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

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1 **Abstract**

2 Clinical scores (i.e. CHA₂DS₂-VASc) are the mainstay of thromboembolic risk management in
3 nonvalvular atrial fibrillation (AF). Nonetheless, they bear some limitations to precisely define risk-
4 benefit ratio of oral anticoagulation (OAC), both with vitamin K antagonists (VKA) and with novel
5 direct oral anticoagulants (DOAC), especially in patients with low-intermediate scores.

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

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1 GLOSSARY

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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

LAA_v 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

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1 **Introduction**

2 Atrial fibrillation (AF) is a known risk factor for thromboembolic events, especially stroke and
3 transient ischemic attack (TIA)¹. Indeed, recent data suggest that eliminating the arrhythmia may
4 achieve superior results, compared to simple rate control, in terms of survival², stroke incidence³
5 and decline in cognitive functions⁴. However, when rhythm control strategy is not indicated or fails,
6 oral anticoagulation (OAC), both with vitamin K antagonists (VKA) or novel direct oral
7 anticoagulants (DOAC), is , the only treatment to prevent thromboembolic events. For these reasons
8 on a daily basis, physicians are required to perform an accurate assessment of the risk-benefit ratio
9 for VKAs or each different DOACs⁵ in patients with AF, balancing the implicit bleeding risk.
10 Several clinical scores, such as the CHA₂DS₂-VASc score, have been proposed and more less
11 reliably identify patients potentially benefiting from OAC⁶, considering clinical variables that most
12 strongly predict not only strokes/TIAs but also AF recurrences following transcatheter ablation⁷ and
13 electrical or pharmacological cardioversions⁸. Even if usually reliable, CHA₂DS₂-VASc score still
14 remains inadequate in several clinical circumstances, particularly in patients at low/intermediate
15 risk (i.e., CHA₂DS₂-VASc 1), for whom net clinical benefit of VKAs and even of DOACs is
16 seriously counterbalanced by the bleeding risk^{9,10,11,12}. Trying to overcome this gap in evidence and
17 recommendations, a number of alternative parameters have been investigated, evaluating their value
18 to guide clinical decision-making. Special focus, in fact, has been directed towards the left atrium
19 (LA) and left atrial appendage (LAA), as they harbour the vast majority of thrombi forming during
20 nonvalvular AF^{13,14}.

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

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1 **Spontaneous echocontrast and thrombi**

2 Any discussion concerning LA and LAA and the risk of thromboembolic events in patients with AF
3 has to deal first with the two strongest predictors of cardioembolic stroke, the presence of thrombi
4 or spontaneous echo-contrast (SEC) in the LA or LAA¹⁵. The relationship between these findings
5 and the risk of subsequent cardioembolic stroke is known since the dawning of echocardiography.
6 Presence of thrombi represents the ultimate stage before the clinical event, even if their presence
7 doesn't necessarily end in peripheral embolization^{16,17}. SEC represents instead the most obvious
8 visual representation of the blood stasis occurring during atrial dysrhythmias. Its presence is graded,
9 depending from intensity, on a scale ranging from 0 to 4 (0, absence of SEC; 4, severe SEC with
10 intense echodensity and very slow swirling patterns in the LAA and usually LA; 1, 2 and 3 mild,
11 mild to moderate and moderate SEC, respectively, with intermediate features compared to 0 and
12 4)¹⁸, and its relationship with subsequent embolic events has been consistently demonstrated^{19,20}.

13 Prevalence of thrombi is highly variable depending on clinical setting: in consecutive,
14 anticoagulated patients undergoing AF ablation, they have been reported in 0.6%-3.6% of the
15 patients^{21,22}, while higher figures have been described in different clinical settings (up to 5.9%-
16 16.5%^{23,24,25}). Prevalence of SEC, also varies widely: for example it ranged from 35% in the large
17 cohort of anticoagulated patients undergoing AF ablation enrolled by Puwanant et al. (80% of
18 patients with CHADS₂ score 0-1, 13% valvular AF, 9% with left ventricular ejection fraction
19 [LVEF] < 35%)²¹, to 8% in the study by Kleemann and colleagues (nonvalvular AF, CHADS₂ score
20 0-1).

