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An Overview on Left Atrial Appendage

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Abstract:

The left atrial appendage (LAA) is a small, ear-shaped muscular structure connected to the left atrium of the heart. Although once considered a vestigial remnant, it has gained significant clinical interest due to its role in cardiovascular physiology and pathology. The LAA contributes to atrial reservoir function, secretion of atrial natriuretic peptides, and regulation of left atrial pressure. However, it is also the most common site of thrombus formation in patients with atrial fibrillation, which substantially increases the risk of ischemic stroke. Recent advances in imaging and interventional cardiology have enabled better assessment of LAA morphology and function, as well as the development of percutaneous and surgical occlusion techniques as alternatives to anticoagulation therapy.

Keywords: Left atrial appendage; Atrial fibrillation; Thrombus; Stroke prevention; LAA occlusion; Cardiac anatomy.

Introduction:

The left atrial appendage (LAA) is a muscular extension of the left atrium with a distinctive morphology that varies widely among individuals. It plays an important role in atrial function, acting as a reservoir and contributing to pressure regulation. Recent studies have highlighted its clinical importance beyond a structural cardiac feature **(1).**

In patients with atrial fibrillation (AF), the LAA has been identified as the main site of thrombus formation, responsible for more than 90% of left atrial thrombi in non-valvular AF cases. This makes it a central target for stroke prevention strategies **(2).**

Advances in imaging techniques such as transesophageal echocardiography (TEE), cardiac CT, and MRI have significantly improved the ability to assess LAA morphology and thromboembolic risk. Imaging has become essential in guiding interventional procedures as well as patient selection **(3).**

In recent years, interventional cardiology has provided alternative approaches to anticoagulation, with the development of percutaneous and surgical LAA occlusion devices. These strategies have proven effective for patients who are not suitable candidates for long-term anticoagulation therapy **(4).**

LA: Normal Anatomy and Function

Because LA structural remodeling and AF are closely related, it is recommended that LA size and anatomy be assessed routinely in all AF patients. LA size is typically assessed with standard 2-dimensional (2D) echocardiography. The LA anteroposterior diameter derived from a conventional parasternal long-axis view is used to estimate LA size. However, because asymmetrical remodeling occurs in LA dilation, it is recommended that LA volumes be assessed using a volumetric method, such as the modified Simpson biplane method of discs (Figure 1). With the use of 3-dimensional (3D) imaging modalities, LA volumes can be assessed even more accurately **(5).** Real-time 3D echocardiographic measurements of LA volumes have been validated against computed tomography (CT) and cardiovascular magnetic resonance (CMR), and the technique has improved diagnostic accuracy and reproducibility compared with 2D echocardiography (Figure 1). Normal reference values for 3D LA volume are 15 to 42 ml/m^2 in men and 15 to 39 ml/m^2 in women. Furthermore, assessment of pulmonary vein anatomy is relevant when an ablation procedure is considered in AF patients. It has been demonstrated that pulmonary vein anatomy is highly variable. Variations in the number and location of

the pulmonary veins are associated with outcome in catheter ablation procedures for AF . Typically, CT or CMR is performed before the ablation procedure to assess pulmonary vein anatomy. The 3D reconstructed images provide detailed information on LA and pulmonary vein anatomy that can be used to guide the ablation procedure **(6).**

