high-grade HAT.

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