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

1 prescription has to be made; second, these alterations are recorded by trans-esophageal
2 echocardiography (TEE) and only rarely by trans-thoracic echocardiography (TTE).
3 For these reasons, other parameters have been assessed, often referring to thrombi or SEC as
4 surrogate study end-points.

5

6 **Morphological and structural assessment**

7 *Left atrium*

8 During AF, LA enlargement is a common finding, as it comes both as a cause and as a consequence
9 of the arrhythmia^{26,27}. Since echocardiography became available, a correlation between LA
10 dimensions as measured by antero-posterior (AP) diameter and thromboembolic risk was sought,
11 resulting in contradictory data^{28,29,30,31}. In 1995, data from a prospective cohort of 1,371 men and
12 1,728 women (of whom approximately 1.8% with AF) included in the Framingham study reported a
13 significant association between LA AP diameter as measured by M-mode echocardiography and the
14 risk of stroke and death. The relative risk of stroke was 2.4 per 10 mm increment in men (95% CI,
15 1.6 to 3.7) and 1.4 in women (95% CI, 0.9 to 2.1), and, when controlling for prevalent and interim
16 AF, it remained significant, even if with a weaker association (2.0 for men, 1.2 for women)³². More
17 recently a study on 500 consecutive patients, admitted to hospital for stroke or TIA (15.6% with
18 AF), confirmed LA AP diameter as an independent predictor for SEC/thrombi³³ and LA AP
19 diameter, evaluated by multi-detector computed tomography (CT) in 67 patients admitted to
20 hospital for stroke was found to be significantly increased as compared to AF controls without
21 stroke³⁴. On the other side, a meta-analysis performed on individual data from 1,066 patients
22 enrolled in three large clinical trials from late 80s ó early 90s^{35,36,37} showed that LA AP diameter
23 did not predict stroke neither at univariate analysis nor when adjusted for clinical predictors³⁸.
24 Similar results arose from a prospective study assessing the prognostic implications of SEC¹⁵ and
25 by a post-hoc analysis³⁹ of the Atrial Fibrillation Follow-up Investigation of Rhythm Management

1 (AFFIRM) trial⁴⁰, a study in which 4,060 patients with recurrent AF were randomised to rhythm
2 control strategy vs. rate control strategy.

3 Given these data inconsistencies it becomes evident that other LA parameters need to be assessed in
4 relationship to thromboembolic events. LA area related, in AF patients, to TEE high-risk features
5 for thromboembolic events⁴¹ and, when integrated with LV dysfunction, evidently enhanced the
6 performance of CHADS₂ and CHA₂DS₂-VASc clinical scores to recognize patients at high
7 thromboembolic risk⁴². However, also for LA area data are contradictory, as, for example, in the
8 1994 study by Fatkin and colleagues, no significant relationship arose between LA area and SEC or
9 LA thrombi¹⁸.

10 LA volume assessed by transthoracic echocardiography has been more widely tested, and,
11 especially when indexed for body surface (left atrial volume index, LAVI), it showed more
12 consistent interaction with clinical events. LA volume, both total and indexed for body surface,
13 significantly related to LAA thrombi at TEE examination^{41,43,44}. In two distinct studies from
14 populations based in Olmsted County, increased LAVI ($\times 32$ ml/mq) related to cardiovascular
15 adverse events: in the first report, enrolling 1,160 elderly patients (75.5 years) in sinus rhythm (SR),
16 the predictive value of LAVI was validated in a multivariate model⁴⁵, while in the second study,
17 which involved 46 young adults (< 60 years) with lone AF followed for a median of 27 years, the
18 association was confirmed only in a univariate setting, due to the low number of index events⁴⁶.