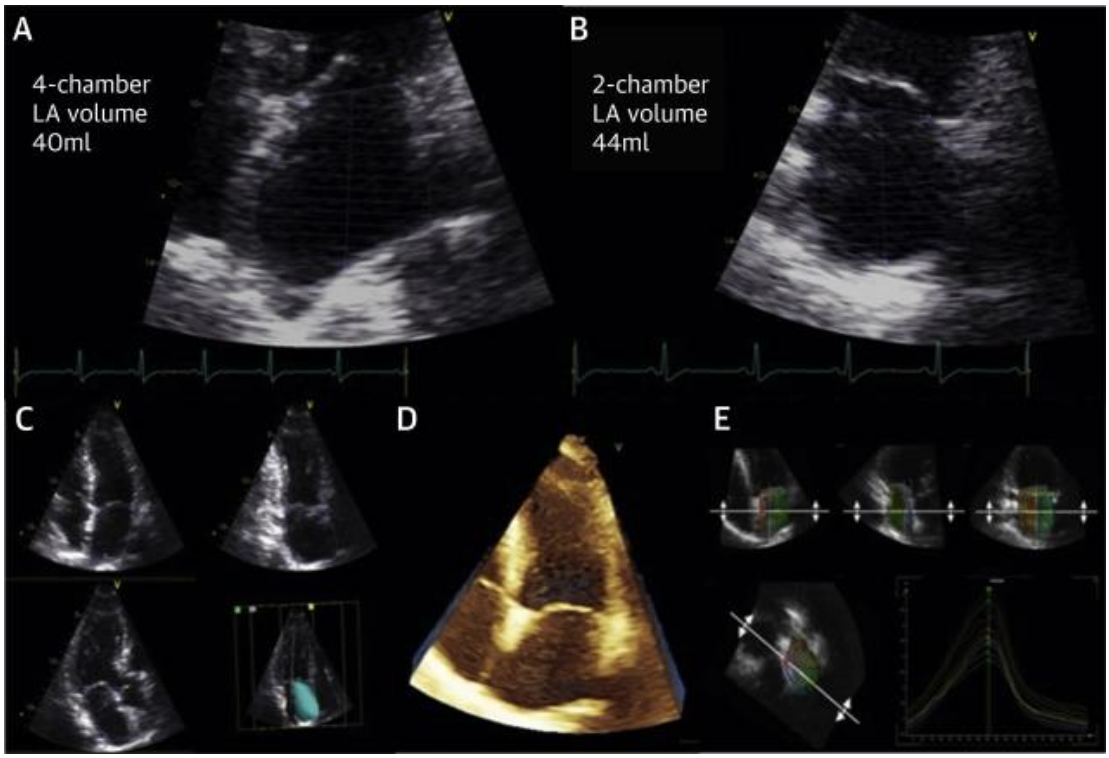


Fig (1): LA Volume Assessment Using 2D and 3D Echocardiography **(7).**

(A and B) The 2-dimensional (2D) echocardiographic measurement of left atrial (LA) volume using the Simpson biplane approach in the apical 4-chamber **(A)** and 2-chamber **(B)** views are shown. The LA appendage is not included in the tracing of the endocardial border. **(C)** Real-time 3-dimensional (3D) echocardiographic measurement of LA volumes is shown. LA volumes may be obtained with improved anatomic alignment, by tracing the blood tissue interface on 3D-guided triplane images in the apical 4-, 2-, and 3-chamber views **(C)**. Live-3D **(D)** and full-volume multibeat reconstructions **(E)** may also be used to measure LA volumes at any phase of the cardiac cycle, providing improved alignment at the geometric center of the left atrium **(7).**

In addition to the anatomic information of the LA, assessment of LA function is important because it contributes 30% of the left ventricular (LV) stroke volume. Impaired LA function has been associated with increased risk of stroke and AF. Normal LA function can be divided into 3 distinct phases. During ventricular systole, the LA serves as a reservoir for blood drained by the pulmonary veins. During early ventricular diastole, the LA is a conduit for the pulmonary venous return. During late systole, the booster pump function of the LA completes the LV filling. Whereas the LA reservoir function is determined by atrial compliance, atrial relaxation, and contractility, as well as LV systolic function and end-systolic volume, the LA conduit function is influenced by LA compliance and LV relaxation and compliance, and the LA booster pump function is influenced by venous return, LV end-diastolic pressures, and systolic reserve. These 3 functions can be assessed with echocardiographic and CMR techniques. How anatomic and functional assessment of the LA permits stratification of patients with AF is discussed in the next sections **(8).**

- **Left Atrial Remodeling: Substrate for Atrial Fibrillation**

Left atrial (LA) remodeling, characterized by LA dilation, myocardial fibrosis, and electromechanical conduction delays, forms a critical substrate for atrial fibrillation (AF). Recent advancements in imaging

techniques have allowed for a more comprehensive understanding of the structural and functional changes in the LA that contribute to the onset and persistence of AF. Among these techniques, three-dimensional imaging is preferred for assessing LA volumes, which play a crucial role in the therapeutic decision-making process for AF patients. Studies have demonstrated that LA volume is a stronger determinant of the success of radiofrequency catheter ablation compared to the type of AF (e.g., paroxysmal vs. persistent) **(9).**

Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging has significantly advanced the understanding of atrial fibrosis, a hallmark of structural LA remodeling in AF. This imaging modality highlights areas of fibrosis as bright white regions within the atrial myocardium by using gadolinium contrast, which accumulates in the extracellular space. A dynamic threshold algorithm further delineates fibrotic regions, classifying fibrosis into stages ranging from stage 1 (<10% fibrosis) to stage 4 (≥30% fibrosis). The extent of LA fibrosis has been shown to affect the efficacy of catheter ablation for AF, with lower fibrosis levels (stages 1 and 2) associated with reduced risk of arrhythmia recurrence. The DECAAF (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation) study found that each 1% increase in fibrosis independently raised the risk of arrhythmia recurrence by 6%, underscoring the importance of pre-ablation fibrosis assessment **(7).**

LA function assessment provides additional insights into the consequences of structural remodeling. Reduced LA reservoir function and increased maximum LA volume are strongly associated with an elevated risk of AF or atrial flutter. Advanced echocardiographic techniques, such as tissue Doppler imaging (TDI) and strain imaging, allow for detailed evaluation of LA function. For instance, reduced LA reservoir strain has been correlated with LA wall fibrosis on CMR. In patients undergoing catheter ablation, preserved LA reservoir function has been predictive of maintaining sinus rhythm and is independently associated with LA reverse remodeling **(10).**

Electrical remodeling, another aspect of LA remodeling, is marked by slow conduction areas, shortened atrial refractoriness, and increased nonuniform anisotropy, all of which contribute to re-entrant circuits and AF. Noninvasive parameters such as the PA-TDI interval (P-wave to peak A′-wave on tissue Doppler imaging) have been shown to reflect electrical and mechanical delays caused by LA fibrosis. Prolonged PA-TDI duration is associated with new-onset AF and higher risks of AF recurrence after catheter ablation **(11).**

Additionally, the role of adipose tissue in LA remodeling has garnered attention. Fatty tissue accumulation in the LA subepicardium is a universal finding; however, in AF patients, this tissue exhibits significant remodeling with increased fibrosis. Studies using computed tomography (CT) have linked greater amounts of posterior LA adipose tissue with a higher likelihood of AF. Each gram increase in this tissue was associated with a 1.32-fold increase in the odds of having AF **(12).**

