Do left atrial appendage morphology and function help predict thromboembolic risk in atrial fibrillation??

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Abstract

Clinical scores (i.e. CHA_2DS_2-VASc) are the mainstay of thromboembolic risk management in nonvalvular atrial fibrillation (AF). Nonetheless, they bear some limitations to precisely define risk-benefit ratio of oral anticoagulation (OAC), both with vitamin K antagonists (VKA) and with novel direct oral anticoalants (DOAC), especially in patients with low-intermediate scores.

Cardiovascular imaging, allowing to directly visualize those patho-physiological alterations which may lead to the formation of intracardiac thrombi, offers itself as a unique tool helping to refine thromboembolic risk stratification. Many parameters have been tested, focusing primarily on functional and morphological variables of the left atrium (LA) and left atrial appendage (LAA). LA volume and LAA peak flow velocity have, since long-time, been associated with increased thromboembolic risk, while some new parameters, as LA fibrosis assessed by late-gadolinium enhanced (LGE) magnetic resonance imaging (MRI), LA and LAA strain and LAA morphology have more recently shown some ability in predicting embolic events in AF patients. Overall, however, these parameters have seen, to date, a scarce clinical implementation, especially due to inconsistency of validated cut-offs and/or strong clinical evidences driven by technical limitations, such as expensiveness of the technologies (i.e. MRI or computed tomography), invasiveness (i.e. transesophageal echocardiography) or limited reproducibility (i.e. LGE MRI). In conclusion, to date, cardiovascular imaging plays a limited role, however, validation and diffusion of the new techniques hereby systematically presented hold the potential to refine thromboembolic risk stratification in nonvalvular AF.

1 GLOSSARY
2

3D three-dimensional

AF atrial fibrillation

AP antero-posterior

AUC area under the curve

CT computed tomography

DOAC direct oral anticoagulant

LA left atrium

LAA left atrial appendage

LAA_{max} area maximal area of LAA

LAAv LAA peak flow velocities

LAVI left atrial volume index

LGE late gadolinium enhancement

LVEF *left ventricular ejection fraction*

MRI magnetic resonance imaging

OAC oral anticoagulation

SEC spontaneous echo-contrast

SR sinus rhythm

TDI tissue-Doppler imaging

TEE trans-esophageal echocardiography

TIA transient ischemic attack

TTE trans-thoracic echocardiography

VKA vitamin K antagonist

3
4

Introduction

Atrial fibrillation (AF) is a known risk factor for thromboembolic events, especially stroke and transient ischemic attack (TIA)[1]. Indeed, recent data suggest that eliminating the arrhythmia may achieve superior results, compared to simple rate control, in terms of survival[2], stroke incidence[3] and decline in cognitive functions[4]. However, when rhythm control strategy is not indicated or fails, oral anticoagulation (OAC), both with vitamin K antagonists (VKA) or novel direct oral anticoalants (DOAC), is , the only treatment to prevent thromboembolic events. For these reasons on a daily basis, physicians are required to perform an accurate assessment of the risk-benefit ratio for VKAs or each different DOACs[5] in patients with AF, balancing the implicit bleeding risk. Several clinical scores, such as the CHA_2DS_2-VASc score, have been proposed and more less reliably identify patients potentially benefiting from OAC[6], considering clinical variables that most strongly predict not only strokes/TIAs but also AF recurrences following transcatheter ablation[7] and electrical or pharmacological cardioversions[8]. Even if usually reliable, CHA_2DS_2-VASc score still remains inadequate in several clinical circumstances, particularly in patients at low/intermediate risk (i.e., CHA_2DS_2-VASc 1), for whom net clinical benefit of VKAs and even of DOACs is seriously counterbalanced by the bleeding risk[9,10,11,12]. Trying to overcome this gap in evidence and recommendations, a number of alternative parameters have been investigated, evaluating their value to guide clinical decision-making. Special focus, in fact, has been directed towards the left atrium (LA) and left atrial appendage (LAA), as they harbour the vast majority of thrombi forming during nonvalvular AF[13,14].

Aim of the present article is to methodologically review these alternative parameters and their application to nonvalvular AF, discussing if and which may aid the physician in everyday activity.