19 Although suggestive LA enlargement is strictly dependent on its underlying cause. Indeed, Ayirala
20 and colleagues reported that the predictive value of LAVI for LAA thrombi at TEE was stronger
21 when LA enlargement was associated with a reduction in LVEF⁴⁷, while, in an Olmsted County-
22 based cohort of 2,042 patients with more than 45 years (3% with a history of AF), Pritchett et al.
23 found that the relationship between LAVI and mortality did not persist when controlling for
24 diastolic dysfunction⁴⁸, a possible predictor *per se* of embolic events in AF⁴⁹. Despite the

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

3 Eventually, progresses in magnetic resonance imaging (MRI), particularly with the development of
4 late-gadolinium enhancement (LGE) imaging, have been employed to assess structural changes of
5 atrial myocardium. Particularly, a dedicated protocol, first developed by a research group based in
6 Salt Lake City, allowed to semi-quantify LA fibrosis and to classify it in four classes based on its
7 extension (Utah classes I-IV)⁵⁰. LA LGE extent assessed by this method related to AF recurrence
8 after ablation⁵¹ and, more interestingly, to the presence of thrombi detected by TEE⁵² and with a
9 medical history of previous stroke⁵³ (**figure 1**). Despite its brilliant promises, this technique has
10 embraced to date little diffusion, probably due to the high costs of MRI and the absence of
11 prospective validation⁵⁴. This type of analysis is moreover penalised by the development of
12 different algorithms in different centres, a substantial limit to the standardisation of the results. For
13 this reason, a public challenge was launched trying to determine the better performing algorithm
14 and, even if no definite results were reached, this attempt may be a foundation stone in the diffusion
15 and widespread adoption of this evaluation⁵⁵.

16

17 *Left atrial appendage*

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

21 Usually, LAA abnormalities are related to LA alterations^{56,57,58}, even if some peculiar traits can be
22 found, making a dedicated analysis of LAA worth a chance. Indeed, LAA enlargement doesn't
23 always coincide with increased LA size (and viceversa)⁵⁹, and, at least in patients in SR, LAA peak

1 flow velocity doesn't relate to any echocardiographic parameter connected with LA except than A₀
2 measured at tissue-Doppler imaging (TDI)⁶⁰.

3 Pollick and colleagues reported that a bigger maximal LAA (LAA_{max}) area (and not LA AP
4 diameter) as measured by TEE related to the presence of thrombi and/or SEC in 19 non-
5 anticoagulated patients with valvular and nonvalvular AF⁵⁹, and, while another study confirmed this
6 finding⁶¹, other laboratories failed to consistently relate LAA area to an increased risk of stroke⁶² or
7 thromboembolic events^{63,64}.

8 LAA size analysis by CT or MRI also generally did not provide strong evidences in favour of a role
9 of LAA volume. Two studies reported a direct correlation between increased LAA volumes and
10 previous stroke, even after controlling for possible confounding factors, with an ideal cut-off for
11 significant risk increase at 34 ml³ ⁶⁵, but the majority of experiences did not confirm this
12 relationship^{66,67,68,69}.

13 More recently, LAA morphology, by CT or MRI, has been proposed to be described in four
14 different morphologies (Cactus, Chicken Wing, Windsock and Cauliflower) based on the
15 characteristics of the main and secondary lobes⁷⁰. By this categorization LAA morphology related
16 to thromboembolic events: it was first demonstrated that, in patients undergoing AF transcatheter
17 ablation, Chicken Wing, the most frequent LAA morphology, independently related to the absence
18 of previous stroke/TIA⁶⁹, and that the prevalence of silent cerebral ischemic lesions increased with
19 growing complexity of LAA morphology, from Cactus, the more simple, through Chicken Wing,
20 Windsock and Cauliflower, the more complex⁷¹ (**figure 2**). Once again, further studies brought
21 controversial results: two experiences, indeed, confirmed the existence of a relationship between
22 LAA morphology and cerebrovascular events, even if with some slight differences (Kimura and
23 colleagues identified Cauliflower as the high-risk morphology⁷², Kosiuk et al. Chicken Wing⁷³),
24 while other studies failed to report any correlation between LAA morphology and previous stroke⁷⁴

1 and incident stroke or TIA after AF ablation⁶⁷. Concerning LAA morphology the main limitations
2 seems to relate to the reproducibility of the classification by CT or MRI⁷⁴. More interestingly,
3 however, a recent study by Petersen and colleagues, assessed LAA morphology by three-
4 dimensional (3D) TEE, which resulted non-inferior to CT and MRI [*data in press*], and found a
5 correlation, corroborated by multivariate linear regression analysis, between non-Chicken Wing
6 LAA morphologies and reduced LAA flow velocities⁷⁵. These latter studies are particularly
7 promising, as validation of LAA morphology description by echocardiographic techniques may
8 enhance the routine clinical implementation of this analysis, helping to refine thromboembolic risk
9 stratification.