LAA Anatomy and Function

The LAA is a finger- or stump-like extension of the LA with lobes that may harbor up to 90% of thrombi that occur in patients with AF. In contrast to the smooth-walled LA, the LAA contains pectinate muscles that form a complex network of muscular ridges. The transition between the rough endocardium of the LAA to the smooth-walled LA is demarcated by the ostium of the LAA, well defined posteriorly by the ridge that separates the superior left pulmonary vein. The shape of the LAA is largely variable and can be classified based on the shape and number of lobes (Figure 2) **(13).** Important anatomic relationships of the LAA to take into account when planning transcatheter closure and radiofrequency ablation of this structure include the superior left pulmonary vein, the mitral valve, and the circumflex coronary artery (Figure 3). The LAA also has important mechanical and endocrinological functions: the LAA has contractile properties, and its distensibility is larger than the LA, contributing to LA pressure modulation. In addition, the concentration of atrial natriuretic peptide is largest in the LAA. Through activation of stretch-sensitive receptors and the effects of the atrial natriuretic peptide on heart rate, diuresis, and natriuresis, the LAA helps to modulate the LA pressure **(14).**

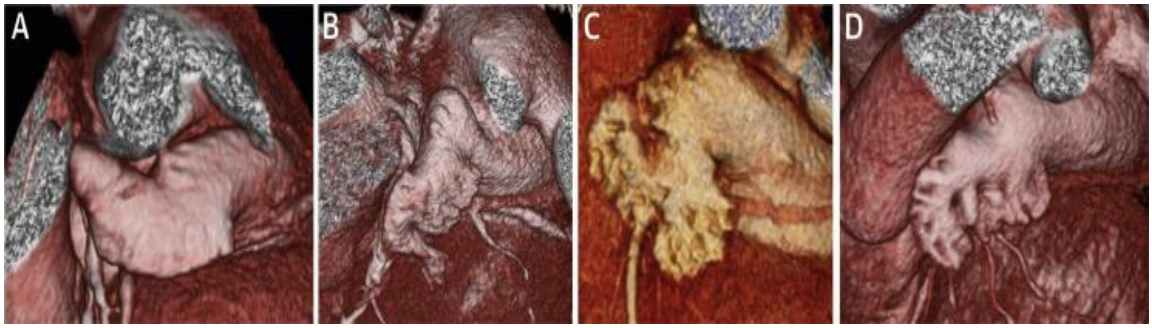


Fig (2): Morphology of the LAA **(7).**

The classification of the left atrial appendage (LAA) morphology is based on the shape of the central and secondary lobes: windsock **(A)** (with 1 central lobe), chicken wing **(B)** (with a central lobe bended), cauliflower **(C)** (when the central lobe is short and with several lobes leading to a distal width larger than the proximal part), and cactus **(D)** (with a central lobe leading to several secondary lobes superior and inferiorly) **(7).**

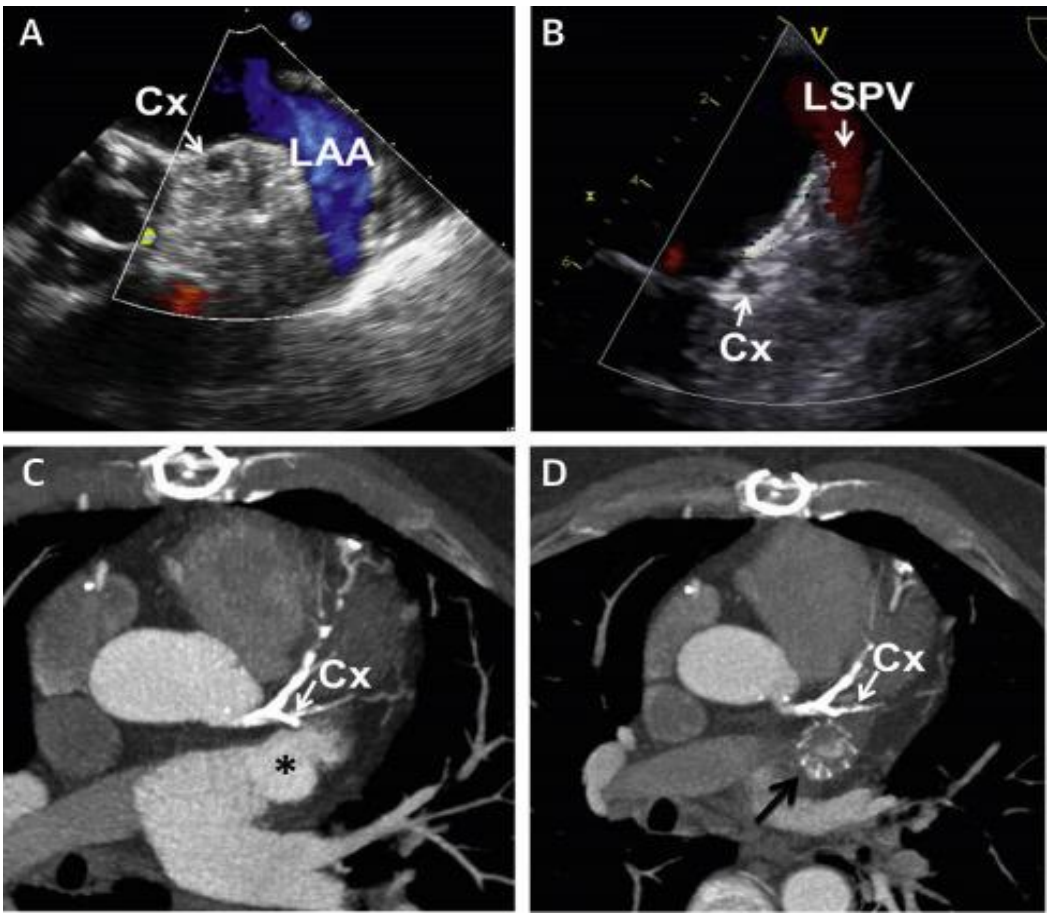


Fig (3): Anatomic Relationships of the LAA to Consider in Transcatheter Closure Procedures **(7).**

