Evaluation of the Left Atrial Appendage with Real-Time
Three-Dimensional Transesophageal Echocardiography:
Implications For Catheter-Based Left Atrial Appendage Closure

Nucifora et al: RT3DTEE Imaging of LAA

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Abstract

Background—Precise knowledge of left atrial appendage (LAA) orifice size is crucial for correct sizing of LAA closure devices. Aim of the present study was to determine the performance of real-time three-dimensional transesophageal echocardiography (RT3DTEE) for LAA orifice size assessment, compared to two-dimensional transesophageal echocardiography (2DTEE), and to investigate the impact of atrial fibrillation (AF) on LAA orifice size.

Methods and Results—137 patients (38 controls, 31 with paroxysmal AF, 38 with persistent AF and 30 with permanent AF) underwent 2DTEE and RT3DTEE. Both techniques were used to measure LAA orifice area. Clinically-indicated 64-slice computed tomography (CT) was used as reference technique in 46 patients. 2DTEE underestimated LAA orifice area, compared to RT3DTEE (1.99±0.94 cm^2 vs. 3.05±1.27 cm^2; p<0.001). RT3DTEE showed higher correlation with CT for the assessment of LAA orifice area, compared to 2DTEE (r=0.92, 95%CI 0.85-0.95, vs. r=0.72, 95%CI 0.54-0.83, respectively). At Bland-Altman analysis, RT3DTEE underestimated LAA orifice area, compared to CT. However, RT3DTEE showed smaller bias (0.07 cm^2 vs. 0.72 cm^2) and narrower limits of agreement (-0.71 to 0.85 cm^2 vs. -0.58 to 2.02 cm^2) with CT, compared to 2DTEE. Among AF patients, a progressive increase in RT3DTEE-derived LAA orifice area was observed with increasing frequency of AF (p<0.001). At multivariate analysis, AF and left atrial volume index (p<0.001 for both) were independently associated with RT3DTEE-derived LAA orifice area.

Conclusions—RT3DTEE is more accurate than 2DTEE for the assessment of LAA orifice size. A progressive increase in LAA orifice area is observed with increasing frequency of AF.

Key Words: atrial fibrillation; left atrial appendage; real-time three-dimensional transesophageal echocardiography
The left atrial appendage (LAA) is the source of thrombi in more than 90% of patients with non-valvular atrial fibrillation (AF);¹,² accordingly, removal or occlusion of the LAA may represent an effective therapeutic strategy to reduce the risk of stroke in these subjects. Previous studies have suggested the surgical exclusion of the LAA as a safe and effective procedure among AF patients undergoing open-heart surgery or coronary artery bypass grafting surgery.³,⁴ More recently, catheter-based closure of the LAA has been proposed as a potential therapeutic approach for patients with AF ineligible or non-compliant to anticoagulation therapy; to this end, three devices have been specifically designed for percutaneous LAA closure and clinically tested.⁵-⁷ Precise knowledge of LAA anatomy (and, in particular, of LAA orifice size) is crucial for correct sizing and safe placement of LAA closure devices;⁸ this information is commonly provided by two-dimensional transesophageal echocardiography (2DTEE).⁸ However, 2DTEE does not adequately allow complete spatial visualization of the LAA. Consequently, three-dimensional imaging modalities, such as computed tomography (CT), cardiac magnetic resonance or real-time three-dimensional transesophageal echocardiography (RT3DTEE), may be more appropriate.⁹-¹⁴ In particular, RT3DTEE may represent the first-line approach, since it can provide full view of the LAA without radiation exposure and contrast administration.

Scarce data are however available regarding the performance of RT3DTEE for the characterization of LAA anatomy, as compared to 2DTEE.¹³ In addition, unknown is the impact of presence and type (i.e. paroxysmal, persistent and permanent) of AF on LAA orifice size, as assessed by RT3DTEE.

Accordingly, the aim of this study was threefold. First, to compare the RT3DTEE
findings with those obtained with conventional 2DTEE. Second, to evaluate the accuracy of RT3DTEE- and 2DTEE-derived measurements of LAA orifice size, using 64-slice CT as reference technique. Third, to investigate the impact of presence and type of AF on LAA dimension and particularly on LAA orifice size.

Methods

Study population

A total of 137 consecutive patients (99 with a history of paroxysmal [n=31], persistent [n=38] or permanent [n=30] non-valvular AF and 38 without a history of AF) who underwent clinically indicated transthoracic and transesophageal echocardiography were prospectively included. Paroxysmal, persistent and permanent AF were diagnosed according to the American Heart Association/American College of Cardiology/European Society of Cardiology criteria. Briefly, paroxysmal AF was defined as self-terminating episodes of AF lasting ≤7 days whereas persistent AF was defined as episodes lasting >7 days, requiring pharmacologic or electric cardioversion; patients were considered as having permanent AF when cardioversion has failed or has not been attempted.

