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# Stroke risk evaluation for patients with atrial fibrillation: Insights from left atrial appendage

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Left atrial appendage (LAA) is believed to be a common site of thrombus formation in patients with atrial fibrillation (AF). However, the commonly-applied stroke risk stratification model (such as CHA<sub>2</sub>DS<sub>2</sub>-VASC score) does not include any structural or hemodynamic features of LAA. Recent studies have suggested that it is important to incorporate LAA geometrical and hemodynamic features to evaluate the risk of thrombus formation in LAA, which may better delineate the AF patients for anticoagulant administration and prevent strokes. This review focuses on the LAA-related factors that may be associated with thrombus formation and cardioembolic events.

## KEYWORDS

left atrial appendage, atrial fibrillation, stroke, association, risk evaluation

## Introduction

Atrial fibrillation (AF) is the most common sustained rhythm disorder worldwide (1–4), and the worldwide AF incidence is approximately 1–2% (3–6), and the prevalence increases with age. In general, patients with AF have higher morbidity and mortality rates due to increased risk of stroke (7–10). The risk of ischemic stroke related to AF, increases from 4.6% for ages 50 through 59 years to 20.2% for ages 80 through 89 years (11). Therefore, AF prevalence is expected to dramatically increase with an aging population in the coming years (12).

In AF patients, irregular heart rhythm disturbs blood flow, which can lead to blood stagnation and clot formation, with subsequent dislodgment and embolization in the brain resulting in thromboembolic events (13–15). There is an agreement that AF increases stroke risk by 5-fold (16), where AF-related strokes are associated with greater disability, higher medical cost, poorer functional outcomes, and a lower chance of being discharged to home compared to non-AF-related strokes (17).

In AF patients with thromboembolic event, studies have revealed that more than 90% of thrombi originate in the left atrial appendage (LAA) (18–20), which is the remnant of the embryonic left atrium and originates from the primordial pulmonary vein and its branches (21–24). However, the commonly applied stroke risk scoring model (*viz.*: CHA<sub>2</sub>DS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc, shown in the following Table 1) in the clinic incorporates only patient demographics and clinical data (25), but do not include any morphological or hemodynamic information about the LAA, and we think that with the LAA information added, some high stroke risk patients but with low scores would be identified.

Recent studies have shown extensive evidence that it is necessary to include some important LAA features to better evaluate the thromboembolic risk and prevent stroke risk. This study serves to overview of current concepts and recent developments in the relationship between stroke risk and LAA risk-related characteristics.

## LAA characteristics related with stroke

A number of studies have focused on the stroke-related LAA characteristics. These characteristics can be classified into three groups: shape, morphology and hemodynamics. In the following paragraphs we elucidate the relationship between these characteristic groups and stroke risk.

### LAA shape

Shape is an intuitive term for describing the external form, contours, or outline of the LAA, and various classification approaches have been proposed for describing LAA shape (26–29). In these classification schemes, a widely accepted classification, first proposed by Wang et al. (26), classifies LAA into 4 types: cactus, chicken wing, windsock and cauliflower (Figure 1). This classification was derived from 612 patients

based on characteristics of bend, lobes and overall length. Where the characteristics were used as the guidance for LAA closure.

Di Biase et al. (31) conducted an initial study to investigate the relationship between LAA shape and stroke risk. In their study, 932 AF patients were classified into four groups based on Wang's shape types obtained using computer tomography (CT)/magnetic resonance imaging (MRI), and they found that the chicken wing LAA type was less likely to have a stroke/transient ischemic attack (TIA), and the cauliflower was the highest stroke risk type. As the first study to focus on the association between stroke risk and LAA shape, Di Biase's research obtained considerable attention. Subsequent independent investigations conclusively established chicken wing as the "safe" LAA type (32, 33), and from that point to present, the consensus that chicken wing type LAA is least likely to result in stroke (*i.e.*, is the "safe" LAA type) is widely accepted in clinical practice (34).

After recognition of chicken wing as the LAA shape with lowest risk, questions remained regarding high-risk LAA shapes, motivating a series of investigations to figure out the "unsafe" LAA types, which found that all the three non-chicken wing LAA shapes were "unsafe" (35–39). Specifically speaking, Lee et al. (39) conducted a case-control study on 255 patients based on the history of cardiovascular adverse events, and concluded that the cauliflower type is associated with an increased risk of stroke. Deng et al. (37) evaluated stroke risk *via* detection of spontaneous echo contrast (SEC) or thrombi using 3D transesophageal echocardiography (TOE) in 320 AF patients and found that the cauliflower LAA type was associated with a higher prevalence of SEC or thrombi. Adukauskaite et al. (35) found that windsock was the highest stroke-prone LAA type

TABLE 1 Definition of CHA<sub>2</sub>DS<sub>2</sub>-VASc or CHADS<sub>2</sub> (17).