Spontaneous echocontrast and thrombi

Any discussion concerning LA and LAA and the risk of thromboembolic events in patients with AF has to deal first with the two strongest predictors of cardioembolic stroke, the presence of thrombi or spontaneous echo-contrast (SEC) in the LA or LAA[15]. The relationship between these findings and the risk of subsequent cardioembolic stroke is known since the dawning of echocardiography. Presence of thrombi represents the ultimate stage before the clinical event, even if their presence doesn't necessarily end in peripheral embolization[16,17]. SEC represents instead the most obvious visual representation of the blood stasis occurring during atrial dysrhythmias. Its presence is graded, depending from intensity, on a scale ranging from 0 to 4 (0, absence of SEC; 4, severe SEC with intense echodensity and very slow swirling patterns in the LAA and usually LA; 1, 2 and 3 mild, mild to moderate and moderate SEC, respectively, with intermediate features compared to 0 and 4)[18], and its relationship with subsequent embolic events has been consistently demonstrated[19,20].

Prevalence of thrombi is highly variable depending on clinical setting: in consecutive, anticoagulated patients undergoing AF ablation, they have been reported in 0.6%-3.6% of the patients[21,22], while higher figures have been described in different clinical settings (up to 5.9%-16.5%[23,24,25]). Prevalence of SEC, also varies widely: for example it ranged from 35% in the large cohort of anticoagulated patients undergoing AF ablation enrolled by Puwanant et al. (80% of patients with $CHADS_2$ score 0-1, 13% valvular AF, 9% with left ventricular ejection fraction [LVEF] < 35%)[21], to 8% in the study by Kleemann and colleagues (nonvalvular AF, $CHADS_2$ score 0-1).

Despite their strong and consistent ability to predict stroke and other cardioembolic events, these parameters, however, present, at least, two main limitations: first, they represent an advanced grade of prothrombotic state, the last step before a clinical event, so that they're rarely useful for patients with recent onset of AF or at low/intermediate clinical risk in whom a decision on OAC

prescription has to be made; second, these alterations are recorded by trans-esophageal echocardiography (TEE) and only rarely by trans-thoracic echocardiography (TTE).

For these reasons, other parameters have been assessed, often referring to thrombi or SEC as surrogate study end-points.

Morphological and structural assessment

Left atrium

During AF, LA enlargement is a common finding, as it comes both as a cause and as a consequence of the arrhythmia[26,27]. Since echocardiography became available, a correlation between LA dimensions as measured by antero-posterior (AP) diameter and thromboembolic risk was seeked, resulting in contradictory data[28,29,30,31]. In 1995, data from a prospective cohort of 1,371 men and 1,728 women (of whom approximately 1.8% with AF) included in the Framingham study reported a significant association between LA AP diameter as measured by M-mode echocardiography and the risk of stroke and death. The relative risk of stroke was 2.4 per 10 mm increment in men (95% CI, 1.6 to 3.7) and 1.4 in women (95% CI, 0.9 to 2.1), and, when controlling for prevalent and interim AF, it remained significant, even if with a weaker association (2.0 for men, 1.2 for women)[32]. More recently a study on 500 consecutive patients, admitted to hospital for stroke or TIA (15.6% with AF), confirmed LA AP diameter as an independent predictor for SEC/thrombi[33] and LA AP diameter, evaluated by multi-detector computed tomography (CT) in 67 patients admitted to hospital for stroke was found to be significantly increased as compared to AF controls without stroke[34]. On the other side, a meta-analysis performed on individual data from 1,066 patients enrolled in three large clinical trials from late 80s ï early 90s[35,36,37] showed that LA AP diameter did not predict stroke neither at univariate analysis nor when adjusted for clinical predictors[38]. Similar results arose from a prospective study assessing the prognostic implications of SEC[15] and by a post-hoc analysis[39] of the Atrial Fibrillation Follow-up Investigation of Rhythm Management

(AFFIRM) trial[40], a study in which 4,060 patients with recurrent AFwere randomised to rhythm control strategy vs. rate control strategy.

Given these data inconsistencies it becomes evident that other LA parameters need to be assessed in relationship to thromboembolic events. LA area related, in AF patients, to TEE high-risk features for thromboembolic events[41] and, when integrated with LV dysfunction, evidently enhanced the performance of $CHADS_2$ and CHA_2DS_2-VASc clinical scores to recognize patients at high thromboembolic risk[42]. However, also for LA area data are contradictory, as, for example, in the 1994 study by Fatkin and colleagues, no significant relationship arose between LA area and SEC or LA thrombi[18].