Patients with left ventricular systolic dysfunction (left ventricular [LV] ejection [EF] fraction <50%), significant (moderate or severe) valvular heart disease, prosthetic heart valve or mitral valve repair, congenital heart disease, and technically inadequate echocardiographic studies were not included.

For each patient, the presence of coronary risk factors (systemic hypertension,
hypercholesterolemia, diabetes mellitus, positive family history and cigarette
smoking) and history of CAD was recorded. A history of CAD was defined as the
presence of previous acute coronary syndrome, percutaneous or surgical coronary
revascularization, and/or one or more angiographically documented coronary stenosis
≥50% luminal diameter.

A subset of 46 patients (10 control patients, 20 patients with paroxysmal AF and 16
patients with persistent AF) underwent also clinically indicated 64-slice cardiac CT;
in this group of subjects, 64-slice CT was used as reference technique to test the
accuracy of RT3DTEE and 2DTEE-derived measurement of LAA orifice area, which
is the main determinant of the size of LAA closure device.

**Transthoracic echocardiography**

Two-dimensional transthoracic echocardiography was performed using a
commercially available system (Vivid 7 Dimension, GE Healthcare, Horten, Norway)
equipped with a 3.5-MHz transducer. Standard M-mode, 2-dimensional images and
Doppler and color-Doppler data were acquired from the parasternal and apical views
(4-, 2- and 3-chamber) and digitally stored in cine-loop format; analyses were
subsequently performed offline using EchoPAC version 7.0.0 (GE Healthcare,
Horten, Norway).

The LV end-diastolic (EDV) and end-systolic (ESV) volumes were measured
according to the Simpson’s biplane method and LVEF was calculated as 
\[
\frac{(EDV-ESV)}{EDV} \times 100.\]  
LV mass was calculated using the formula proposed by
Devereux.\[^{17}\] Left atrial volume (LAV) was measured at end-ventricular systole (i.e.
from the frame immediately preceding mitral valve opening) using the Simpson’s biplane method. All measurements were normalized for the body surface area.

**Transesophageal echocardiography**

Transesophageal echocardiography was performed using commercially available fully sampled matrix-array TEE transducer and ultrasound system (X7-2t Live 3D TEE transducer, iE33, Philips Medical Systems, Andover, Mass). All images were digitally stored for offline analysis (QLAB cardiac 3DQ, Philips Medical Systems).

**Two-dimensional transesophageal echocardiography.** 2DTEE was performed according to a standard clinical protocol. The LAA was imaged at 0°, 45°, 90°, and 135°. The 2D images were analyzed on-line. Measurements of maximum (D1) and minimum (D2) diameters of LAA orifice were obtained from orthogonal planes (0° and 90°, and 45° and 135°), from the origin of the left circumflex artery to the roof of the LAA, below the ligament of Marshall. The LAA orifice area was then calculated as previously described, using the following equation:

\[
\text{LAA orifice area} = \pi \times \frac{D1}{2} \times \frac{D2}{2}
\]

The larger of the two calculated orifice areas (on the basis of 0° and 90°, and 45° and 135°) was then chosen. An eccentricity index, measured as D1/D2 ratio, was used to assess the LAA orifice geometry. An eccentricity index=1 would represent a perfect circle while progressively higher eccentricity index represent progressively more ellipsoid geometry. Similarly, the LAA depth (i.e. the distance from LAA orifice to the tip of LAA) was measured at 0°, 90°, 45° and 135°; from these 4 views, the
longest LAA depth was then chosen.\textsuperscript{13}

