Background—The value of left atrial (LA) diameter, volume, and strain to risk stratify hypertrophic cardiomyopathy patients for new-onset atrial fibrillation (AF) was explored.

Methods and Results—A total of 242 hypertrophic cardiomyopathy patients without AF history were evaluated by (speckle-tracking) echocardiography. During mean follow-up of 4.8±3.7 years, 41 patients (17%) developed new-onset AF. Multivariable analysis showed LA volume (≥37 mL/m²; hazard ratio, 2.68; 95% confidence interval, 1.30–5.54; P=0.008) and LA strain (≤23.4%; hazard ratio, 3.22; 95% confidence interval, 1.50–6.88; P=0.003), but not LA diameter (≥45 mm; hazard ratio, 1.67; 95% confidence interval, 0.84–3.32; P=0.145), as independent AF correlates. Importantly, 59% (n=24) of AF events occurred despite a baseline LA diameter <45 mm, observed in 185 patients. In this patient subset, LA strain (area under the curve 0.73) and LA volume (area under the curve 0.83) showed good predictive value for new-onset AF. Furthermore, patients with LA volume <37 vs ≥37 mL/m² and LA strain >23.4% vs ≤23.4% had superior 5-year AF-free survival of 93% vs 80% (P=0.003) and 98% vs 74% (P=0.002), respectively. Importantly, LA volume <37 mL/m² and strain >23.4% yielded high negative predictive value (93% and 98%, respectively) for new-onset AF. Likelihood ratio test indicated incremental value of LA volume assessment (P=0.011) on top of LA diameter to predict new-onset AF in hypertrophic cardiomyopathy patients with LA diameter <45 mm, which tended to increase further by addition of LA strain (P=0.126).

Conclusions—LA diameter, volume, and strain all relate to new-onset AF in hypertrophic cardiomyopathy patients. In patients with normal LA size, however, both LA volume and strain further refine risk stratification for new-onset AF.

Key Words: atrial fibrillation ■ atrial remodeling ■ cardiomyopathy, hypertrophic ■ echocardiography

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Original Article

Left Atrial Size and Function in Hypertrophic Cardiomyopathy Patients and Risk of New-Onset Atrial Fibrillation

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Primary hypertrophic cardiomyopathy (HCM), caused by sarcomeric gene mutation(s), encompasses increased risk for arrhythmia, heart failure, and (sudden) cardiac death.1,2 Atrial fibrillation (AF) is more prevalent compared with the general population, typically affecting ≈20% of HCM patients at an annual incidence of >2%.3-5 Importantly, one third of patients are diagnosed before the age of 50 years.3 HCM patients who develop AF are vulnerable to symptoms, impaired exercise tolerance, hospitalization for heart failure, and, importantly, known to have worse prognosis.3,4 AF increases by 4-fold the risk of mortality independent of other known mortality risk factors, mainly caused by heart failure and stroke-related death.3,4,6 In addition, AF is associated with an 8-fold increased risk of thromboembolism in HCM patients, occurring at an annual incidence of 3.75%.3,6 Early mortality or persistent neurological disability are common in these patients, even more if onset of AF occurs at younger age.3 Therefore, accurate risk stratification for new-onset AF in HCM patients should be a priority and may have an impact on follow-up and management strategies.

Left atrial (LA) diameter has consistently been identified as a strong predictor of AF development in HCM patients.3,5 It has been suggested that the extent of atrial remodeling and therefore risk for AF might be better reflected by 2-dimensional (2D) assessed LA volume rather than unidimensional LA diameter.7,8 2D speckle-tracking echocardiography is a novel method for accurate assessment of LA function, expressed as reservoir strain, more sensitive than LA size or volume. To date, only one small study in HCM patients linked impaired LA strain to AF requiring hospitalization.9 We
WHAT IS KNOWN
• In patients with hypertrophic cardiomyopathy (HCM), accurate risk stratification for atrial fibrillation (AF) is crucial as this arrhythmia, being more prevalent than in general population, increases mortality risk 4-fold and thromboembolic risk 8-fold, independently of known risk factors.
• Increased left atrial (LA) diameter determined by 2-dimensional echo has been correlated to occurrence of AF in patients with HCM.

WHAT THE STUDY ADDS
• LA diameter, volume, and function (as measured by LA strain) all independently relate to new-onset AF in HCM patients.
• Over 50% of HCM patients develop new-onset AF despite preserved baseline LA diameter of <45 mm.
• Both LA volume (≥37 mL/m²) and strain (≤23.4%) improve prediction of new-onset AF in HCM patients, particularly in the subgroup of patients with preserved LA diameter, and may therefore be preferred over diameter for risk stratification.

hypothesized that LA volume and LA strain may yield incremental value over LA diameter to risk stratify HCM patients for new-onset AF. The aim of current study is to explore the clinical value of all 3 LA parameters in relation to new-onset AF in a large HCM population.