LA volume assessed by transthoracic echocardiography has been more widely tested, and, especially when indexed for body surfaced (left atrial volume index, LAVI), it showed more consistent interaction with clinical events. LA volume, both total and indexed for body surface, significantly related to LAA thrombi at TEE examination[41,43,44]. In two distinct studies from populations based in Olmsted County, increased LAVI (Ó32 ml/mq) related to cardiovascular adverse events: in the first report, enrolling 1,160 elderly patients (75.5 years) in sinus rhythm (SR), the predictive value of LAVI was validated in a multivariate model[45], while in the second study, which involved 46 young adults (< 60 years) with lone AF followed for a median of 27 years, the association was confirmed only in a univariate setting, due to the low number of index events[46].

Although suggestive LA enlargement is strictly dependent on its underlying cause. Indeed, Ayirala and colleagues reported that the predictive value of LAVI for LAA thrombi at TEE was stronger when LA enlargement was associated with a reduction in LVEF[47], while, in an Olmsted County-based cohort of 2,042 patients with more than 45 years (3% with a history of AF), Pritchett et al. found that the relationship between LAVI and mortality did not persist when controlling for diastolic dysfunction[48], a possible predictor *per se* of embolic events in AF[49]. Despite the

aforementioned data, however, to date, no conclusive evidence supports the use of LA enlargement markers to predict embolic events in AF.

Eventually, progresses in magnetic resonance imaging (MRI), particularly with the development of late-gadolinium enhancement (LGE) imaging, have been employed to assess structural changes of atrial myocardium. Particularly, a dedicated protocol, first developed by a research group based in Salt Lake City, allowed to semi-quantify LA fibrosis and to classify it in four classes based on its extension (Utah classes I-IV)[50]. LA LGE extent assessed by this method related to AF recurrence after ablation[51] and, more interestingly, to the presence of thrombi detected by TEE[52] and with a medical history of previous stroke[53] **(figure 1)**. Despite its brilliant promises, this technique has embraced to date little diffusion, probably due to the high costs of MRI and the absence of prospective validation[54]. This type of analysis is moreover penalised by the development of different algorithms in different centres, a substantial limit to the standardisation of the results. For this reason, a public challenge was launched trying to determine the better performing algorithm and, even if no definite results were reached, this attempt may be a foundation stone in the diffusion and widespread adoption of this evaluation[55].

Left atrial appendage

Concerning LAA dimensions, interpretation of existing literature is, unfortunately, even more inconclusive. A paucity of data has been published and, since LAA measurements are far less standardized than LA, generalizations of results and comparisons are indeed challenging.

Usually, LAA abnormalities are related to LA alterations[56,57,58], even if some peculiar traits can be found, making a dedicated analysis of LAA worth a chance. Indeed, LAA enlargement doesnôt always coincide with increased LA size (and viceversa)[59], and, at least in patients in SR, LAA peak

flow velocity doesnôt relate to any echocardiographic parameter connected with LA except than Aô measured at tissue-Doppler imaging (TDI)[60].

Pollick and colleagues reported that a bigger maximal LAA (LAA_{max}) area (and not LA AP diameter) as measured by TEE related to the presence of thrombi and/or SEC in 19 non-anticoagulated patients with valvular and nonvalvular AF[59], and, while another study confirmed this finding[61], other laboratories failed to consistently relate LAA area to an increased risk of stroke[62] or thromboembolic events[63,64].

LAA size analysis by CT or MRI also generally did not provide strong evidences in favour of a role of LAA volume. Two studies reported a direct correlation between increased LAA volumes and previous stroke, even after controlling for possible confounding factors, with an ideal cut-off for significant risk increase at 34 ml^3 [65], but the majority of experiences did not confirm this relationship[66,67,68,69].