\textit{Real-time three-dimensional transesophageal echocardiography.}

Acquisition of RT3DTEE images of the LAA has been previously described;\textsuperscript{13} briefly, RT3DTEE imaging was performed acquiring a pyramidal data set large enough to include the entire LAA, using the zoom mode. Subsequently, pyramidal data sets were cropped along designated x-, y-, and z-axes or by using an arbitrary cropping plane, to remove remaining non-relevant anatomic structures and to improve the visualization of LAA. The image was then rotated in order to provide an “en-face” view of the LAA (Figure 1). The 3D data sets were analyzed off-line with a dedicated software (QLab-3DQ, Philips Medical Systems), as previously described.\textsuperscript{13} The 3D data sets of the LAA were assessed using the multiplanar reconstruction (MPR) mode of QLab-3DQ software, which allows visualization and alignment of the LAA in the three different dimensions. The LAA long-axes were aligned using MPR, allowing visualization of the LAA orifice in the short-axis (Figure 1). The area of the LAA orifice, as well as the maximum (D1) and minimum (D2) diameters of LAA orifice, were measured from the short-axis view, along a plane connecting the origin of the left circumflex artery to the roof of the LAA, below the ligament of Marshall.\textsuperscript{8} An eccentricity index of the LAA orifice was measured as previously described for 2DTEE. The LAA depth (i.e. the longest distance from LAA orifice to the tip of LAA) was measured from the long-axes views.

All 2D and 3D measurements of LAA were performed at ventricular end-systole. In
patients who were in AF at the time of transthoracic and transesophageal
echocardiography, measurements from ≥3 cardiac cycles were averaged.

**Sixty-four-slice computed tomography**

A subset of 46 patients (10 control patients, 20 patients with paroxysmal AF and 16 patients with persistent AF) underwent also clinically indicated 64-slice CT (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) within 1 month of transthoracic and transesophageal echocardiography. All patients were in sinus rhythm during the CT scan. A retrospective ECG-gating protocol was used. Scanning parameters were the following: detector collimation of 0.625 mm, total z-axis coverage of 40 mm per rotation, gantry rotation speed of 0.35 seconds, tube voltage of 120 kV, a pitch of 0.16–0.24 and ECG modulated tube current ranging from 400 mA to 800 mA. The bolus tracking technique (SmartPrep) was used to trigger the acquisition, with a four-cavity view as the region of interest. A total of 70–100 ml of iodinated, non-ionic contrast agent (Optiray 350, Mallinckrodt, St Louis, MO, USA) was injected continuously into the antecubital vein (80–100 ml at 5.0 ml/s), followed by a 30-ml saline flush injected at a flow rate of 3.0 ml/s. Scanning was initiated during a single breath hold for an acquisition time of 5–7 seconds. All images were reconstructed with an effective slice thickness of 0.625 mm. ECG-gating protocol reconstruction of the image data was performed starting from early systole (10% of R–R interval) and ending at end diastole (90% of R–R interval) using 10% steps. Reconstructed image data were transferred to a remote workstation (Advantage Windows 4.3, GE Healthcare) for post-processing. For the purpose of the current
study, image data sets reconstructed at end-systole (40% of R-R interval) were used for analysis. Using MPR, measurements of the area of the LAA orifice were performed from the short-axis view, as well as the maximum (D1) and minimum (D2) diameters of LAA orifice. An eccentricity index of LAA orifice was measured as previously described for RT3DTEE and 2DTEE. The LAA depth (i.e. the longest distance from LAA orifice to the tip of LAA) was measured from the long-axes views.

In order to avoid measurements bias, all analyses were performed in blinded fashion by different operators.

Statistical analysis
Continues variables are expressed as mean and standard deviation. Categorical data are presented as absolute numbers and percentages. Differences in continuous variables between two groups were assessed using Student t test or Mann-Whitney U test, if appropriate. Differences in continuous variables between more than 2 groups were assessed using the one-way ANOVA test or the Kruscal-Wallis test, when appropriate; if the result of analysis was significant, post-hoc test with Bonferroni’s correction was applied. Chi-square test or Fisher exact test, when appropriate, were computed to assess differences in categorical variables.

The measurements of the LAA (i.e. LAA orifice area, maximum and minimum diameters of LAA orifice, eccentricity index of the LAA orifice area and LAA depth) were compared between RT3DTEE and 2DTEE with the paired t-test. Correlation
between RT3DTEE- and 2DTEE-derived LAA orifice areas with
CT-derived LAA orifice area was summarized using linear regression analysis and
Pearson correlation coefficients. The method of Bland and Altman was used for
agreement analysis between RT3DTEE, 2DTEE and CT-derived measurements of LAA
orifice area. Concordance correlation coefficient (CCC) was evaluated to assess intra-
and inter-observer reproducibility of CT, RT3DTEE and 2DTEE-derived measurement of
LAA orifice area, repeating the analysis 1 month later by the same observer who
performed the first analysis and by a second independent observer.

Univariate and multivariate linear regression analysis (enter method) were performed
to evaluate the relationship between LAA orifice area (measured with RT3DTEE) and
the following variables: age, male gender, body surface area, AF, coronary risk
factors, coronary artery disease, LVEDV index, LVESV index, LVEF, LV mass
index and LAV index. Only significant variables at univariate analysis were entered
as covariates in the multivariate model.