Methods

Patient Population
Patients ≥18 years of age with a clinical diagnosis of HCM based on otherwise unexplained ventricular hypertrophy, comprising a left ventricular (LV) wall thickness of ≥15 mm, were selected from an ongoing echocardiographic and clinical database. Patients with a history of AF before or at the moment of echocardiography, no additional clinical follow-up visit after baseline echocardiography, and insufficient image quality to allow LA strain assessment were excluded.

Baseline characteristics, including age, sex, cardiovascular risk factors, medication use, presence of implantable cardioverter defibrillator (ICD), and results of sarcomere mutation testing, if performed, were extracted from the departmental electronic patient information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). In addition, at baseline, all HCM patients had 12-lead ECG and 24-hour ambulatory electrocardiography (Holter) registration.

As recommended, patients were followed up on a yearly basis at our and the referring institution, comprising a clinical visit and 12-lead ECG or Holter recordings performed at the discretion of the treating physician based on symptoms, presence of enlarged LA, or for sudden cardiac death risk stratification. Device interrogation was performed every 3 to 6 months in ICD recipients.

The study was approved by the internal review board that waived the need for written informed consent for retrospective evaluation of prospectively collected clinical data.

Echocardiographic Analysis
Comprehensive 2D transthoracic echocardiography was performed in all patients in the left lateral decubitus using commercially available ultrasound systems (System-5, Vivid-7 and E9; GE-Vingmed, Milwaukee, WI) equipped with a 3.5-MHz or M5S transducers. Conventional ECG-triggered 2D B-mode, M-mode, pulsed wave, continuous wave and color-Doppler images were acquired in still or cine-loop format and analyzed off-line (EchoPAC version 112; GE Medical Systems, Horten, Norway). From a short-axis view at basal, mid, and apical levels, the maximal LV end-diastolic wall thickness was assessed. Septal LV wall thickness and LV diameters were calculated from parasternal long-axis views, as recommended.10 Simpson biplane method was used for evaluation of LV volumes and to calculate LV ejection fraction. Diastolic parameters, including E/A and E/E’ were assessed using pulsed wave Doppler at the tips of the mitral leaflets and from tissue Doppler imaging at the level of the lateral annulus, respectively. A multi-integretive approach was used to grade presence of mitral regurgitation as grade 1 (trivial), 2 (mild), 3 (moderate), or 4 (severe), as recommended.11 In addition, systolic anterior movement of the anterior mitral leaflets was evaluated from M-mode parasternal acquisition. Presence of LV resting intraventricular or outflow tract gradient was systematically explored by pulsed wave Doppler and quantified by continuous wave Doppler.

LA Analysis
LA diameter was derived from parasternal long-axis B-mode view, and LA volume was measured at end systole with the Simpson biplane rule. All volumes were indexed to body surface area. LA 2D speckle-tracking longitudinal strain was measured as peak systolic reservoir strain, as previously reported.12 The smallest region of interest was set to include the thin atrial wall. The average value of both the apical 2-chamber and 4-chamber views was used. Mean frame rate for LA strain analysis was 57 frames per second. The intra- and interobserver variability for LA strain analysis in our department has been previously reported.12

End Point
New-onset AF at outpatient or emergency room visit, defined as an irregular heart rhythm without distinct P-waves documented on ECG, Holter registration (if duration ≥30 seconds), or after expert analysis from device recordings in patients with ICD, comprised the study end point.13 Furthermore, AF was categorized as clinical if symptomatic and silent if asymptomatic or with unclear symptoms.

Statistical Analysis
Normally distributed and skewed continuous data are presented as mean±SD and median interquartile range, respectively, whereas percentages are used for categorical data. Comparison between groups was based on Student t, Mann–Whitney U, Fisher exact, or χ² tests, when appropriate. A linear Cox regression base model was compared with nonlinear spline models of second and third degree for all 3 LA parameters (diameter, volume, and strain) to assess linearity of the relation of the LA parameters with the study end point. Thereafter, the study population was stratified based on LA diameter <45 or ≥45 mm, a cutoff value proposed by most recent HCM guidelines.2 Given current lack of generally accepted cutoffs for LA volume and strain in this patient population, stratification was based on evaluation of the relation found on Cox regression and different spline models. In addition, Cox proportional hazards regression analysis was performed to identify univariable associates of new-onset AF. Kaplan–Meier cumulative survival curves free of AF were constructed for all LA parameters, stratified according to their cutoff values and compared by log-rank test. Time-dependent ROC curve (receiver operating curve) estimation using Inverse Probability of Censoring Weighting was used to calculate C statistics for new-onset AF at 5 years for all 3 dichotomized LA parameters. The Inverse Probability of Censoring Weighting procedure was additionally used to calculate sensitivity, specificity, negative predictive value, and positive predictive value for all 3 LA parameters, using their cutoff values. Parameters at a significance threshold of P≤0.05 at univariable level were entered into the multivariable analysis, using multiple imputation to account for missing data (E/E’, n=60). We generated 100 multiple imputed data sets. Results were combined using Rubin rules. Multivariable testing was performed for each dichotomized LA parameter of interest separately (diameter, volume, and strain). Finally, likelihood ratio test
and Nagelkerke $R^2$ statistic was computed to explore the potential incremental value of adding LA volume and strain on top of LA diameter in relation to the study end point. Similar statistical analysis was performed, restricting the study population to patients with LA diameter $<45$ mm, generally regarded as being at low risk for new-onset AF. SPSS version 20.0 (SPSS Inc, Chicago, IL) and R version 3.2.1 were used for statistical analysis (packages survival, mice, and timereg). A $P$ value of $<0.05$ was considered statistically significant, all tests being 2 sided.