More recently, LAA morphology, by CT or MRI, has been proposed to be described in four different morphologies (Cactus, Chicken Wing, Windsock and Cauliflower) based on the characteristics of the main and secondary lobes[70]. By this categorization LAA morphology related to thromboembolic events: it was first demonstrated that, in patients undergoing AF transcatheter ablation, Chicken Wing, the most frequent LAA morphology, independently related to the absence of previous stroke/TIA[69], and that the prevalence of silent cerebral ischemic lesions increased with growing complexity of LAA morphology, from Cactus, the more simple, through Chicken Wing, Windsock and Cauliflower, the more complex[71](**figure 2**). Once again, further studies brought controversial results: two experiences, indeed, confirmed the existence of a relationship between LAA morphology and cerebrovascular events, even if with some slight differences (Kimura and colleagues identified Cauliflower as the high-risk morphology[72], Kosiuk et al. Chicken Wing[73]), while other studies failed to report any correlation between LAA morphology and previous stroke[74]

and incident stroke or TIA after AF ablation[67]. Concerning LAA morphology the main limitations seems to relate to the reproducibility of the classification by CT or MRI[74]. More interestingly, however, a recent study by Petersen and colleagues, assessed LAA morphology by three-dimensional (3D) TEE, which resulted non-inferior to CT and MRI *[data in press]*, and found a correlation, corroborated by multivariate linear regression analysis, between non-Chicken Wing LAA morphologies and reduced LAA flow velocities[75]. These latter studies are particularly promising, as validation of LAA morphology description by echocardiographic techniques may enhance the routine clinical implementation of this analysis, helping to refine thromboembolic risk stratification.

Functional assessment

Left atrium

LA and LAA function impairment that lead to blood stasis are, indeed, at the base of thrombus formation[76].

As for LA size, an impaired LA function has been associated with an unfavourable outcome in non-AF patients: a reduced LA function index (a multiparametric index incorporating LA size, LA emptying fraction and LV outflow velocity-time integral) significantly related to incident stroke or TIA at follow up in 893 patients without a known history of AF not on OAC[77], while a reduced LA longitudinal strain, as assessed by speckle tracking, was able to predict development of adverse events including, among others, AF, stroke or TIA and cardiovascular death in 312 patients in SR[78].

More in details, within AF patients, $CHADS_2$ and CHA_2DS_2-VASc scores significantly related to an increased LAVI and a reduced LA emptying fraction (LAEF) in a sub-analysis of the ENGAGE AF-TIMI 48 study. LAVI and LAEF also inversely related to each other, even if only LAVI was confirmed as an independent predictor after adjusting for confounding factors[79]. An association between LA function and $CHADS_2$ and CHA_2DS_2-VASc scores was also confirmed when LAEF

was assessed by 3D echocardiography[80].

In addition, since its introduction and widespread diffusion, strain analysis by speckle tracking has been increasingly applied also in this field, reporting very promising results. Even if a prospective validation has yet to been provided, a reduced global longitudinal strain proved to relate to the extent of fibrosis at MRI[81] and not only to an increased $CHADS_2$ or CHA_2DS_2-VASc score[80,82,83], but to an improved $CHADS_2$ and CHA_2DS_2-VAScscores ability to identify patients with recent acute embolic events and to predict mortality at follow up[83,84]. Interestingly, peak negative and positive atrial strain were able to discriminate patients with previous stroke or TIA in an AF-cohort with low intermediate $CHADS_2$ score (Ò1, of whom 30% with CHA_2DS_2-VAScÒ1)[85].

Left atrial appendage

LAA function has been thoroughly investigated since a correlation between reduced LAA peak flow velocities (LAAv) and increased thromboembolic risk was demonstrated. LAAv tend to reduce during the course of AF and more decreased values strongly related to the presence of SEC[18], and of LAA thrombi[33] and predicted cardioembolic events in a sub-analysis of the SPAF-III study[86]. Despite overall consistent results, this parameter has embraced a very limited clinical implementation, partly due to the variable and widely ranging cut-offs reported (in the 3 aforementioned studies, LAAv relating to adverse events were < 35 cm/s, < 55 cm/s and < 20 cm/s, respectively [18,33,86]), and, partly, because LAAv measurement require TEE.

To overcome this latter limitation, surrogate markers of reduced LAAv have been investigated. As TEE studies reported a correlation between reduced LAA wall acceleration as measured by TDI and increased thromboembolic risk[87,88], an evaluation of those TDI parameters by TTE has been attempted, with garbed success. With a good feasibility (> 90%), LAA wall velocity, evaluated mainly by LAA tip acceleration on a short-axis view, significantly related to reduced LAAv, presence of SEC or thrombi and previous stroke[89,90,91](**figure 3**). Moreover, these results were prospectively validate in a cohort of 179 patients with previous thromboembolic stroke related to

AF, in whom an LAA wall velocity < 8.7 cm/s independently predicted recurrent stroke or cerebrovascular death[92]. TDI was also used to assess septal and lateral mitral annular aô wave velocities, which strongly related to reduced LAAv and SEC[60,93].