A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was
performed using the SPSS (SPSS 15.0, Chicago, Illinois) and MedCalc (MedCalc 10.0,
Mariakerke, Belgium) software packages.

Results

Baseline characteristics of the study population

Baseline characteristics of the study population are shown in Table 1. The acquisition
of 2DTEE and RT3DTEE images was possible in all patients without complications.
In particular, as regard to RT3DTEE, the LAA was always completely imaged within the 3D dataset, enabling a 100% feasibility of LAA assessment.

**Comparison between RT3DTEE, 2DTEE and CT**

As shown in Table 2, 2DTEE provided significant lower measurements of LAA orifice area, maximum and minimum diameter of LAA orifice, eccentricity index of LAA orifice and depth of LAA, as compared to RT3DTEE.

By linear regression analysis (Figure 2), RT3DTEE showed better correlation with CT in the assessment of LAA orifice area, compared to 2DTEE ($r=0.92$, 95% CI 0.85-0.95, vs. $r=0.72$, 95% CI 0.54-0.83, respectively). At Bland–Altman analysis (Figure 3), both RT3DTEE and 2DTEE underestimated the LAA orifice area, as compared to CT. However, RT3DTEE showed smaller bias and narrower limits of agreement with CT, as compared to 2DTEE (Figure 3). Intra- and interobserver reproducibility of CT-derived measurement of LAA orifice area was good (CCC = 0.97 [95%CI = 0.96–0.99] and = 0.96 [95%CI 0.94–0.98], respectively). Intra- and interobserver reproducibility of RT3DTEE-derived measurement of LAA orifice area was also good (CCC = 0.97 [95%CI = 0.95–0.98] and = 0.94 [95%CI 0.90–0.97], respectively) and better than that observed for 2DTEE (CCC = 0.92 [95%CI = 0.86–0.95] and = 0.88 [95%CI 0.79–0.93], respectively).

**Relation between AF and LAA dimension**

Baseline clinical and 2DTTE characteristics of each group are shown in Table 3. No significant differences among groups were observed for most of the baseline clinical
characteristics. Similarly, no significant differences among groups were observed in LV volumes, LVEF and LV mass.

No significant difference in LAV index was observed between control patients and patients with history of paroxysmal AF; conversely, a progressive increase in LAV index was observed with increasing frequency of AF (Table 3).

As shown in Figure 4, no significant difference in LAA orifice area, maximum and minimum diameter of LAA orifice, eccentricity index of LAA orifice and depth of LAA was observed between control patients and patients with history of paroxysmal AF. Conversely, a progressive increase in LAA dimension (i.e. LAA orifice area, maximum and minimum diameter of LAA orifice and depth of LAA) and a progressive reduction of eccentricity index of LAA orifice were observed with increasing frequency of AF (Figure 4).

**Determinants of LAA orifice area**

Table 4 shows the results of univariate and multivariate linear regression analysis performed to determine the factors related to LAA orifice area in the study population. At univariate analysis, several variables were significantly related to LAA orifice area: age, AF, hypertension, diabetes mellitus, and LAV index. However, at multivariate analysis, only AF and LAV index ($p<0.001$ for both) were independently associated with LAA orifice area.
Discussion

The results of the present study can be summarized as follows: 1) RT3DTEE-derived measurements of LAA orifice area are closely related with CT measurements, which is the gold standard for LAA anatomic evaluation; 2) 2DTEE significantly underestimates LAA dimension and orifice size, as compare to RT3DTEE; 3) a progressive increase in LAA dimension and a progressive reduction of eccentricity index of LAA orifice are observed with increasing frequency (i.e. from paroxysmal to permanent form) of AF episodes; 4) AF, as well as LAV index, are independently related to LAA orifice area.

Imaging techniques for LAA orifice size assessment

Precise knowledge of LAA orifice dimension is crucial for correct sizing and safe placement of LAA closure device; usually, the size of the device is chosen few millimeters larger than the diameter of the LAA orifice (Table 5), in order to ensure sufficient and stable positioning of the device itself. Even though device migration, dislodgement or embolization, cardiac perforation and pericardial effusion are rarely described, especially when the procedure is performed by experienced operators, significant over- or under-sizing of the device may potentially increase the risk of such complications. Commonly, assessment of LAA orifice size is performed using 2DTEE; however, 2DTEE has some limitations, which are inherent to its two-dimensional nature. When using 2DTEE, measurements need to be performed in multiple views and
foreshortening and limited echo planes may potentially lead to imperfect estimation of LAA orifice size, as shown by the results of the present study. Three-dimensional imaging modalities, such as CT, cardiac magnetic resonance and RT3DTEE, should therefore be preferred.\(^9\)\(^{–}\)\(^14\) However, CT is associated with non-negligible radiation exposure, while cardiac magnetic resonance is expensive and not widely available. In addition, both these techniques cannot be performed at bedside and do not provide real-time images of the LAA. Thus, RT3DTEE may represent the first-line approach, due to its ability to provide real-time three-dimensional en face views of the LAA without radiation exposure and contrast administration.