Letter	Risk factor	Score
C	Congestive heart failure	1
H	Hypertension	1
A <sub>2</sub>	Age ≥ 75	2
D	Diabetes mellitus	1
S <sub>2</sub>	Stroke history	2
V	Vascular disease	1
A	Age 65–74	1
Sc	Sex category ( <i>i.e.</i> , female sex)	1

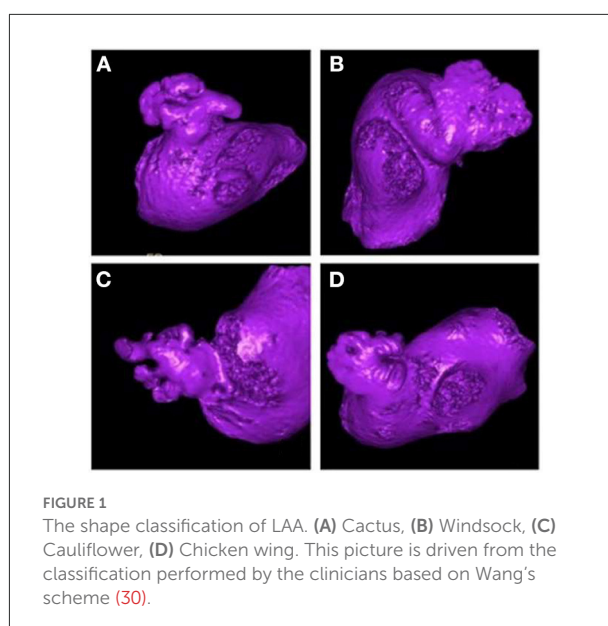


TABLE 2 Studies on association between stroke risk and LAA shape based on Wang's scheme.

LAA classification	References	Patients	Imaging modality	Judge for stroke risk	Conclusions	
Wang's model: cactus, chicken wing, windsock and cauliflower	Di Biase et al. (31)	932	CT/MRI	Prior stroke	<b>Chicken wing</b> less likely to have suffered the prior stroke; <b>Cauliflower</b> more likely to have suffered a cerebrovascular ischemic event	"Safe" LAA type
	Lee et al. (32)	360	CT	Prior stroke	<b>Chicken wing</b> associated with lower prevalence of stroke	
	Luperico et al. (33)	2596	CT/TEE/MRI	Prior thromboembolic events (TE)	<b>Chicken wing</b> less likely to develop TE	
	Lee et al. (39)	255	CT	Prior CETIA or CES	<b>Cauliflower</b> associated with increased risk of CETIA and CES	"Unsafe" LAA type
	Adukauskaitė et al. (35)	158	CT	Prior cardio-embolic (CE) stroke	<b>Windsock</b> associated with CE stroke	
	Deng et al. (37)	320	TEE	Detection of SEC or thrombi	<b>Cauliflower</b> associated with higher prevalence of SEC or thrombi	
	Anselmino et al. (36)	348	CT/MRI	Silent cerebral ischemia (SCI) burden	<b>Cauliflower</b> and <b>windsock</b> associated with prevalence of SCI	
	Kimura et al. (38)	80	CT	Prior stroke	<b>Cauliflower</b> considered as the most stroke-prone LAA type	
Smit et al. (40)	908	CT	Prior stroke and/or transient ischemic attack	<b>Swan</b> shape independently associated with prior stroke/TIA		
Two types: chicken wing & non-chicken wing	Kong et al. (41)	219	CT	Prior stroke	<b>Non-chicken wing</b> : an independent predictor of stroke	
	Du et al. (42)	555	CT	Detection of LA/LAA thrombus	<b>Non-chicken wing</b> : a powerful predictor of LA/LAA thrombosis	
	Yaghi et al. (43)	172	CT	Prior stroke	The prevalence of <b>non-chicken wing</b> type higher in patients with CE stroke	

TEE, Transoesophageal echocardiography; MRI, Magnetic Resonance Imaging; LAA: left atrial appendage.

based on a stroke history assessment of 158 patients. Anselmino et al. (36) reached the conclusion that cauliflower and windsock are associated with a higher prevalence of silent cerebral ischemia based on a study of 348 AF patients. Kimura et al. (38) performed a case-control study investigating the high-risk LAA type in 80 AF patients with low CHADS<sub>2</sub> score, and found cauliflower to be the most stroke-prone LAA type. Additionally, Smit et al. (40) developed a new 4-type classification scheme (chicken wing, swan, cauliflower and windsock) and evaluated stroke risk as a function of prior stroke history. Their results demonstrated that the swan LAA type (LAA presented a second sharp curve folding the structure back) was independently associated with the prior stroke history. Given the results of these studies, researchers subsequently combined the three "non-chicken wing" shapes into a single category and conducted studies to confirm an "unsafe" designation for risk of stroke on the "non-chicken wing" type (41–43). The simplification and efficiency of this two-type classification scheme is widely recognized in clinic (33, 34).

However, it is worth mentioning that several studies did not justify the origin of the emboli, as many studies considered that most strokes for AF patients are resulted from the cardioembolic origin. We think it is important to determine the embolic origin in future studies.

Detailed information on Wang's scheme of LAA shape types and the related studies on the association between stroke risk is summarized in Table 2.

Although Wang's scheme is widely accepted in clinical application, however, several studies have revealed marked variability in shape classification based on the scheme. Both Wu et al. (44) and Khurram et al. (45) pointed out the high inter-observer variability in the classification schemes based on Wang's shape description.