Eventually a similar proceeding than with TDI was attempted with LAA strain, even if data are, to date, scarce. In fact, LAA strain predicted the presence of LAA thrombi[25], and feasibility of the evaluation by TTE was confirmed in a series of 82 patients, in whom negative peak strain rate and time-to-peak positive strain independently related to the presence of LAA thrombi or sludge with an AUC of 0.89[94].

Finally, LAA emptying determined by velocity encoded-MRI had a good correlation with LAAv as measured by Pulsed Doppler at TEE, opening the doors of LAA functional evaluation to a new technique[95].

Conclusion

LAVI and functional parameters of both LA and LAA consistently predicted stroke in patients with AF, while promising results came from the application of more recent techniques such as strain and LAA morphology assessment.

Clinical application of these parameters, however, is to date limited, mostly due to lack of large-scale prospective validation and consequent inability to suggest significant cut-offs.

In our opinion, to date, parameters, such as severely reduced LAAv or markedly enlarged LA, may aid, in a case-by-case approach, as complementary tools to guide OAC prescription in controversial and ambiguous cases. In addition, LAA and LA imaging, particularly with the development of technologies such as TDI or speckle tracking, bears a promising potential.

Conflicts of interest: no conflicts of interest pertaining the present work have been reported.

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FIGURE LEGENDS

Figure 1. Late-gadolinium enhanced (LGE) magnetic resonance images representing fibrotic areas of left atrium as seen in antero-posterior view. The four images show different stages of increasing LGE burden (Utah classes, divided by quartiles): stage I (**A**: 2.7% enhancement), Stage II (**B:** 10.2% enhancement), Stage III (**C:** 19.4%), and Stage IV (**D:** 38.4% enhancement). Left atrial enhancement is represented as **green** areas to enhance contrast with non-enhanced tissue. Higher stages have been associated with LA appendage thrombi and history of previous stroke (see text for details). Reproduced with permission from Daccarett M et al. J Am Coll Cardiol 2011;57:831-8.

Figure 2. Left atrial appendage morphologies as represented in order of increasing complexity, which has been reported to relate to a growing burden of silent cerebral ischemia: from the simpler, Cactus (A, a dominant central lobe with small chambers extending in all directions), to the more complex, Cauliflower (D, complex internal characteristics with lack of a dominant lobe). Intermediate forms Chicken Wing (B, an obvious bend in the proximal or middle part of the dominant lobe) and Wind Sock (C, a dominant lobe plus secondary or even tertiary lobes arising from the dominant lobe) are as well represented. Reproduced with permission from Anselmino M et al. Heart Rhythm 2014;11(1):2-7.

Figure 3. Left atrial appendage wall velocity (TTE-LAWV) as measured by trans-thoracic tissue Doppler imagin (DTI). Placing sample volume at left atrial appendage (LAA) tip from the parasternal short-axis view in diastole, DTI velocities were obtained and the peak wall velocity of downward atrial waveform within each RR interval was averaged. Reduced TTE-LAWV related to history of previous stroke and predicted recurrent cerebrovascular events at follow up in those same patients[92]. *AoV,* Aortic valve. Reproduced with permission from Tamura H et al. J Am Soc

Figure 1.