In the present study, 2DTEE-derived measurements of LAA dimension were compared with those obtained with RT3DTEE; in addition, the accuracy of RT3DTEE- and 2DTEE-derived measurements of LAA orifice size was assessed, using 64-slice CT as reference technique. Importantly, all the patients had adequate RT3DTEE images for visualization and quantitation of the LAA, confirming the good feasibility previously reported by other groups.\(^13\) Of note, 2DTEE significantly underestimated LAA dimensions, as compared to RT3DTEE. Importantly, RT3DTEE was significantly more accurate and reproducible than 2DTEE in the measurement of LAA orifice size, probably because RT3DTEE, by using the MPR mode, allows correct identification and direct planimetric measurement of the LAA orifice area. Conversely, 2DTEE estimates the LAA orifice area using the equation: LAA orifice area = \(\pi \times (D_1/2) \times (D_2/2)\). Consequently, small errors in the measurements of the diameters can be amplified, therefore reducing accuracy and reproducibility.

These results are in line with those previously described in a smaller study population.
by Shah and colleagues and have relevant clinical implications. On the basis of 2DTEE-derived measurement of LAA orifice size, LAA occlusion device may be frequently undersized; early clinical experience of LAA occlusion have indeed shown that the size of the device correctly matching the size of the LAA orifice is often 20%-40% larger than predicted by 2DTEE. This obviously exposes the patient to the need of intra-procedural device resizing and to potential complications. In addition, patients not suitable for LAA occlusion because of too large LAA, may inappropriately be referred to device implantation; in the present study, indeed, according to the size of LAA closure devices and to the maximum diameter of LAA orifice recommended for device implantation (Table 5), all patients would be considered suitable for device implantation on the basis of 2DTEE measurements. Conversely, on the basis of RT3DTEE measurements, 26 (19%) patients (1 with paroxysmal AF, 11 with persistent AF and 14 with permanent AF) would not be suitable for PLAATO device implantation, 5 (4%) patients (all of whom with permanent AF) would not be suitable for WATCHMANN LAA system implantation and 15 (11%) patients (9 with persistent AF and 6 with permanent AF) would not be suitable for Amplatzer Cardiac Plug implantation.

**Impact of presence and type of AF on LAA dimension**

Prior studies have demonstrated that LA dimension, function and wall fibrosis are strictly related to the AF burden. Conversely, few data are available regarding the impact of AF on the dimension and morphology of LAA orifice. According to previous post-mortem studies, AF patients have a significantly larger LAA, compared
to patients with normal sinus rhythm;\textsuperscript{25} in addition, these studies have shown that the shape of the LAA orifice is elliptical rather than round.\textsuperscript{25-27} The present study extends these previous observations, providing meaningful information on the impact of clinical and structural variables on LAA orifice area. A progressive increase in LAA dimension was indeed observed with increasing frequency of AF. Importantly, AF, as well as LAV index, were independently associated with LAA orifice area, possibly reflecting a stretch of the LAA orifice in an enlarged LA, which is frequently observed in AF patients. Of note, the progressive increase in LAA dimension with increasing frequency of AF was associated with a progressive decrease in its eccentricity index (which means that the LAA orifice was progressively less elliptical and more round-shape). These findings have significant clinical implications. On the basis of pre-specified anatomical LAA maximum diameter requirements (Table 5), as shown above, most of paroxysmal AF patients would qualify for percutaneous LAA closure; however, taking into account that all the available occluders have a round shape, a round implant over an oval-shaped orifice (usually observed in this subgroup of AF patients) may lead to incomplete sealing of the orifice, and to residual leaks.\textsuperscript{27} The clinical significance of residual leaks after device implantation is still questioned. It has been postulated that residual leaks may be a risk for thrombi formation and embolic events in patients with partially occluded LAAs, therefore leading to the need of continued anticoagulation therapy.\textsuperscript{28,29} This suggests that, among AF patients with non-dilated and elliptical LAA orifice, devices may need to be elliptical to adequately occlude the LAA orifice.