Example of a patient receiving an AMULET device closure **(A and B)**. Note the anterior position of the circumflex coronary artery (Cx) relative to the left atrial appendage (LAA) at baseline **(A)**. After insertion of the device, the Cx is patent, and the flow of the left superior pulmonary vein (LSPV) is not compromised **(B)**. In **C and D**, an example of a patient receiving a WATCHMAN device is shown. The anterior spatial

relationship of the Cx and the LAA **(asterisk)** can be analyzed with computed tomography **(C)**. Note the close proximity of the deployed device to the Cx **(black arrow) (D) (7).**

The LAA is also an important source of AF. Of 987 patients undergoing radiofrequency catheter ablation, 27% showed firing from the LAA, whereas in 8.7%, the LAA was the only source of arrhythmia. The BELIEF (Effect of Empirical Left Atrial Appendage Isolation on Long-Term Procedure Outcome in Patients With Longstanding Persistent Atrial Fibrillation Undergoing Catheter Ablation) study showed that the addition of electrical LAA isolation to extensive ablation of the LA resulted in lower rates of AF recurrence at 12-month follow-up, as compared with extensive ablation of the LA alone (44% vs. 72%) **(15).**

Echocardiography is the imaging technique of first choice to evaluate the LAA. Particularly, transesophageal echocardiography (TEE) permits accurate assessment of the LAA anatomy and is the reference standard to diagnose thrombus (sensitivity 100% and specificity 99%). The presence of dense spontaneous echo contrast and large dimensions of the LAA (>34 cm^3) have been associated with increased risk of stroke. The use of ultrasound contrast agents during TEE improve the diagnostic accuracy for LAA thrombus and reduces the number of uncertain results from 17.8% to 5.6%. The function of the LAA is most commonly assessed with pulsed-wave Doppler tracing of the LAA flow. In AF, the LAA flow pattern is characterized by saw tooth signals of variable amplitude (Figure 4). LAA systolic velocities <20 cm/s have been associated with spontaneous echo contrast and risk of stroke **(15).**

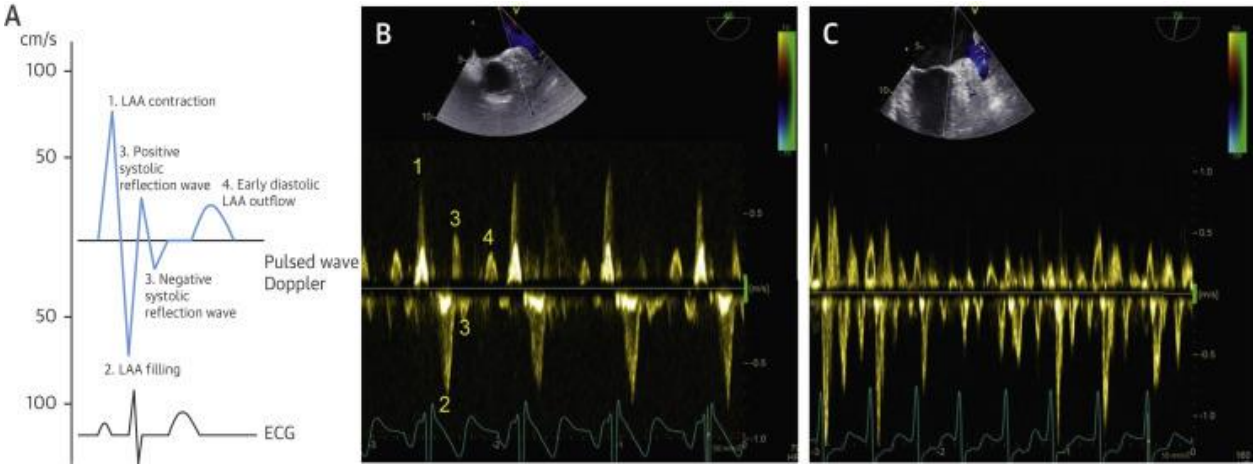


Fig (4): Assessment of LAA Function **(7).**

(A) A schematic pulsed-wave Doppler recording of the left atrial appendage (LAA) flow velocities across the cardiac cycle (electrocardiogram). **(B)** The pulsed-wave Doppler recording of a patient in sinus rhythm is displayed. Note that the **numbers** correspond to the wave reflections during LAA contraction, LAA filling, late systolic reflections, and early diastolic LAA outflow as in the schematic representation of **A**. During atrial fibrillation, the pulsed-wave Doppler pattern of the LAA flow resembles a saw tooth **(C) (7).**

3D imaging techniques such as 3D TEE, CMR, and CT provide accurate measurements of the LAA appendage size, visualization of LAA thrombus, and assessment of the anatomic spatial relationships to be considered for transcatheter LAA closure. 3D TEE is key during the planning and guidance of transcatheter LAA closure. By aligning the multiplanar reformation planes, the dimensions of the ostium and the landing zone where the closure device will be deployed can be measured (Figure 5) **(16).** However, the morphology of the LAA is better visualized with multidetector row CT. CT provides comprehensive information for selection of LAA closure device in AF patients with relative or absolute contraindications for oral anticoagulation. Currently available devices differ in size, shape, and methodology of deployment **(17):** whereas the Amplatzer AMULET (St. Jude Medical, Plymouth, Massachusetts) consists of a self-expandable nitinol distal lobe anchored in the

neck of the LAA and a proximal disc that enhances the complete closure of the ostium, the WATCHMAN device (Boston Scientific, Natick, Massachusetts) is a nitinol cage with 10 peripheral anchors and a fabric cap that is anchored in the ostium of the LAA. The LARIAT device, by contrast, is a combined endocardial and epicardial method to exclude the LAA. The anatomic prerequisites for each device are well defined by the manufacturers (Figure 6). The evidence from a limited number of randomized trials has demonstrated that transcatheter LAA closure is noninferior to warfarin in AF patients. However, there remain several safety and patient selection concerns that will be addressed in on-going post-marketing surveillance registries and randomized trials **(18).**