Table 3 illustrates the diversity in the prevalence among Wang LAA shape types observed by different investigators. Such disparity indicates that rigorous ascertainment based on these rather subjective descriptors is difficult and not reliably reproducible. The need for greater objectivity in defining

LAA classification parameters enabling reliable assessment of associations with stroke risk led to the development of morphology parameters.

## LAA morphology

The LAA morphology classification approach, with characteristics categorized by means of dimensional level, is superior to the LAA shape scheme in terms of objectivity and reproducibility and is widely studied.

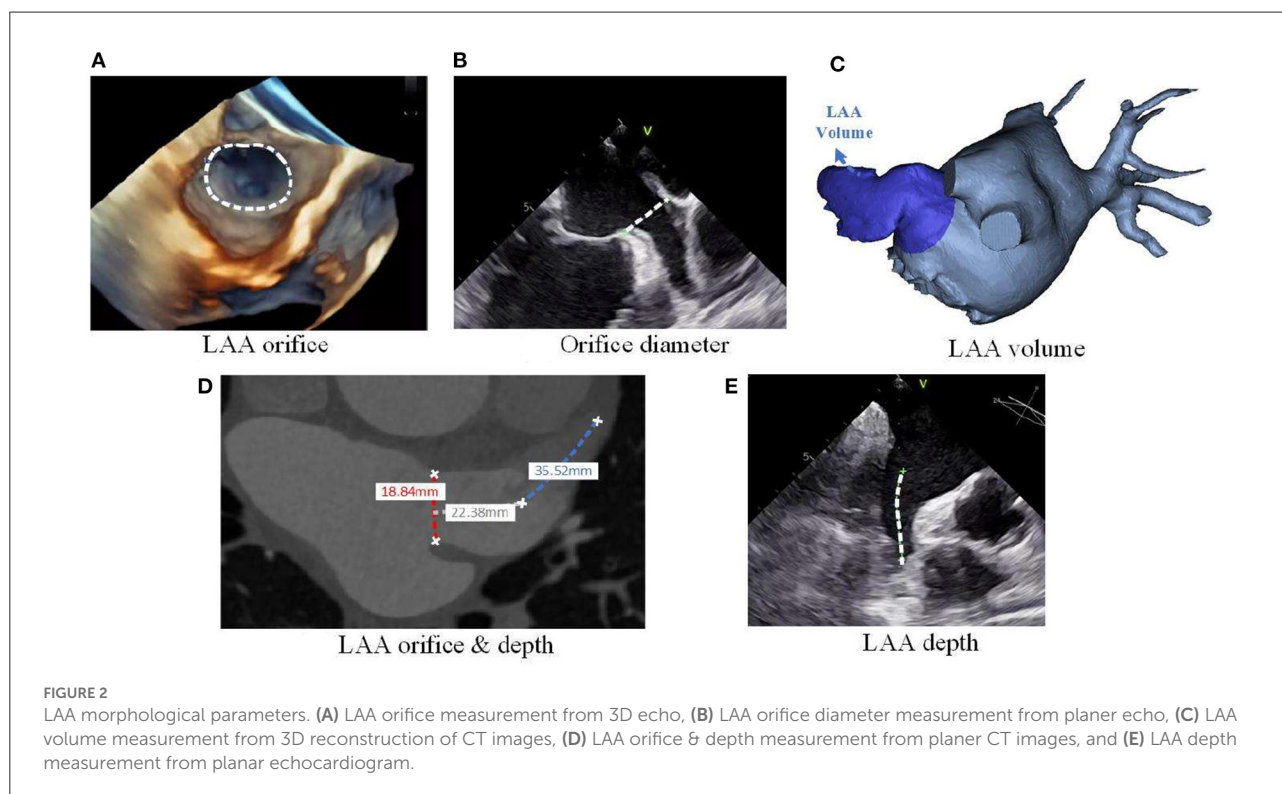
TABLE 3 Prevalence of LAA shapes in different studies.

References	Sample size	Prevalence (%)			
		Chicken wing	Cactus	Windsock	Cauliflower
Wang et al. (26)	612	18.3	5.9	46.7	29.1
Di Biase et al. (31)	932	48	30	19	3
Lee et al. (32)	360	43.1	30	13	13.9
Deng et al. (37)	320	14.1	42.8	13.4	29.7
Du et al. (42)	555	67.9	18.7	11.2	2.2

Among these morphological characteristics, the LAA orifice (see Figure 2A) attracts a lot of focus, and a number of studies have revealed the correlation between orifice size and the stroke risk. In these studies, LAA orifice is consistently shown to be positively related to the stroke risk, both for its area (35, 46, 47) and diameter (41, 45, 48–50) (see Figure 2B). Although the positive relationship is widely accepted, the cut-off value of the orifice size for determining the high stroke risk is seldom calculated. Only Lee et al. (46, 47) gave the different criteria of  $>3.5 \text{ cm}^2$  and  $>4 \text{ cm}^2$  respectively in their two studies, with the criterion being larger for those with low  $\text{CHA}_2\text{DS}_2\text{-VASc}$  scores.