On the other side, as shown above, a non-negligible proportion of patients with
persistent or permanent AF would not qualify for percutaneous LAA closure, due to an oversized LAA orifice. Of note, Beinart and colleagues recently demonstrated, by using magnetic resonance angiography, larger LAA dimensions in AF patients with history of stroke and transient ischemic attack as compared to patients without history of embolic events. In addition, after adjustment for traditional stroke risk factors, LAA dimension emerged as an independent and powerful predictor of stroke and transient ischemic attack in AF patients; the authors explain this finding hypothesizing that larger LAAs probably are more prone to low blood flow, blood stasis and therefore to thrombus formation. Consequently, and accordingly to the results of the present study, many of the AF patients who may benefit more from percutaneous LAA closure, would not be suitable for the procedure; this has important engineering implications for the future development of larger LAA closure devices.

Conclusions

RT3DTEE is more accurate than 2DTEE for the assessment of LAA orifice size; accordingly, RT3DTEE should be preferred for the correct sizing of LAA closure devices. Of note, LAA orifice becomes larger and more round-shaped with increasing frequency of AF; this indicates that devices with multiple sizes and shapes may be needed to ensure an adequate LAA occlusion in all AF patients. Accordingly, further technological improvement to ensure complete LAA sealing and to prevent device leak because of shape or eccentricity issues appears to be required.
Disclosures
None.

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*Circulation.* 2002;105:1887-1889


Table 1. Baseline characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=137)</th>
<th>Patients who underwent 64-slice CT (n=46)</th>
<th>Remaining patients (n=91)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68±11</td>
<td>66±11</td>
<td>69±11</td>
<td>0.23</td>
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<tr>
<td>Male gender (%)</td>
<td>87 (64%)</td>
<td>31 (67%)</td>
<td>56 (62%)</td>
<td>0.50</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.91±0.22</td>
<td>1.90±0.22</td>
<td>1.91±0.21</td>
<td>0.73</td>
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<td>Hypertension (%)</td>
<td>91 (66%)</td>
<td>34 (74%)</td>
<td>57 (63%)</td>
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<td>Hypercholesterolemia (%)</td>
<td>68 (50%)</td>
<td>30 (65%)</td>
<td>38 (42%)</td>
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<td>Diabetes mellitus (%)</td>
<td>21 (15%)</td>
<td>5 (11%)</td>
<td>16 (18%)</td>
<td>0.30</td>
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<td>Family history of CAD (%)</td>
<td>24 (18%)</td>
<td>7 (15%)</td>
<td>17 (19%)</td>
<td>0.61</td>
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<td>Smoking (%)</td>
<td>31 (23%)</td>
<td>11 (24%)</td>
<td>20 (22%)</td>
<td>0.80</td>
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<td>CAD (%)</td>
<td>42 (31%)</td>
<td>18 (39%)</td>
<td>24 (26%)</td>
<td>0.13</td>
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<tr>
<td>Atrial fibrillation (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>- Absent</td>
<td>38 (28%)</td>
<td>10 (22%)</td>
<td>28 (31%)</td>
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<tr>
<td>- Paroxysmal</td>
<td>31 (23%)</td>
<td>20 (43%)</td>
<td>11 (12%)</td>
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<tr>
<td>- Persistent</td>
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<tr>
<td>- Permanent</td>
<td>30 (22%)</td>
<td>0 (0%)</td>
<td>30 (33%)</td>
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CAD: coronary artery disease.
Table 2. Comparison between 2DTEE-derived and RT3DTEE-derived measurements of the LAA in the study population ($n=137$)

<table>
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<tr>
<th></th>
<th>2DTEE</th>
<th>RT3DTEE</th>
<th>p value</th>
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<tr>
<td>LAA orifice area (cm$^2$)</td>
<td>1.99±0.94</td>
<td>3.05±1.27</td>
<td>&lt;0.001</td>
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<tr>
<td>Maximum diameter of LAA orifice (cm)</td>
<td>1.69±0.39</td>
<td>2.23±0.45</td>
<td>&lt;0.001</td>
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<td>Minimum diameter of LAA orifice (cm)</td>
<td>1.43±0.37</td>
<td>1.65±0.43</td>
<td>&lt;0.001</td>
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<td>Eccentricity index of LAA orifice</td>
<td>1.21±0.19</td>
<td>1.36±0.27</td>
<td>&lt;0.001</td>
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<tr>
<td>Depth of LAA (cm)</td>
<td>2.67±0.77</td>
<td>2.82±0.79</td>
<td>0.001</td>
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</tbody>
</table>