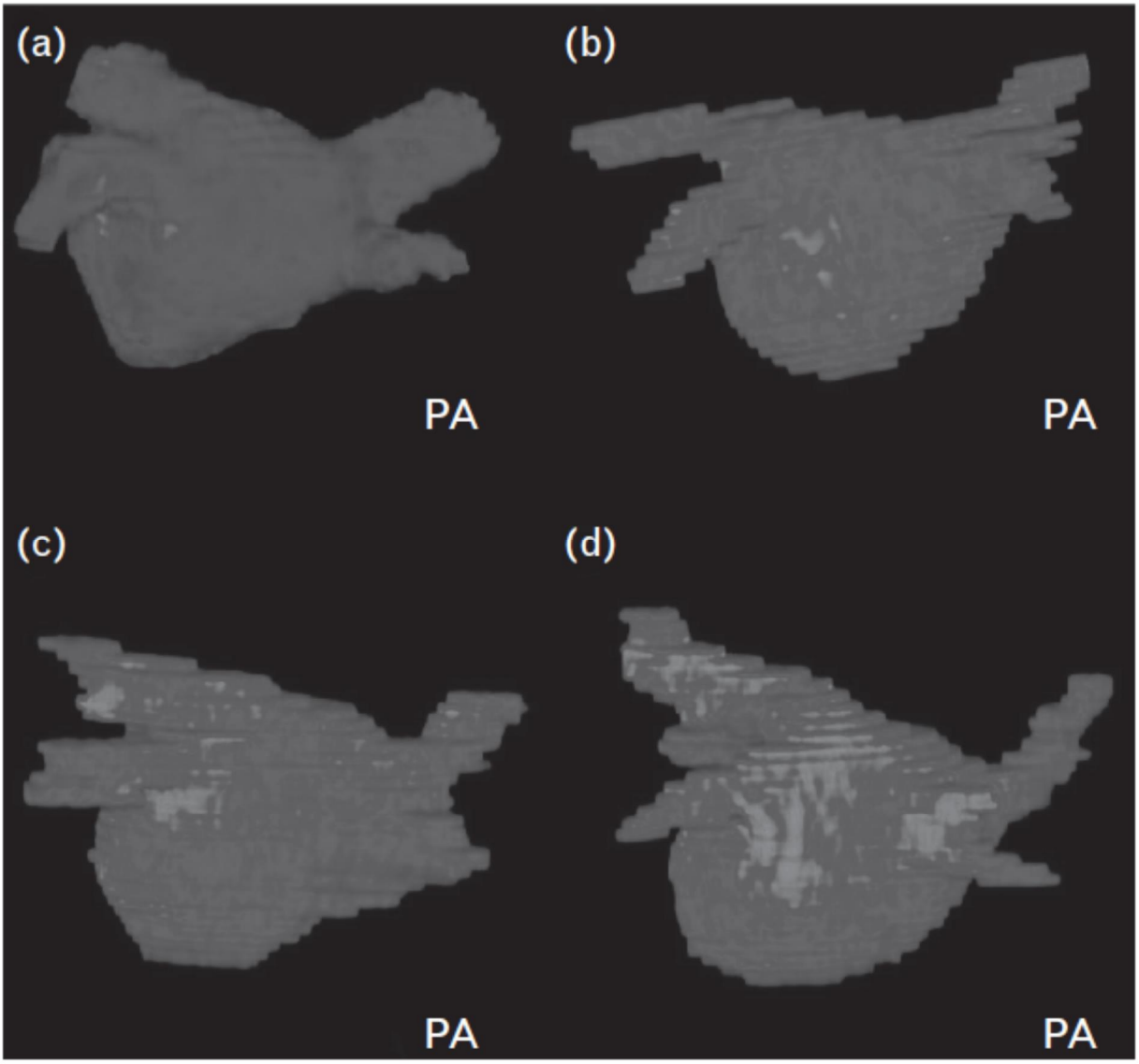

Figure 2.