Though the large orifice is believed to relate to the high stroke risk, Khurram et al. (45) draw a contrary conclusion that a smaller LAA orifice diameter is associated with prevalent stroke. In seeking for the reasons for such different conclusions regarding the association between LAA orifice and stroke risk, we found that these studies used different definitions of LAA orifice (Figure 3).

Intuitively speaking, the LAA orifice would be the section at the interface between the LAA and LA (Figure 3, blue dashed line). This intuitive definition was used by Khurram et al. (45). However, an anatomical definition of the LAA orifice exists, and it is usually specified as the section aligning with the left upper pulmonary vein ridge and the circumflex coronary (51) (Figure 3, red dashed line). This seems more accurate and less subjective compared to the intuitive definition, and is used as the measurement method for LAA orifice in (52). However, several studies have defined the LAA orifice as the narrowest



portion at the entrance into the left atrium (49, 53). We deduced that this wide-spread definition had its origins in studies of LAA occlusion, as the location of occlusion is usually defined as the narrowest portion (Figure 3, orange dashed line), which would be defined as the LAA neck in our context. The differing definitions caused the diversity of conclusions. In this regard, a clear and unified definition of LAA orifice would be required in the future studies.

Apart from LAA orifice, LAA volume (see Figure 2C) is another prominent parameter. Several studies on the associations between LAA volume and stroke risk have shown that AF patients with a history of stroke/TIA tend to exhibit a larger LAA volume (48, 49, 54–57). However, the specific cardiac phase for defining the LAA volume was not clearly defined in most of the above-mentioned studies. Only Chen et al. (55) clearly stated their LAA volume was at the end-diastolic phase, and the results showed that LAA end-diastolic volume was positively associated with the stroke risk. Although consensus has been achieved regarding a qualitative relationship between the LAA volume and stroke risk, a cut-off value or quantitative relationship was not defined in most of the related studies. Chen et al. (55) and Burrell et al. (54) proposed cut-off values of 8.6 and 34 cm<sup>3</sup>, respectively, for judging stroke risk, although the two values reflect a large disparity which could be attributed to differences in cardiac cycle phase. In this regard, the specific cardiac cycle phase of LAA volume should be defined clearly in future studies, which will allow a standardized comparison among different studies. However, it is worth to mention that the LA will be dilated with the impact from AF, and so the volume of LAA will also be enlarged. Meanwhile, these morphology characteristics would be better compared with the normalizations to the other patient specific characteristics [e.g.,: body mass index (BMI), body surface area (BSA)], so that

these morphology characteristics could be compared between different patients.

Different from the focus on LAA volume for a specific cardiac phase, Al-Issa et al. (58) focused on the changes in LAA volume during the whole cardiac cycle. In their study, the LAA area change ratio (known as regional function) was measured by CT and used to denote the volume change, and the result showed this parameter was significantly associated with stroke risk history, where stroke/TIA group tended to have a lower area change ratio compared with the control group.

In addition to the above-mentioned characteristics, some other characteristics were also studied, such as the angle of LAA bend (59), the depth (48, 53) (see Figures 2D,E) and the number of lobes (52, 60). In these studies, the acute angle, increased depth and large number of lobes was each considered as a high-risk morphology of LAA. All these morphological characteristics suggest that the stroke risk is increased with the increasing of LAA morphology complexity. Detailed information on the associations between stroke risk and LAA morphological parameters are summarized in Table 4.

To better quantify this complexity, Kaminski et al. (62) used different parameters to describe the whole LAA. In their study, different parametric schemes with various parameters were used to describe the different LAA types. In addition to Bieging et al. (63), where they assessed the LAA shape using statistical shape analysis on the “surface” of the LAA, Sanatkhani et al. (64) also performed an analysis to parametrize the LAA region’s appearance based on principal components and eigen shapes. And also, Slipsager et al. (65) conducted the unsupervised clustering based on the LAA shapes, which result into two clusters: chicken wing and non-chicken wing shapes.

Although the morphology parameters are considered to be an objective approach for characterizing the LAA, the morphology parameter features are inherently isolated from the complex LAA geometry, and it lacks a comprehensive and mechanistic perspective for stroke evaluation. Under this circumstance, the hemodynamic analysis attracted the attention, for that the hemodynamic description utilizes the entire 3D dataset and is more comprehensive compared to the single or several morphological parameters. Furthermore, the study of hemodynamics is aligned with Virchow’s triad used to characterize the relationship between blood flow and thrombus formation. In this regard, evaluating the stroke risk from the aspect of hemodynamics in the LAA may be an optimal approach for evaluation of stroke risk.