2DTEE: two-dimensional transesophageal echocardiography; LAA: left atrial appendage; RT3DTEE: real-time three-dimensional transesophageal echocardiography.
Table 3. Clinical and transthoracic echocardiography characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=38)</th>
<th>Paroxysmal AF (n=31)</th>
<th>Persistent AF (n=38)</th>
<th>Permanent AF (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±11</td>
<td>64±10</td>
<td>71±13</td>
<td>71±9</td>
<td>0.016</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>24 (63%)</td>
<td>21 (68%)</td>
<td>26 (68%)</td>
<td>16 (53%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.87±0.24</td>
<td>1.91±0.20</td>
<td>1.94±0.19</td>
<td>1.92±0.23</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>17 (45%) *</td>
<td>22 (71%)</td>
<td>28 (74%)</td>
<td>24 (80%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>22 (58%)</td>
<td>16 (52%)</td>
<td>13 (34%)</td>
<td>17 (57%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2 (5%) †</td>
<td>2 (7%) †</td>
<td>4 (11%) †</td>
<td>13 (43%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>6 (16%)</td>
<td>4 (13%)</td>
<td>9 (24%)</td>
<td>5 (17%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>11 (29%)</td>
<td>4 (13%)</td>
<td>8 (21%)</td>
<td>8 (27%)</td>
<td>0.41</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>12 (32%)</td>
<td>10 (32%)</td>
<td>11 (29%)</td>
<td>9 (30%)</td>
<td>0.99</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>58±17</td>
<td>60±18</td>
<td>64±17</td>
<td>65±20</td>
<td>0.33</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>22±8</td>
<td>21±8</td>
<td>23±9</td>
<td>25±10</td>
<td>0.22</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62±8</td>
<td>65±5</td>
<td>65±7</td>
<td>61±6</td>
<td>0.065</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>92±18</td>
<td>94±34</td>
<td>96±24</td>
<td>100±27</td>
<td>0.68</td>
</tr>
<tr>
<td>LAV index (ml/m²)</td>
<td>11±2 §</td>
<td></td>
<td></td>
<td>10±3 #</td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LAV: left atrial volume; LV: left ventricular. Remaining abbreviations as in Table 1.

Post-hoc tests:

*: p <0.05 vs. permanent AF.
†: p <0.01 vs. permanent AF.
‡: p <0.05 vs. persistent AF.
§: p <0.01 vs. persistent AF.
||: p <0.001 vs. persistent AF.
Table 4. Univariate and multivariate regression analyses to determine the independent correlates of LAA orifice area in the study population

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>-0.016</td>
</tr>
<tr>
<td><strong>Body surface area</strong></td>
<td>0.059</td>
</tr>
<tr>
<td><strong>AF</strong>*</td>
<td></td>
</tr>
<tr>
<td>- Paroxysmal</td>
<td>-0.055</td>
</tr>
<tr>
<td>- Persistent</td>
<td>0.56</td>
</tr>
<tr>
<td>- Permanent</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>-0.11</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Family history of CAD</strong></td>
<td>-0.005</td>
</tr>
<tr>
<td><strong>Smoke</strong></td>
<td>0.076</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>-0.021</td>
</tr>
<tr>
<td><strong>LV EDV index</strong></td>
<td>0.10</td>
</tr>
<tr>
<td><strong>LV ESV index</strong></td>
<td>0.097</td>
</tr>
<tr>
<td><strong>LV EF</strong></td>
<td>-0.017</td>
</tr>
<tr>
<td><strong>LV mass index</strong></td>
<td>0.074</td>
</tr>
<tr>
<td><strong>LAV index</strong></td>
<td>0.70</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1 and 2.

*: AF was entered as a categorical variable, with four possible levels (i.e.: 0 = no AF; 1 = paroxysmal AF; 2 = persistent AF; 3 = permanent AF). Three degrees of freedom test was used.
Table 5. Size of LAA closure devices and maximum diameter of LAA orifice recommended for device implantation.8,19

<table>
<thead>
<tr>
<th>Device</th>
<th>Device size</th>
<th>Recommended maximum diameter of LAA orifice</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAATO</td>
<td>(20–32 mm)</td>
<td>13.6-26.5 mm</td>
</tr>
<tr>
<td>WATCHMANN</td>
<td>(21–33 mm)</td>
<td>17–31.9 mm</td>
</tr>
<tr>
<td>Amplatzer Cardiac Plug</td>
<td>(16–30 mm)</td>
<td>12.6–28.5 mm</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
Figure Legends

**Figure 1.** “En-face” view of the left atrial appendage (LAA), obtained using real-time three-dimensional transesophageal echocardiography (panel A); the LAA long-axes were aligned using the multiplanar reconstruction mode of QLab-3DQ software, allowing visualization of the LAA orifice in the short-axis (panel B). The area of the LAA orifice, as well as the maximum and minimum diameters of LAA orifice, were measured from the short-axis view, along a plane connecting the origin of the left circumflex artery (LCx) to the roof of the LAA, below the ligament of Marshall (LoM). MV: mitral valve.