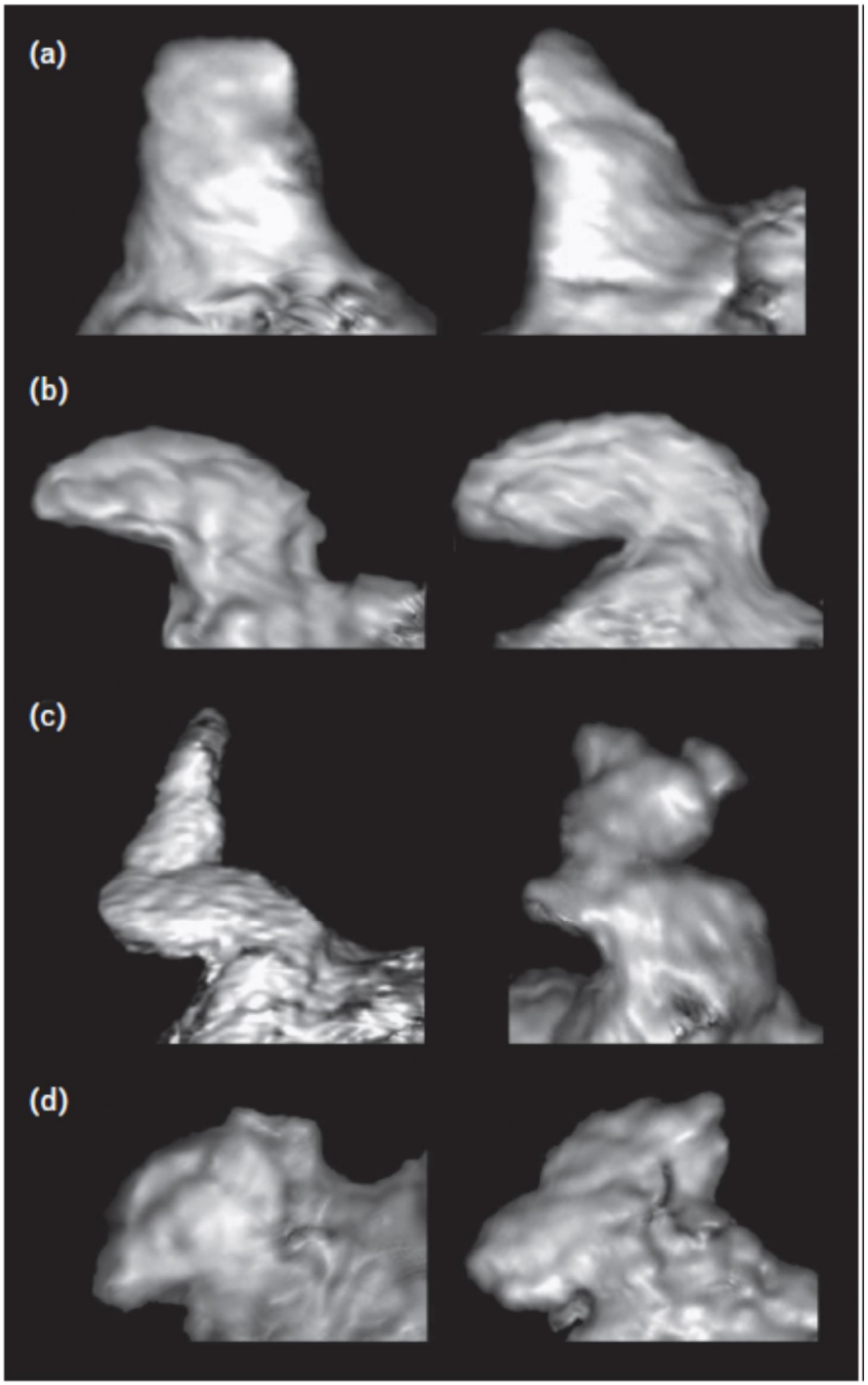

Figure 3.