## LAA hemodynamics

LAA flow velocity accounts for the majority of studies on the hemodynamic characteristics. Verhorst et al. (66) firstly evaluated the stroke risk using peak LAA velocity (both emptying and filling) and concluded that peak LAA velocity may

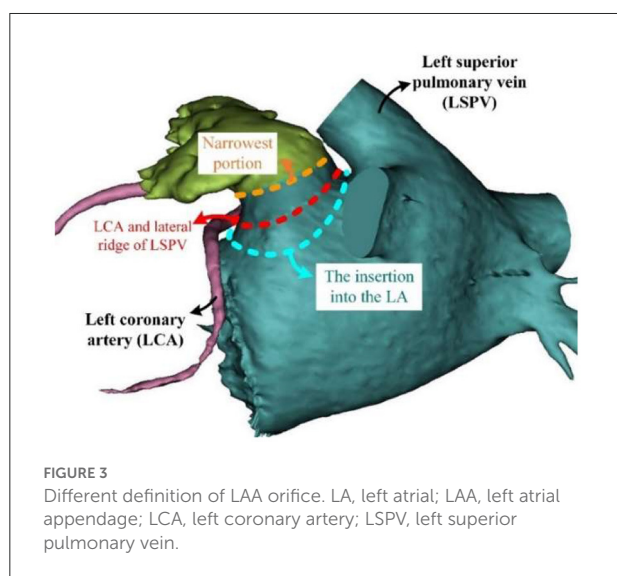


TABLE 4 Studies on the association between stroke risk and LAA morphological parameters.

Parameters	References	No.	Modality	Criterion	Relation	Cut-off
Orifice (area)	Adukauskaitė et al. (35)	158	CT	PriS	Positive (Pos)	-
	Lee et al. (46)	218	CT	PriS	Pos	3.5 cm <sup>2</sup>
	Lee et al. (47)	66	CT	PriS	Pos	4 cm <sup>2</sup>
Orifice (diameter)	Khurram et al. (45)	678	CT	PriS	Negative (Neg)	-
	Kong et al. (41)	219	CT	PriS	Pos	-
	Jeong et al. (49)	88	CT	PriS	Pos	-
	Sakr et al. (50)	50	TEE	PriS	Pos	-
	Beinart et al. (48)	144	MRI	PriS/TIA	Pos	-
Volume	Beinart et al. (48)	144	MRI	PriS/TIA	Pos	-
	Korhonen et al. (56)	151	CT	PriS	Pos	-
	Jeong et al. (49)	88	CT	PriS	Pos	-
	Taina et al. (57)	122	CT	PriS	Pos	-
	Chen et al. (55)	444	TEE	DoT	Pos	8.6 ml
	Burrell et al. (54)	96	MRI	PriS	Pos	34 cm <sup>3</sup>
Volume change	Al-Issa et al. (58)	36	CT	PriS/TIA	Neg	-
Bend	Yaghi et al. (59)	408	CT	PriS/TIA	Pos	-
Depth	Beinart et al. (48)	144	MRI	PriS/TIA	Pos	-
	Chen et al. (55)	444	TEE	DoT	Pos	-
	Dudzińska et al. (61)	169	CT	PriS	Pos	-
Lobes	Yamamoto et al. (52)	564	TEE	DoT	Pos	-
	Wang et al. (60)	472	TEE	DoT	Pos	-

PriS: Prior Stroke; TIA: Transient ischaemic attack; DoT: Detection of thrombus; TEE: Transoesophageal echocardiography; MRI: Magnetic Resonance Imaging.

potentially identify patients at high risk for systemic embolism. In subsequent studies, both peak LAA filling and emptying velocity were found to exhibit significant difference between the stroke and non-stroke patient groups (50). In a series of related studies, the peak LAA emptying velocity (pLAAev) was then used to quantify LAA flow velocity, revealing a correlation between a lower pLAAev and a higher stroke risk (32, 39, 67–69). However, the cut-off values for pLAAev were neglected in most studies, with only a few studies calculating this value. Generally speaking, the velocity of 20 cm/s is widely accepted as the threshold for determining the stroke risk (70–72). Chen et al. (73) concluded a slightly higher cut-off value of 21.5 cm/s based on study of 307 AF patients. However, Lee et al. (47) found that 37 cm/s could be used as a prognostic threshold for stroke risk in AF patients, with a higher value of 40 cm/s in patients with low CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (46). The large difference for the aforementioned values (~20 vs. ~40 cm/s) may attribute to the different placement of sample volume in the TEE measurement. In Lee et al.'s (46, 47) measurements, the sample volume was placed at the middle portion of the LAA, while the other measurements placed 1–2 cm inside of LAA.

In addition to LAA flow velocity, other hemodynamic parameters such as flow pattern and LAA ejection fraction (LAAef) have also been studied. For LAA flow pattern,

Garciafernandez et al. (74) identified three different flow patterns and studied their association with stroke risk. Their results revealed that the flow pattern characterized by the absence of identifiable flow waves was associated with a higher prevalence of LAA spontaneous contrast (higher stroke risk). Regarding LAAef, consensus was reached that the LAAef is negatively related with the stroke risk (75, 76). Specifically speaking, Park et al. (76) retrospectively studied 176 paroxysmal AF patients, and the result revealed that LAAef was significantly lower in the stroke group compared with the non-stroke group. LAA emptying fraction assessed by the feature-tracking echocardiographic method was put forward by Iwama et al. (75) who found that LAA emptying fraction was significantly reduced in AF patients with thrombus compared to those without thrombus. However, the cut-off values for LAAef were not determined in the studies, which should be considered in the future research. Studies on association of stroke risk and LAA hemodynamic parameters are summarized in Table 5.