10

11 **Functional assessment**

12 *Left atrium*

13 LA and LAA function impairment that lead to blood stasis are, indeed, at the base of thrombus
14 formation⁷⁶.

15 As for LA size, an impaired LA function has been associated with an unfavourable outcome in non-
16 AF patients: a reduced LA function index (a multiparametric index incorporating LA size, LA
17 emptying fraction and LV outflow velocity-time integral) significantly related to incident stroke or
18 TIA at follow up in 893 patients without a known history of AF not on OAC⁷⁷, while a reduced LA
19 longitudinal strain, as assessed by speckle tracking, was able to predict development of adverse
20 events including, among others, AF, stroke or TIA and cardiovascular death in 312 patients in SR⁷⁸.
21 More in details, within AF patients, CHADS₂ and CHA₂DS₂-VASc scores significantly related to
22 an increased LAVI and a reduced LA emptying fraction (LAEF) in a sub-analysis of the ENGAGE
23 AF-TIMI 48 study. LAVI and LAEF also inversely related to each other, even if only LAVI was
24 confirmed as an independent predictor after adjusting for confounding factors⁷⁹. An association
25 between LA function and CHADS₂ and CHA₂DS₂-VASc scores was also confirmed when LAEF

1 was assessed by 3D echocardiography⁸⁰.

2 In addition, since its introduction and widespread diffusion, strain analysis by speckle tracking has
3 been increasingly applied also in this field, reporting very promising results. Even if a prospective
4 validation has yet to be provided, a reduced global longitudinal strain proved to relate to the
5 extent of fibrosis at MRI⁸¹ and not only to an increased CHADS₂ or CHA₂DS₂-VASc score^{80,82,83},
6 but to an improved CHADS₂ and CHA₂DS₂-VAScscores ability to identify patients with recent
7 acute embolic events and to predict mortality at follow up^{83,84}. Interestingly, peak negative and
8 positive atrial strain were able to discriminate patients with previous stroke or TIA in an AF-cohort
9 with low intermediate CHADS₂ score (Ö1, of whom 30% with CHA₂DS₂-VAScÖ1)⁸⁵.

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11 *Left atrial appendage*

12 LAA function has been thoroughly investigated since a correlation between reduced LAA peak
13 flow velocities (LAAv) and increased thromboembolic risk was demonstrated. LAAv tend to reduce
14 during the course of AF and more decreased values strongly related to the presence of SEC¹⁸, and
15 of LAA thrombi³³ and predicted cardioembolic events in a sub-analysis of the SPAF-III study⁸⁶.

16 Despite overall consistent results, this parameter has embraced a very limited clinical
17 implementation, partly due to the variable and widely ranging cut-offs reported (in the 3
18 aforementioned studies, LAAv relating to adverse events were < 35 cm/s, < 55 cm/s and < 20 cm/s,
19 respectively^{18,33,86}), and, partly, because LAAv measurement require TEE.

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

1 AF, in whom an LAA wall velocity < 8.7 cm/s independently predicted recurrent stroke or
2 cerebrovascular death⁹². TDI was also used to assess septal and lateral mitral annular a \emptyset wave
3 velocities, which strongly related to reduced LAAv and SEC^{60,93}.
4 Eventually a similar proceeding than with TDI was attempted with LAA strain, even if data are, to
5 date, scarce. In fact, LAA strain predicted the presence of LAA thrombi²⁵, and feasibility of the
6 evaluation by TTE was confirmed in a series of 82 patients, in whom negative peak strain rate and
7 time-to-peak positive strain independently related to the presence of LAA thrombi or sludge with an
8 AUC of 0.89⁹⁴.
9 Finally, LAA emptying determined by velocity encoded-MRI had a good correlation with LAAv as
10 measured by Pulsed Doppler at TEE, opening the doors of LAA functional evaluation to a new
11 technique⁹⁵.