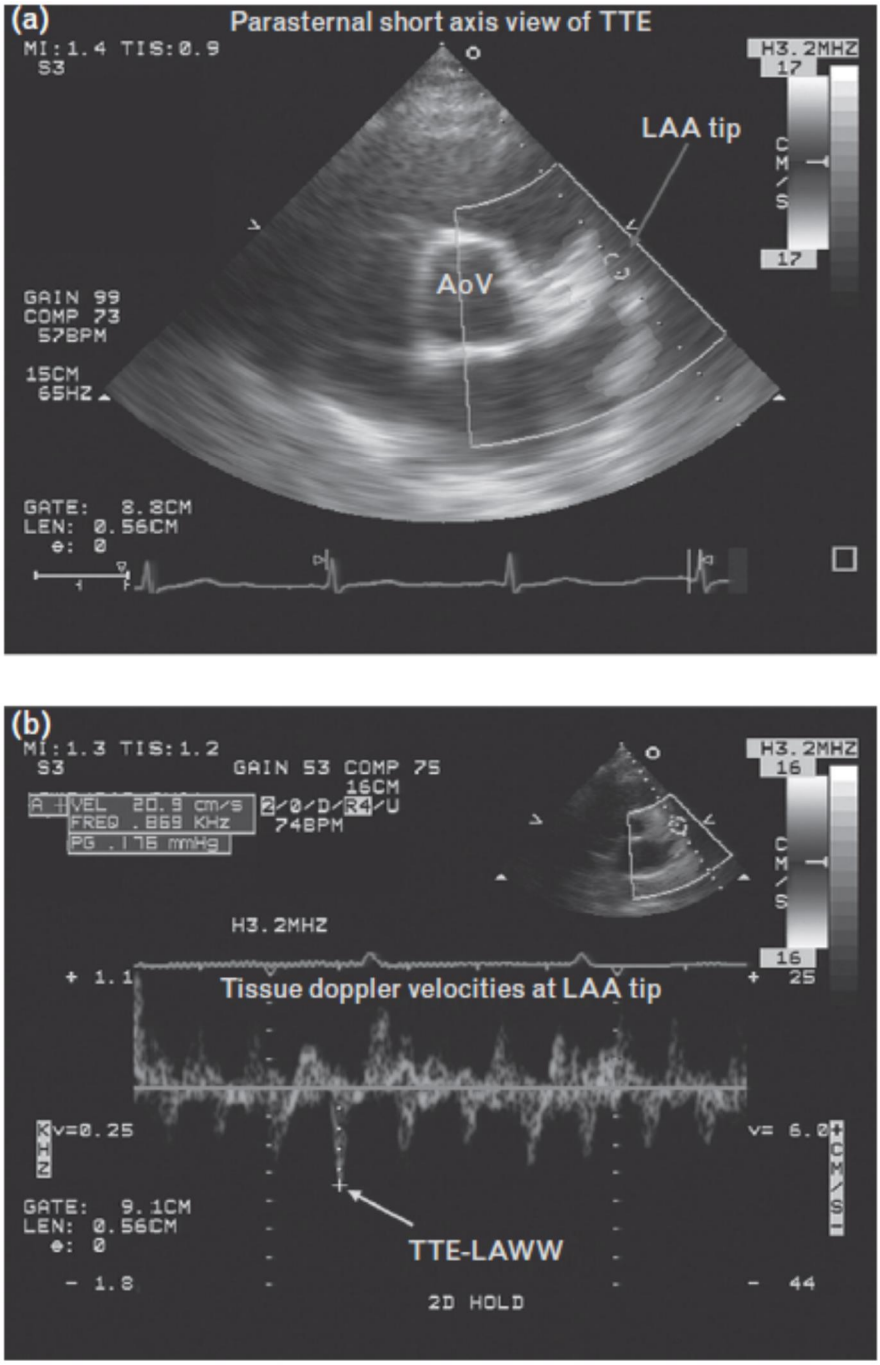
(a)
Parasternal short axis view of TTE
MI:1.4 TIS:0.9
S3
H3.2MHZ
17
LAA tip
AoV
GAIN 99
COMP 73
57BPM
15CM
65HZ
GATE: 8.8CM
LEN: 0.56CM
e: 0
17
(b)
MI:1.3 TIS:1.2
S3
GAIN 53 COMP 75
16CM
74BPM
H3.2MHZ
16
H3.2MHZ
Tissue doppler velocities at LAA tip
+ 1.1
+ 25
v=0.25
v= 6.0
GATE: 9.1CM
LEN: 0.56CM
e: 0
TTE-LAWW
- 1.8
- 44
2D HOLD

Table 1. Left atrial and appendage parameters tested for thromboembolic risk prediction in AF patients.

Parameter	No. of patients	Strength	Reproducibility	End-point	Feasibility	Technical limitations	Stroke prediction discordance
Left atrium AP diameter	+++	+	+++	+++	+++		Documented for nonatrial fibrillation patients; controversial for atrial fibrillation patients
Left atrium volume	+++	++	++	+++	+++		Documented for nonatrial fibrillation patients; controversial for atrial fibrillation patients
LAA size	–	+/–	–	+	+/–	Wide variability of methods and results	
LAA morphology	+	+	+/–	+	+/–	Low reproducibility of morphological stratification; MRI or angio-CT required (except one study performed by three-dimensional TEE)	
Left atrium LGE	+	+++	?	+	+/–	Lack of standardized algorithm; gadolinium enhanced-MRI required	One single study
Left atrium strain	+	+++	++	+	+++	Speckle tracking technique required	Only surrogate end points
LAAv	++	+++	+++	+++	+	TEE required	
LAA strain	+/–	++	++	++	+++	Not computable in 100% of the cases (TTE with TDI in >90% of cases)	Limited data available