Although evaluation of stroke risk by means of LAA hemodynamic parameters is particularly convincing, the availability of direct clinical measurements of these parameters is often limited. Alternatively, computational fluid dynamics (CFD) method has been used to obtain these parameters. CFD is a numerical analysis approach for predicting the

TABLE 5 Studies on association between stroke risk and LAA hemodynamic parameters.

Parameters	References	Patients	Criterion	Modality	Relation	Cut-off
Peak velocities	Patrick et al. (66)	54	PriS	TEE	Negative (Neg)	-
	Sakr et al. (50)	50	PriS	TEE	Neg	-
pLAAev	Goldman et al. (68)	721	Risk features	TEE	Neg	-
	Lee et al. (32)	360	PriS	TEE	Neg	-
	Lee et al. (39)	255	TIA/ PriS	TEE	Neg	-
	Taguchi et al. (69)	32	PriS	TEE	Neg	-
	Bernhardt et al. (67)	271	SEC	TEE	Neg	-
	Kamp et al. (70)	88	Prior events	TEE	Neg	20 cm/s
	Negrotto et al. (72)	306	DoT	TEE	Neg	20 cm/s
	Miyazaki et al. (71)	88	Embolic event*	TEE	Neg	20 cm/s
	Lee et al. (47)	218	PriS	TEE	Neg	37 cm/s
Flow pattern	Lee et al. (46)	279	PriS	TEE	Neg	40 cm/s
	Chen et al. (73)	307	DoT	TEE	Neg	21.5 cm/s
LAAef	Garciafernandez et al. (74)	39	SEC/DoT	TEE	TypeIII	-
LAAef	Park et al. (76)	176	PriS/TIA	TEE	Neg	-
	Iwama et al. (75)	142	DoT	TEE	Neg	-

TEE, Transoesophageal echocardiography; MRI, Magnetic Resonance Imaging; PriS, Prior Stroke; TIA, Transient ischemic attack; SEC, Spontaneous echo contrast; DoT: Detection of thrombus.

behavior of fluid flows whereby the hemodynamic details of LA and LAA can be obtained and visualized. Utilizing the CFD method, Gracia-Isla et al. (77) not only obtained the velocity profile located at the LAA orifice, but also calculated the other hemodynamic descriptors such as time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI), endothelial cell activation potential (ECAP), relative residence time (RRT), and vortex structures in four different LAA models.

Based on CFD, some other studies applied more intuitive and quantitative methods in evaluating thrombus formation. Bosi et al. (78) used contrast dye to simulate blood stasis in the LAA and then evaluated the risk of thrombus formation in the LAA (Figure 4A). Additionally, Masci et al. (79, 80) and Fang et al. (81) adopted a fluid particle distribution simulation in analyzing thrombus formation risk (Figure 4B). Similarly, Sanatkhani et al. put forward a mean residence time of blood-borne particles (82) and asymptotic concentration remaining (83) inside LAA for evaluating thrombus formation. In a further study, Yan et al. (84) applied a numerical thrombus model presented by Menichini et al. (85) to predict thrombus formation risk. This thrombus model included not only the flow characteristics, but also the biomedical characteristics of platelets and coagulation.

In addition to studies assumed the boundary walls to be rigid to simulate the idealized AF conditions (77, 78, 86–88). Different ways were applied to realize the wall motion, several studies applied the immersed boundary analysis to fulfill the fluid-structure interactions, where the walls were moved with the impact from the fluid flows (89–91). Followingly, with the

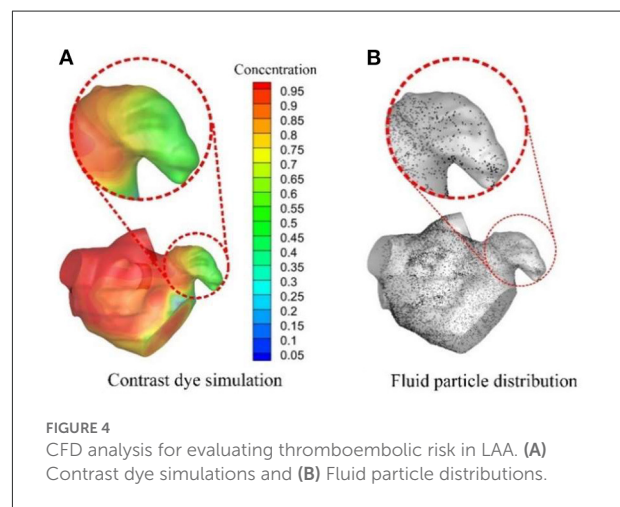


FIGURE 4  
CFD analysis for evaluating thromboembolic risk in LAA. (A)  
Contrast dye simulations and (B) Fluid particle distributions.