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15 **Conclusion**

16 LAVI and functional parameters of both LA and LAA consistently predicted stroke in patients with
17 AF, while promising results came from the application of more recent techniques such as strain and
18 LAA morphology assessment.
19 Clinical application of these parameters, however, is to date limited, mostly due to lack of large-
20 scale prospective validation and consequent inability to suggest significant cut-offs.
21 In our opinion, to date, parameters, such as severely reduced LAAv or markedly enlarged LA, may
22 aid, in a case-by-case approach, as complementary tools to guide OAC prescription in controversial
23 and ambiguous cases. In addition, LAA and LA imaging, particularly with the development of
24 technologies such as TDI or speckle tracking, bears a promising potential.

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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 imaging (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 patients⁹². *AoV*, Aortic valve. Reproduced with permission from Tamura H et al. *J Am Soc*

Figure 1.

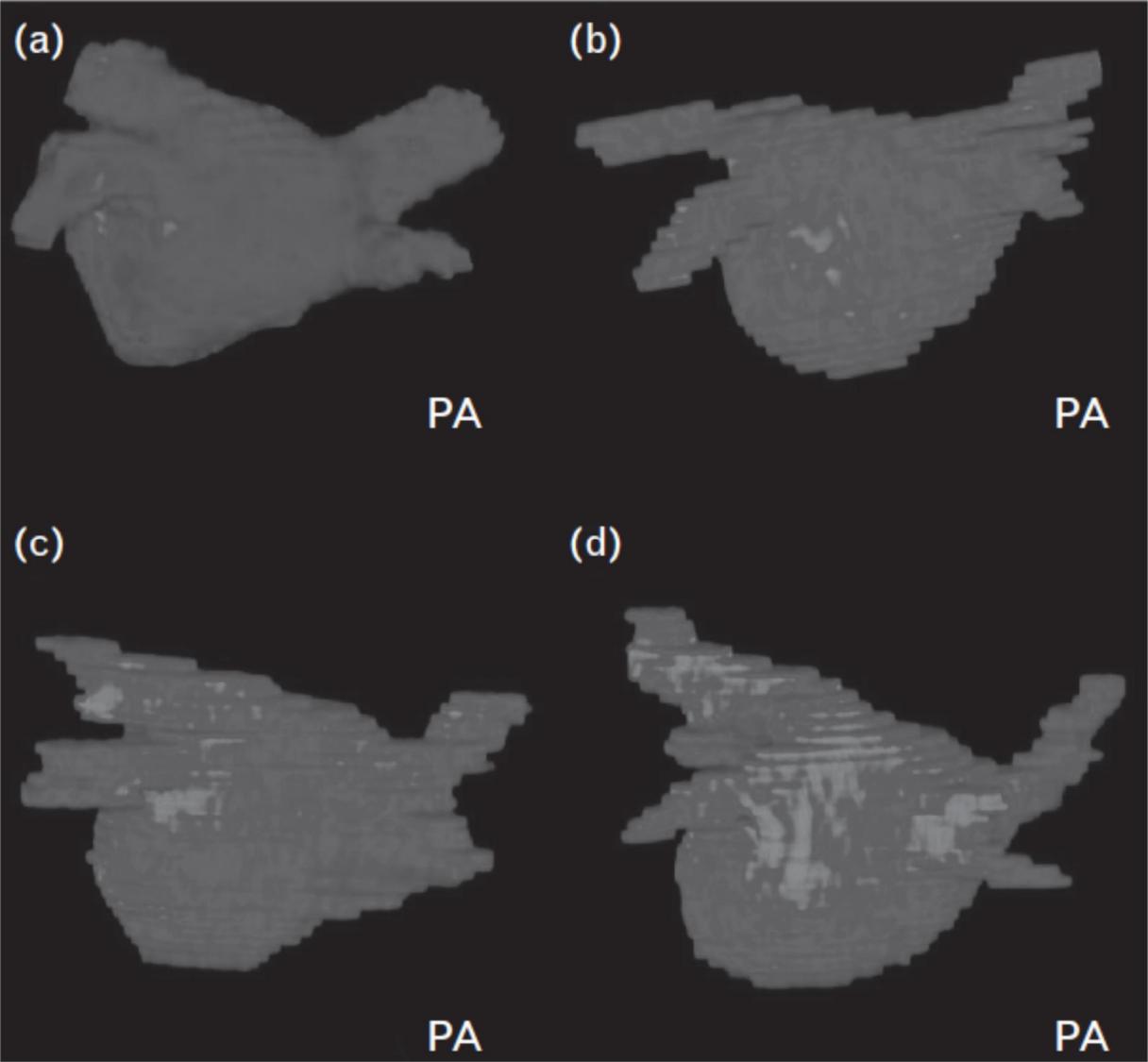


Figure 2.