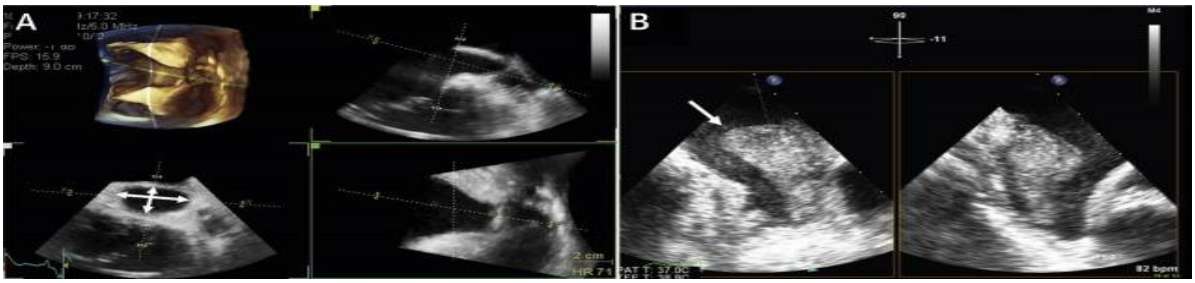
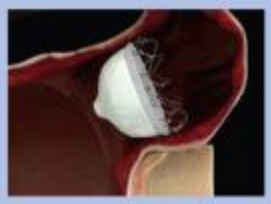
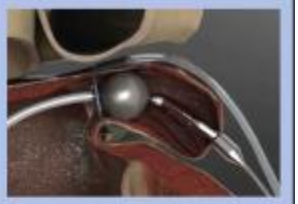


Fig (5): Assessment of LAA Dimensions and Evaluation of Thrombus Before Transcatheter Closure **(7).**

(A) The multiplanar reformation planes from 3-dimensional transesophageal echocardiography volume acquisition. The planes are aligned to obtain the cross-sectional view of the left atrial appendage (LAA) ostium. The presence of large thrombus is a contraindication for transcatheter closure of the LAA **(B, arrow) (7)**.

WATCHMAN	AMULET	WAVECREST	LARIAT
			

• The LAA length should be larger than the width (the depth of the main anchoring lobe should be ≥19 mm)
• Landing zone diameters 17-31 mm
• Absence of LAA thrombus
	• The landing zone is measured 10 mm distally from the ostial plane (the depth of the main anchoring lobe should be >12 mm)
	• Landing zone diameters 11-31 mm
		• Required depth of the main anchoring lobe ≤10 mm
		• The landing zone diameters should be 15-29 mm
			• Ostium diameter should be <40 mm (measured on CT)
			• Contraindications if:
			  • The LAA is oriented superiorly with the apex behind the pulmonary trunk
			  • Multilobed LAA with lobes oriented in different planes exceeding 40 mm
			  • Posteriorly rotated heart
			  • Pericardial disease

Fig (6): Requirements for Transcatheter LAA Closure **(7).** Anatomic characteristics of the left atrial appendage (LAA) for each closure device are summarized. CT = computed tomography.

Left atrial appendage and thrombogenesis

The LAA is thought to be the source of 90% of the thrombi in non-valvular AF (NVAF) and 57% in valvular AF. Left atrial appendage anatomy, function and its's dysfunction plays a key role (*Figure* 7) **(19).**