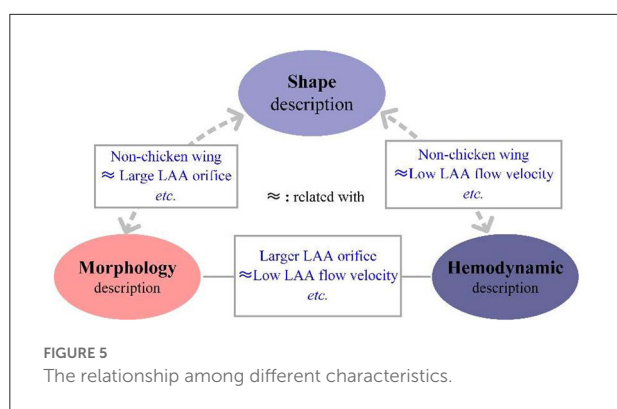
lack of knowledge in the material and mechanical properties for heart walls, several other studies used a four-dimensional displacement vector field directly generated from the medical images, and the displacement field was then applied to the LA structure to move the walls (80, 92–94). Meanwhile, with the lack in the dynamic medical images, several other studies also fulfill the wall motion with the displacements generated from literature (95, 96). To better compare the difference between the rigid walls and moving walls simulation, Duenas-Pamplona et al. (97) performed a comprehensive comparison between the two type simulations, and they found that the rigid wall model can lead to a poor approximation in some cases.

Although several hemodynamic parameters proposed by the CFD models rely on numerical simulations to evaluate thrombus formation risk, further research is required to validate their potential application in stroke risk evaluation in patients.

## Discussion

### Intra-group relationship

As illustrated in the former section, shape, morphology and hemodynamic parameters of the LAA are all validated to be highly associated with the risk of stroke. Several studies have pointed out the subjectivity of the shape classifications and the advantages of morphology and hemodynamic descriptors as objective classifiers, which have led to studies of relationships among these parameters. A number of these studies have established that the non-chicken wing type LAA is usually associated with a larger LAA orifice (32, 33) and higher lobe count (60). Studies on the relationships between shape and hemodynamic parameters revealed that peak LAA flow velocity exhibited significant difference among LAA shapes (72, 78) with a low LAA flow velocity associated with the non-chicken wing LAA type (98) and vice versa (33, 99). In addition, several other studies have identified the relationships between the hemodynamic and morphological parameters. In a multi-linear regression analysis, LAA morphology was found to be the significant determinant of LAA flow velocity (99). In other studies, flow velocity was shown to be negatively correlated with orifice size, and many studies found that a greater orifice size usually resulted in decreased flow velocity (32, 47, 53). CFD was also applied in studies relevant to morphology parameters in which LAA length, orifice area, tortuosity, etc. were studied for their relationship with hemodynamic parameters. Masci et al. (79) concluded that even qualitatively simple LAA morphology could lead to a high probability of thrombus formation. The summarized intra-group relationships are illustrated in the Figure 5.



The relationships among the shape, morphology and hemodynamic parameters highlight the importance of LAA in stroke evaluation, which motivates further studies to find and evaluate the key LAA features.

### Imaging modalities

As shown in the Tables 2, 4, 5, different imaging modalities were used for the evaluation of LAA shape, morphology and hemodynamic parameters, namely the TEE, cardiac CT and MRI modalities.

#### TEE

Compared with other imaging modalities, echocardiography can obtain the image at low cost and with high efficiency, so it is a widely used method in clinics. During the imaging procedure, the probe of TEE is close to the heart with high frequency, and therefore TEE can be used not only to assess the LAA morphology, but also to screen out the thrombus and spontaneous echo contrast (SEC) in the LA/LAA (100), and it is considered as the gold standard modality for detecting the LAA thrombi (100, 101). Additionally, TEE is superior in time resolution, and so it can obtain the LAA hemodynamic parameters (e.g.,: LAA flow profile) within the continuous cardiac cycles (102). Beside the above-mentioned applications, TEE is also applied in the guidance and evaluation during the LAA occlusion operation in most centers, for that TEE allows the real-time imaging, without ionizing radiation or contrast medium. Under this circumstance, TEE is considered as the conventional gold-standard imaging modality for LAA occlusion (103). However, TEE may not be applicable for some cases and it is considered to be a semi-invasive test that carries a small risk to the patient, although very rare, some complications can be life threatening (104, 105).

All in all, TEE is widely applied in the clinical practice related with LAA with its efficient, clear and low-cost imaging procedure. And this imaging modality with high time-resolution is applicable in the shape, morphology and especially the hemodynamic evaluations for the LAA.

#### Cardiac CT

Compared with TEE, cardiac CT offers superior spatial resolution. Its high-quality multi-planar and 3D reconstruction would do much help in the characterization of the LAA anatomy and accurate sizing (31). Therefore, CT has been considered as the gold standard for visualizing the LAA (106, 107), and it is widely applied in the evaluation of shape and morphology parameters. Meanwhile, some studies have also considered cardiac CT with a delayed imaging as a useful modality for the detection of LAA thrombi (108), and therefore it is routinely



performed to screen the LA/LAA thrombi before the AF ablation procedure in clinics. However, compared to TEE, CT imaging modality is limited in the time resolution, it cannot get the real-time visualization of the hemodynamics and LAA structure with the cardiac cycle. To strike the deficiency in the time resolution, it is worth mentioning a new CT-based method proposed by Morelos-Guzman (109), which can calculate the flow velocity with the scans. It is a novel method that can expand the CT application to the hemodynamic parameter evaluation.

In general, cardiac CT is limited in the time resolution, but its high spatial resolution contributes to a wide application in the shape and morphology evaluation for LAA.