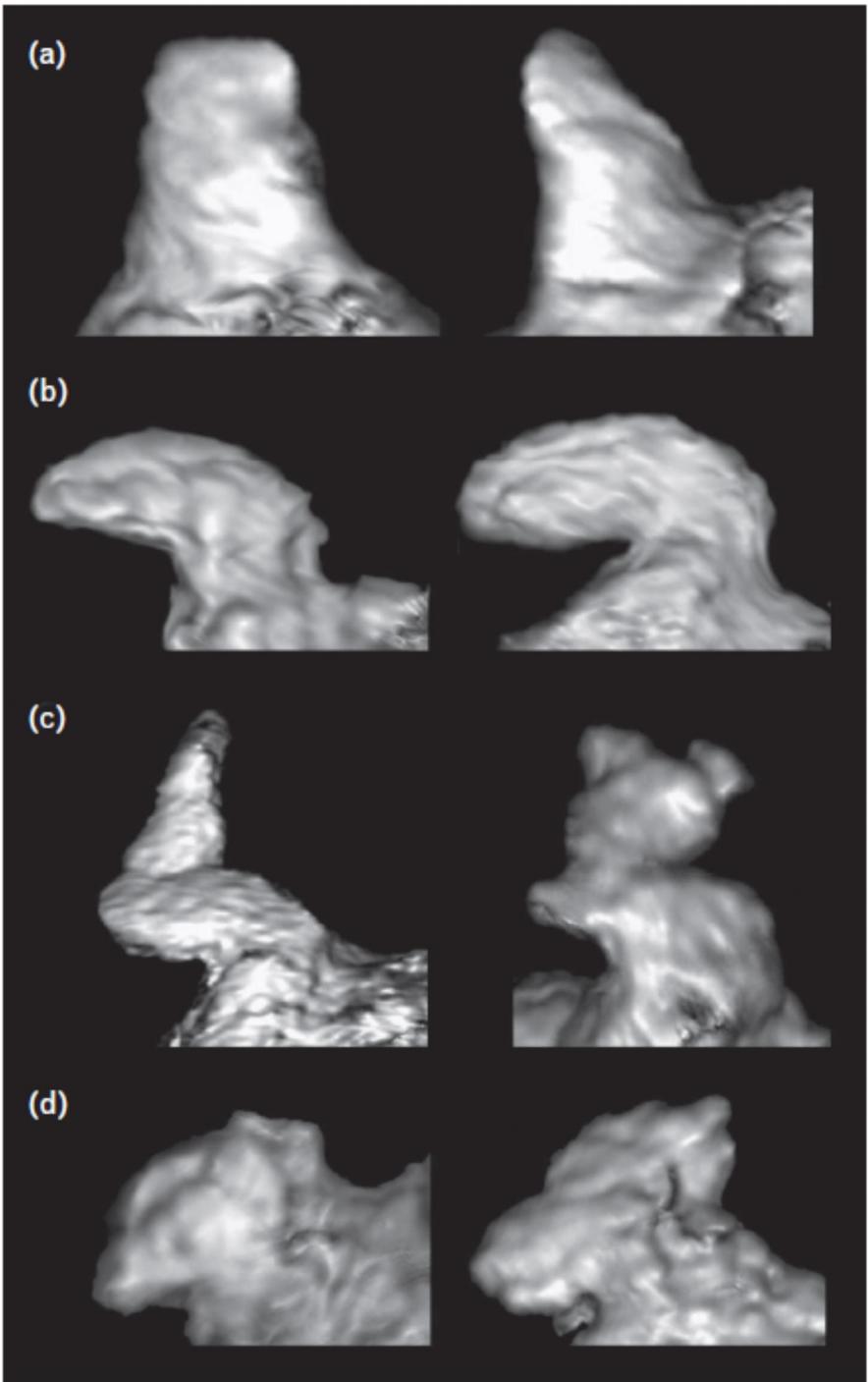


Figure 3.