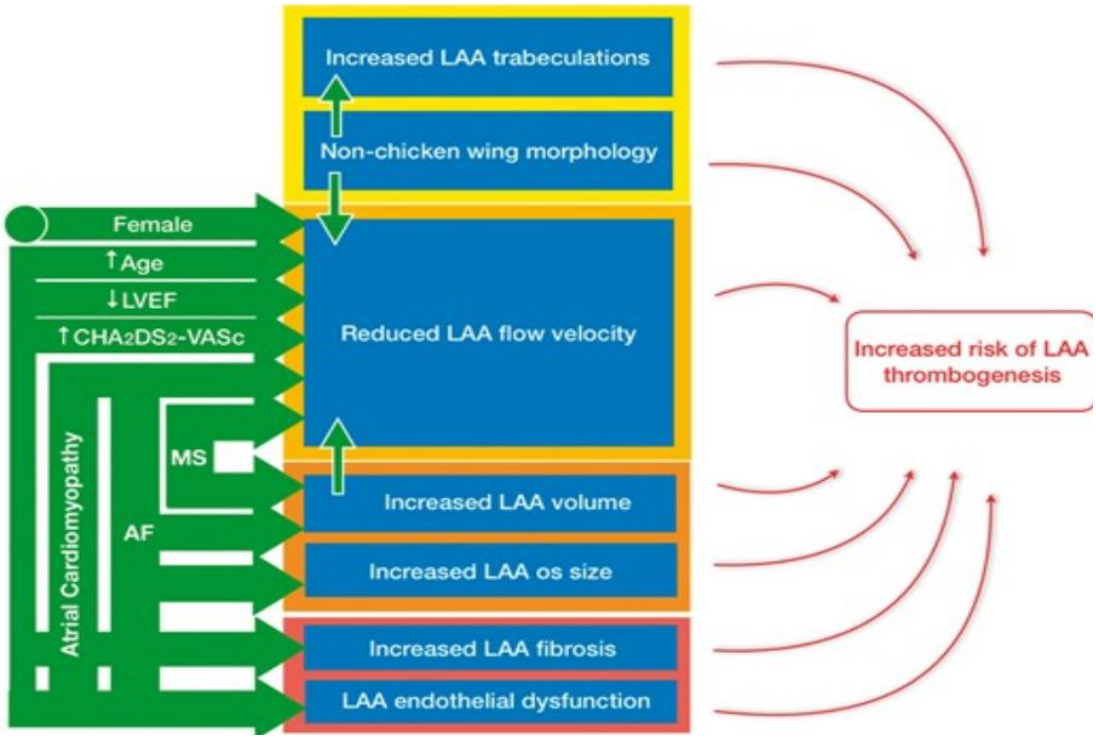


Fig (7): Role of the LAA in thrombogenesis. The green arrows signify the variables that affect the corresponding LAA characteristic. The blue boxes represent LAA characteristics. The gradients in colour from yellow to red represent LAA morphology (yellow), LAA mechanical function (light orange), LAA dimensions (dark orange) and LAA tissue characteristic (red). AF, atrial fibrillation; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; MS, mitral stenosis; os, ostium **(19).**

- **Left atrial appendage anatomy and thrombogenesis**

Left atrial appendage orifice size is independently associated with thromboembolic risk in AF patients. An orifice area >4.5 $cm^2 \pm 1.5$ is associated with an increased incidence of stroke. In other studies, LAA casts from post-mortem hearts were more likely to have thrombus detected if the LAA body and ostium were enlarged. Systemic embolism in the presence of mitral stenosis was over three times more likely to occur in those with a larger LAA. In cryptogenic stroke/transient ischaemic attack (TIA) cohorts, LAA volume (measured by CT scan during mid-diastole) was larger compared with age- and gender-matched controls. In addition, the combination of large orifice area and low flow velocity is significantly associated with stroke risk, including in those with CHA_2DS_2-VASC scores 0–1. Left atrial appendage flow velocity <40 cm/s combined with an orifice area of >4 cm^2, has been shown to be associated with a high odds ratio for stroke **(20).**

In a retrospective study of an AF ablation cohort who had undergone CT scanning, a high burden of LAA trabeculation, was shown to be independently associated with stroke risk, whilst in another study, increased LAA fibrosis, as analysed by late gadolinium enhancement magnetic resonance imaging, was associated with reduced LAA flow **(21).**

- **Left atrial appendage flow velocities and thrombogenesis**

A number of studies have demonstrated increased thromboembolic risk with reduced LAA flow velocity, regardless of rhythm or systolic function **(22).** Values less than 37 cm/s to 55 cm/s, are associated with increased risk of spontaneous echo contrast and thrombus formation. A reduction in LAA contraction is also significantly related to increased embolic events after catheter ablation for paroxysmal AF with one study recommending LAA evaluation prior to invasive interventions, when velocities are <40 cm/s. The effects of LAA flow velocity on thromboembolic risk has been considered a potential variable **(23).**

- **Left atrial appendage endothelial dysfunction and thrombogenesis**

Structural remodelling in the LA due to AF or other pathological process; either due to cardiomyopathy or clinical factors such as diabetes and ageing, can lead to modulation of LAA endothelium resulting in increased expression of prothrombogenic factors, such as von Willebrand factor, vascular cell adhesion molecule-1, and p-selectin. Increased expression of von Willebrand factor has been shown to contribute to local thrombus formation in the LAA independent of AF, which may explain why thrombogenesis can occur in the context of episodes of sinus rhythm **(19).**

- **Left atrial appendage morphology and thrombogenesis**

The chicken wing morphological subtype is associated with lower prevalence of stroke/TIA and the cauliflower subtype with the highest. This has also been confirmed in a meta-analysis which combined eight studies with a total of 2596 patients. Silent cerebral ischaemia has also been shown to correlate with non-chicken wing morphology, particularly the cauliflower subtype Importantly, it has also been demonstrated that low stroke risk patients (CHADS2 0–1), have a 10-fold increase in prior stroke/TIA when they have a non-chicken wing LAA subtype. Additionally, increased number of LAA lobes has been implicated in stroke risk, independent of clinical risk and blood stasis **(19).**

- **Mechanism behind left atrial appendage morphology and thrombogenesis**

The higher incidence of stroke in non-chicken wing subtype could be due to a combination of many factors already mentioned. Firstly, their increased morphological complexity is thought to promote local blood stasis. Secondly, these subtypes demonstrate extensive trabeculations compared with the chicken-wing subtype. Thirdly, studies have shown that LAA morphology is a significant determinant of LAA flow velocity, with the chicken wing subtype positively associated and non-chicken wing subtype negatively associated. In one study, the cauliflower subtype's association with increased thromboembolic risk was in part explained by a larger orifice and having a low flow velocity **(24).** This was analysed further in another study, which concluded that LAA morphology was no longer an associated variable when flow velocity and orifice size were adjusted for **(15).**

- **Atrial fibrillation rhythm, left atrial appendage, and thrombogenesis**

Atrial fibrillation impacts the LAA in many ways to promote its thrombogenic predisposition. The characteristic contractility seen in sinus rhythm is reduced and a decrease in flow velocity ensues. Atrial fibrillation also contributes to remodelling of the LA which leads to LAA dilation, including of the orifice. Endothelial dysfunction also manifests during AF **(26).**

Predictors of Left Atrial Appendage Thrombi

Echocardiography has emerged as a valuable tool for assessing structural and functional cardiac parameters associated with thrombus formation. Transesophageal echocardiography (TEE) is considered the gold standard for detecting LAAT, particularly before cardioversion or ablation procedures. Despite its high sensitivity and specificity, TEE is not always feasible due to logistical challenges, patient-related contraindications, or resource limitations, such as during the COVID-19 pandemic. As a result, transthoracic echocardiography (TTE), a more accessible and non-invasive modality, has been explored for its potential role in predicting LAAT **(27).**