## Cardiac MRI

Cardiac MRI is a noninvasive imaging modality for the structure and hemodynamic evaluation. It has excellent tissue characterization capacity but a lower spatial resolution when compared to the cardiac CT (110). Meanwhile, it is often used to delineate the anatomy of the left atrium but conferring no ionizing radiation to patients. Additionally, MRI can measure the LAA flow velocity and shows a good correlation with TEE (111), and MRI shows the good sensitivity and specificity in evaluating the LAA thrombi (110), thus, it has the potential to be a useful imaging modality for the detection of LAA thrombi. However, similar with CT, the real-time visualization of LAA is not permitted and it is not applicable for patients with pacemakers.

Generally speaking, though the MRI modality is noninvasive and can obtain the shape, morphology and hemodynamic parameters of the LAA, the present number of its application scenarios in LAA are small, most for the patients unsuitable for TEE and CT (110). Its potential capabilities in LAA related evaluation will be strongly stimulated with the high-resolution MRI in the future applications.

## Perspectives

Stroke prevention is the cornerstone of AF management and the anticoagulation decision is currently based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score scheme. This scheme first became part of guideline medical therapy as part of the 2012 European Society of Cardiology updated guidelines (112) as well as the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline for the management of patients with AF (113). Both the European and US guidelines specifically recommend risk stratification with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and delineate that anticoagulation may be considered for males with a score of 1 and females with a score of 2 (113, 114). However, CHA<sub>2</sub>DS<sub>2</sub>-VASc score does not take into account paroxysmal vs. non-paroxysmal AF as well as duration of paroxysmal AF episodes.

Even patients with low CHA<sub>2</sub>DS<sub>2</sub>-VASc score may suffer a stroke. The score also fails to take into consideration the structure (31, 115) and the hemodynamic characteristics for the LAA (37, 116, 117) in addition to other clinical markers (118–120). Thus, additional LAA features and clinical markers may further risk stratify stroke prevention for patients with AF. These two additional predictors may improve the sensitivity and specificity of LAA-related stroke risk.

Meanwhile, with the requirement of large data bank processing, several potential tools (or algorithms) could be utilized for the LAA related studies:

## Computer aided pre-processing

The pre-processing of image segmentation and reconstruction are the foundation for shape and morphology evaluation, while the manual segmentation and reconstruction for a patient-specific data is time-consuming. In this regard, some auto or semi-auto segmentation and reconstruction algorithms were put forward (121–124) to improve the efficiency. Besides the study for the efficient segmentation and reconstruction algorithms, there is also a need for the image-based measurement algorithms. With the measurement algorithms, not only the time of the measurement can be greatly reduced, but also the reproducibility will be improved. In this regard, studies that focus on the auto or semi-auto measurement, like Leventic et al.'s (125) work, should be encouraged in future studies. Clinical studies are also needed to validate the developed algorithms.

## CFD analysis

Blood stasis is one of the three conditions in Virchow's triad, the study of blood stasis requires a comprehensive characterization of the local hemodynamics, and the clinical measurement of echocardiography is currently the main tool to explore the blood flow patterns and velocity profiles. While the echocardiography cannot fully characterize the complexity of 4D blood flow patterns, new imaging techniques like 4D flow MRI or blood speckle tracking are promising but their capability to capture the low flow velocities related to thrombus formation is still unclear. As an alternative, CFD poses a great potential to thoroughly assess the hemodynamics inside the LA/LAA, and several studies have been performed to analyze the hemodynamic parameters in the LAA in relation to thrombogenic risk (72, 80–82, 84).

However, these CFD analysis uses various settings for boundary conditions, LA wall behavior, mesh resolution and etc., and different modeling strategies were used. It has to admit that the optimal strategy is difficult to identify due to the absence of joint benchmark studies with reliable ground truth (126). Meanwhile, there is no consensus on the most appropriate metrics for the quantification of the CFD result. Therefore, the

consensus for the appropriate metrics needed to be reached in the future studies. Based on the consensus, the modeling pipelines would be proposed for improving the capacity to process the increased number specific cases. Moreover, these CFD analysis should be validated with reliable ground truth to form the benchmark studies for optimal strategy in future work, and Duenas-Pamplona et al. (127) proposed an *in-vitro* flow equipment to validate their CFD models. Finally, it is worth to mention the work performed by Morales et al. (96), where they performed a deep learning surrogate models of CFD analysis for thrombus formation risk evaluation in the LAA.

## Conclusion

Stroke prevention remains a major goal in patients in AF. Significant evidence indicates that the assessment of LAA structural and hemodynamic parameters have meaningful implications for the stroke risk evaluation. Future work is needed to understand the role of LAA structural (shape and morphology) and hemodynamic parameters on stratification of stroke risk, especially in patients with low CHA<sub>2</sub>DS<sub>2</sub>-VASC scores. Computer-aided tools will become instrumental in the stroke evaluation with these LAA-related parameters.

## Author contributions

ZL and LZ designed and supervised the study. RF and YL reviewed the literature and wrote the original manuscript. JW

and ZW helped with the literature search. JA and CC modified the article. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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