**Figure 2.** Scatter plots of linear regression analysis for real-time three-dimensional transesophageal echocardiography (RT3DTEE) (panel A) and two-dimensional transesophageal echocardiography (2DTEE) (panel B) measurements of LAA orifice area vs. the computed tomography (CT) reference values.

**Figure 3.** Scatter plots of Bland–Altman analysis for real-time three-dimensional transesophageal echocardiography (RT3DTEE) (panel A) and two-dimensional transesophageal echocardiography (2DTEE) (panel B) measurements of LAA orifice area vs. the computed tomography (CT) reference values.

**Figure 4.** Relation between presence and type of atrial fibrillation (AF) and left atrial appendage orifice area (panel A), maximum diameter of left atrial appendage orifice (panel B), minimum diameter of left atrial appendage orifice (panel C), eccentricity index of left atrial appendage orifice (panel D) and depth of left atrial appendage (panel E).
$r = 0.92 \ (95\% \ CI = 0.85 - 0.95)$
$r = 0.72$ (95% CI = 0.54 - 0.83)
Left Atrial Appendage Orifice Area

ANOVA $p < 0.001$

$p < 0.001$

$p < 0.001$

$p < 0.001$

$\text{cm}^2$

- Controls: $2.16 \pm 0.59$, $n = 38$
- Paroxysmal AF: $2.04 \pm 0.48$, $n = 31$
- Persistent AF: $3.44 \pm 0.80$, $n = 38$
- Permanent AF: $4.71 \pm 0.94$, $n = 30$

$p = 1.0$

$p < 0.001$
Maximum Diameter of Left Atrial Appendage Orifice

ANOVA p < 0.001

p < 0.001

p < 0.001

p < 0.001

p = 0.010

p = 0.001

p = 1.0

2.67 ± 0.35

1.92 ± 0.25

1.94 ± 0.33

2.42 ± 0.38

2.67 ± 0.35

Controls
Paroxysmal AF
Persistent AF
Permanent AF

n = 38
n = 31
n = 38
n = 30

Circulation
Cardiovascular Imaging
Minimum Diameter of Left Atrial Appendage Orifice

ANOVA $p < 0.001$

$p < 0.001$

$p < 0.001$

$p < 0.001$

$p < 0.001$

Circulation Cardiovascular Imaging

<table>
<thead>
<tr>
<th>Group</th>
<th>Diameter (cm) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.30 ± 0.21</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>1.37 ± 0.23</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>1.81 ± 0.26</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>2.19 ± 0.28</td>
</tr>
</tbody>
</table>

n = 38  n = 31  n = 38  n = 30
Eccentricity Index of Left Atrial Appendage Orifice

ANOVA $p < 0.001$

- $p < 0.001$
- $p = 0.001$
- $p = 0.015$
- $p = 1.0$
- $p = 0.27$
- $p = 0.26$

Bar chart showing:

- Controls: $1.50 \pm 0.17$, $n = 38$
- Paroxysmal AF: $1.45 \pm 0.28$, $n = 31$
- Persistent AF: $1.35 \pm 0.19$, $n = 38$
- Permanent AF: $1.24 \pm 0.21$, $n = 30$
Depth of Left Atrial Appendage

ANOVA $p < 0.001$

- $p < 0.001$
- $p = 0.43$
- $p = 0.11$
- $p = 0.001$

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>2.56 ± 0.56</td>
<td>38</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>2.45 ± 0.66</td>
<td>31</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>2.85 ± 0.61</td>
<td>38</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>3.52 ± 0.92</td>
<td>30</td>
</tr>
</tbody>
</table>
Evaluation of the Left Atrial Appendage with Real-Time Three-Dimensional Transesophageal Echocardiography: Implications For Catheter-Based Left Atrial Appendage Closure
Gaetano Nucifora, Francesco F. Faletra, François Regoli, Elena Pasotti, Giovanni Pedrazzini, Tiziano Mocetti and Angelo Auricchio

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