Several studies have highlighted the significance of left atrial (LA) structural parameters, such as left atrial diameter (LAD), surface area (LAA), and indexed volume (LAVI), in LAAT prediction. Scherr et al. demonstrated that LAD >45 mm and a CHADS2 score ≥2 were significant predictors of LA thrombus. However, the predictive power of these individual variables remains suboptimal. More recently, studies have suggested that combining LA parameters with left ventricular ejection fraction (LVEF) may enhance predictive accuracy **(28).**

Novel echocardiographic indices, such as the ratios of LVEF to LAD, LAA, and LAVI, have been proposed as promising predictors of LAAT. These indices have shown statistically significant associations with thrombus formation, particularly in patients with lower CHA2DS2-VASc scores. For instance, an LVEF/LAA ratio <1.7 and LVEF/LAVI ratio <1.1 were identified as strong predictors of LAAT, with an area under the

curve (AUC) of 0.7, reflecting moderate predictive accuracy. Furthermore, these indices demonstrated higher positive predictive values in patients with low thromboembolic risk, suggesting their utility in refining risk stratification **(29).**

The integration of clinical risk scores with echocardiographic parameters has been shown to improve LAAT prediction. For example, Van Chien et al. **(30)** combined the CHA2DS2-VASc score with LAVI and LA longitudinal strain in anticoagulant-naïve patients, achieving robust predictive models. Similarly, Ayirala et al. **(31)** demonstrated that normal LAVI and LVEF in patients with a CHADS2 score of 1 effectively excluded LAAT. These findings underscore the importance of multimodal approaches to risk stratification.

Heart failure (HF) represents a unique subgroup of AF patients with an elevated risk of thromboembolic events. Recent studies, including data from the LATTEE registry, have shown that patients with heart failure with reduced ejection fraction (HFrEF) are at a higher risk of LAAT compared to those with heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF). However, the predictive utility of novel TTE indices in HF patients remains limited, highlighting the need for further research in this area **(32).**

References:

1. Di Biase, L., Burkhardt, J. D., & Santangeli, P. (2023). Left atrial appendage: anatomy, function, and clinical significance. Journal of Cardiovascular Electrophysiology, 34(1), 45–55.
2. Saw, J., Lopes, J. P., & Reisman, M. (2022). Left atrial appendage and thromboembolism in atrial fibrillation: current concepts and emerging therapies. Heart, 108(3), 200–208.
3. Chen, S., Schmidt, B., Bordignon, S., et al. (2021). Imaging of the left atrial appendage: state-of-the-art review. Journal of Clinical Medicine, 10(15), 3328.
4. Boersma, L. V., Ince, H., & Kische, S. (2022). Advances in left atrial appendage closure: devices, techniques, and patient selection. European Heart Journal, 43(18), 1762–1774.
5. Kuo, M. Y.-W. J. A. U. A. S. (2024) Echoes Across the Globe: Insights into Left Atrial Size Assessment in Dogs and Cats.
6. Florescu, D. R., L. P. Badano, M. Tomaselli, C. Torlasco, G. C. Târtea, T. A. Bălșeanu, V. Volpato, G. Parati & D. J. E. H. J.-C. I. Muraru (2022) Automated left atrial volume measurement by two-dimensional speckle-tracking echocardiography: feasibility, accuracy, and reproducibility. 23, 85-94.
7. Delgado, V., L. Di Biase, M. Leung, J. Romero, L. F. Tops, B. Casadei, N. Marrouche & J. J. J. J. o. t. A. C. o. C. Bax (2017) Structure and function of the left atrium and left atrial appendage: AF and stroke implications. 70, 3157-3172.
8. Yang, C., J. Yang, Q. Liu, L. You, J. Wu, Y. Zhang, L. Wang & R. J. B. C. D. Xie (2022) The effect of different preoperative left atrial appendage emptying speeds on left atrial function in patients with persistent atrial fibrillation after left atrial appendage closure combined with catheter ablation. 22, 399.
9. Cunha, P. S., S. Laranjo, J. Heijman & M. M. J. F. i. c. m. Oliveira (2022) The atrium in atrial fibrillation–a clinical review on how to manage atrial fibrotic substrates. 9, 879984.
10. Jain, V., R. Ghosh, M. Gupta, Y. Saijo, A. Bansal, M. Farwati, R. Marcus, A. Klein, B. J. C. d. Xu & therapy (2021) Contemporary narrative review on left atrial strain mechanics in echocardiography: cardiomyopathy, valvular heart disease and beyond. 11, 924.
11. Iwamiya, S., K. Ihara, G. Nitta & T. J. I. J. o. M. S. Sasano (2024) Atrial Fibrillation and Underlying Structural and Electrophysiological Heterogeneity. 25, 10193.
12. Tubeeckx, M. 2024. ERBB4 stimulation as a therapeutic strategy for atrial myopathy and atrial fibrillation. University of Antwerp.
13. Zhai, H., L. Kang, Y. Li, X. Zhao, Q. Chu & R. J. M. Li (2024) The progress of percutaneous left atrial appendage occlusion: A bibliometric analysis from 1994 to 2022. 103, e37742.
14. Mostafa, M. R., M. Magdi, A. Al-abdouh, W. Abusnina, M. Elbanna, B. Abdelazeem, S. L. M. Renjithal, M. A. Mamas & J. J. C. C. Shah (2022) A systematic review and meta-analysis of the impact of the left atrial appendage closure on left atrial function. 45, 614-621.