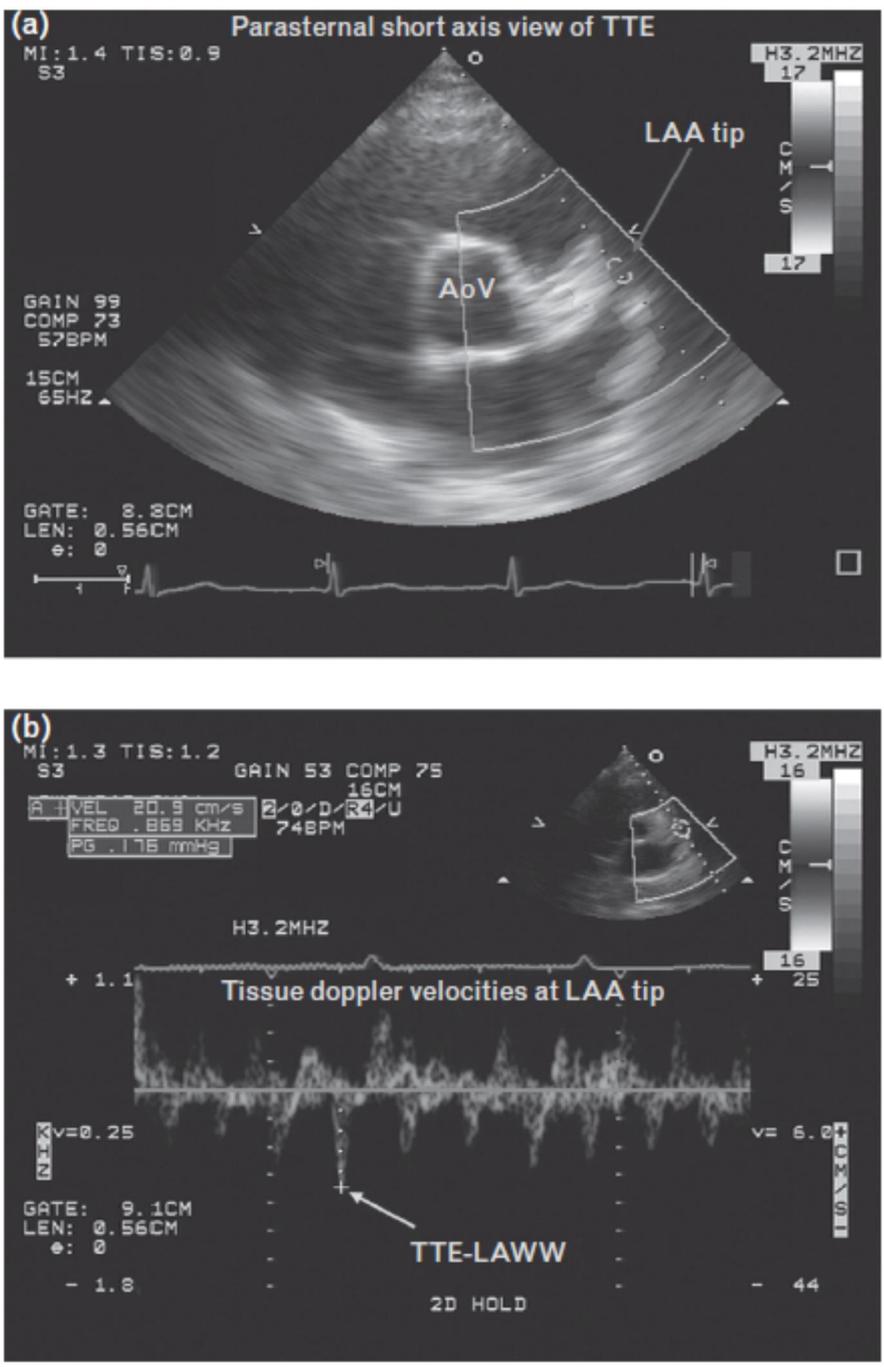


Table 1. Left atrial and appendage parameters tested for thromboembolic risk prediction in AF patients.

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