15. Gagyi, R. B., N. Szegedi, J. Simon, S. Wijchers, R. Bhagwandien, M. H. Kong, P. Ruppersberg & T. J. F. i. C. M. Szili-Torok (2022) Left atrial anatomical variations correlate with atrial fibrillation sources near the left atrial ridge. 9, 928384.
16. Prosper, A., J. Shinbane, A. Maliglig, F. Saremi, A. Wilcox & C. J. J. o. T. I. Lee (2020) Left atrial appendage mechanical exclusion: procedural planning using cardiovascular computed tomographic angiography. 35, W107-W118.
17. Sulague, R. M., T. Whitham, L. M. L. Danganan, V. Effiom, K. Candelario, N. Latif & I. J. J. o. C. M. Hameed (2023) The Left Atrial Appendage and Atrial Fibrillation—A Contemporary Review. 12, 6909.
18. Della Rocca, D. G., R. P. Horton, N. Tarantino, C. J. Van Niekerk, C. Trivedi, Q. Chen, S. Mohanty, A. Anannab, G. Murtaza & K. J. C. C. I. Akella (2020) Use of a novel septal occluder device for left atrial appendage closure in patients with postsurgical and postlariat leaks or anatomies unsuitable for conventional percutaneous occlusion. 13, e009227.
19. Karim, N., Ho, S. Y., Nicol, E., Li, W., Zemrak, F., Markides, V., Reddy, V., & Wong, T. (2020). The left atrial appendage in humans: structure, physiology, and pathogenesis. Ep Europace, 22(1), 5-18.
20. Khurram, I. M., J. Dewire, M. Mager, F. Maqbool, S. L. Zimmerman, V. Zipunnikov, R. Beinart, J. E. Marine, D. D. Spragg & R. D. J. H. r. Berger (2013) Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. 10, 1843-1849.
21. Handke, M., A. Harloff, A. Hetzel, M. Olschewski, C. Bode & A. J. J. o. t. A. S. o. E. Geibel (2005) Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation–a transesophageal echocardiographic study in 500 patients with cerebral ischemia. 18, 1366-1372.
22. Uretsky, S., A. Shah, S. Bangalore, L. Rosenberg, R. Sarji, D. R. Cantales, D. Macmillan-Marotti, F. A. Chaudhry & M. V. J. E. J. o. E. Sherrid (2009) Assessment of left atrial appendage function with transthoracic tissue Doppler echocardiography. 10, 363-371.
23. Dudziñska-Szczerba, K., Kułakowski, P., Michałowska, I., & Baran, J. (2022). Association between left atrial appendage morphology and function and the risk of ischaemic stroke in patients with atrial fibrillation. Arrhythmia & Electrophysiology Review, 11, e09.
24. Lee, Y., H.-C. Park, Y. Lee & S.-G. J. T. A. J. o. C. Kim (2017) Comparison of morphologic features and flow velocity of the left atrial appendage among patients with atrial fibrillation alone, transient ischemic attack, and cardioembolic stroke. 119, 1596-1604.
25. Lee, J. M., Seo, J., UHM, J. S., Kim, Y. J., LEE, H. J., KIM, J. Y., SUNG, J. H., PAK, H. N., LEE, M. H., & Joung, B. (2015). Why is left atrial appendage morphology related to strokes? An analysis of the flow velocity and orifice size of the left atrial appendage. Journal of Cardiovascular Electrophysiology, 26(9), 922-927.
26. Gottlieb, L. A., R. Coronel & L. R. J. H. r. Dekker (2023) Reduction in atrial and pulmonary vein stretch as a therapeutic target for prevention of atrial fibrillation. 20, 291-298.
27. Arnautu, S. F., D. A. Arnautu, A. Lascu, A. A. Hajevschi, C. I. Rosca, A. Sharma, D. C. J. M. S. M. I. M. J. o. E. Jianu & C. Research (2022) A Review of the Role of Transthoracic and Transesophageal Echocardiography, Computed Tomography, and Magnetic Resonance Imaging in Cardioembolic Stroke. 28, e936365-1.
28. Deng, B., Nie, R., Qiu, Q., Wei, Y., Liu, Y., Lv, H., ... & Wang, J. (2021). 3D transesophageal echocardiographic assists in evaluating the morphology, function, and presence of thrombi of left atrial appendage in patients with atrial fibrillation. Annals of Translational Medicine, 9(10).
29. Kaufmann, D., E. Wabich, A. Kapłon-Cieślicka, M. Gawałko, M. Budnik, B. Uziębło-Życzkowska, P. Krzesiński, K. Starzyk, B. Wożakowska-Kapłon & M. J. F. i. C. M. Wójcik (2022) Echocardiographic predictors of thrombus in left atrial appendage—The role of novel transthoracic parameters. 9, 1059111.
30. Van Chien, D., P. Thai Giang, P. T. Son, L. V. Truong, P. J. C. R. Nguyen Son & Practice (2019) Novel models for the prediction of left atrial appendage thrombus in patients with chronic nonvalvular atrial fibrillation. 2019, 1496535.

31. Ayirala, S., Kumar, S., O'Sullivan, D. M., & Silverman, D. I. (2011). Echocardiographic predictors of left atrial appendage thrombus formation. Journal of the American Society of Echocardiography, 24(5), 499-505.
32. Uziębło-Życzkowska, B., A. Kapłon-Cieślicka, M. Kiliszek, M. Gawałko, M. Budnik, K. Starzyk, B. Wożakowska-Kapłon, L. Daniłowicz-Szymanowicz, D. Kaufmann & M. J. N. Wójcik (2022) Increased Body Mass Index and Risk of Left Atrial Thrombus in Nonvalvular Atrial Fibrillation Patients—Data from the Left Atrial Thrombus on Transesophageal Echocardiography (LATTEE) Registry. 14, 3652.