**Results**

**Patient Population**

A total of 242 HCM patients comprised the final population after excluding patients for age $<18$ years old ($n=19$), history of AF ($n=43$), no follow-up visit ($n=4$), and insufficient image quality for LA strain assessment ($n=54, 15\%$). Baseline demographic, clinical, and echocardiographic characteristics of these patients (65% men; mean age, 53±13 years) are provided in Table 1. The patient population showed typical characteristics of HCM such as increased wall thickness (median 21 mm), small LV cavities, and preserved LV function (ejection fraction 68±8%). In addition, the presence of systolic anterior movement of the mitral valve or a significant LV outflow tract obstruction ($\geq 30$ mm Hg) were noted in one third of the patients. Median LA size was slightly or moderately increased, when expressed as diameter (40 mm [36–44]) or volume (37 mL/m² [28–46]), respectively. Median LA reservoir function when expressed as diameter (40 mm [36–44]) or volume (37 mL/m²) was 23.4% (16.9–29.1). By definition, all patients were in sinus rhythm at baseline.

**Study End Point**

During a mean follow-up of 4.8±3.7 years (range, 1.7–7.1) 41 out of 242 patients (17%) experienced new-onset AF, detected by ECG (20/41, 49%), Holter (4/41, 10%), or ICD/device reading (17/41, 41%). Therefore, the majority of patients experienced clinical AF (61% as compared with 39% of patients with silent AF; Table I in the Data Supplement). Particularly, more than half of all events (24/41, 59%) occurred in the subgroup of 185 HCM patients with a baseline LA diameter of $<45$ mm.

**AF in the Overall Population**

Patients with versus without new-onset AF had larger LA size (diameter and volume) and more impaired LA function (strain), as shown in Table 2 (all $P<0.001$). These LA parameters were comparable between patients with clinical versus silent AF (Table I in the Data Supplement).

The study population was then stratified by LA diameter $<45$ versus $\geq 45$ mm, a cutoff value clinically accepted to reflect low versus high risk for new-onset AF in HCM patients. Comparison between a linear base Cox regression model and nonlinear Cox regression spline models for LA volume and strain revealed the relationship between the LA parameters and occurrence of new-onset AF to be linear (Figure I in the Data Supplement). Therefore, patients were also stratified for LA volume and strain using their median value of 37 mL/m² and 23.4%, respectively.

Cox regression analysis identified age, $E/e’$, mitral regurgitation grade, and all dichotomized LA parameters (diameter, volume, and strain) as univariate associates of new-onset AF (all $P<0.05$; Table 3). In addition, survival free from new-onset AF was higher in patients with an LA diameter $<45$ versus $\geq 45$ mm, yielding a 5-year AF-free survival of 88% versus 74%, respectively ($P=0.007$; Figure 1). Similarly, survival free from new-onset AF was higher in patients with an LA volume $\leq 37$ mL/m² (5-year survival 91% versus 77% respectively; $P=0.001$) and LA strain $\geq 23.4$ versus $\leq 23.4$% (5-year survival of 94% versus 75%, respectively; $P=0.001$). C statistics indicated higher 5-year predictive value of new-onset AF for LA volume (0.71) than for LA diameter (0.63), with highest value for LA strain (0.74) (Table 2; Figure 2). Both LA volume and LA strain yielded higher sensitivity, negative, and positive 5-year predictive value for new-onset AF compared with LA diameter, again with highest values obtained for LA strain. Moreover, multivariable analysis after correction for age, $E/e’$, and MR grade (categorical) showed that only LA volume and strain, but not LA diameter, remained independently associated with the study end point, with highest hazard ratio (HR) noted for LA strain: LA diameter $\geq 45$ mm (HR, 1.67; 95% confidence interval [CI], 0.84–3.32); $P=0.145$), LA volume $\geq 37$ mL/m² (HR, 2.68; 95% CI, 1.30–5.54; $P=0.008$), and LA strain (HR, 3.22; 95% CI, 1.50–6.88; $P=0.003$; Table 4). Likelihood ratio test indicated significant incremental predictive value when adding LA volume on top of a model containing LA diameter ($R^2=0.139$) to predict new-onset AF ($P=0.017, R^2=0.159$). Addition of LA strain further improved the predictive value ($P=0.030$; $R^2=0.175$; Figure IIA in the Data Supplement).

**AF in Patients With LA Diameter $<45$ mm**

A total of 185 patients were identified with LA diameter $<45$ mm. Compared with patients with LA diameter $\geq 45$ mm, these subjects showed less extensive LV hypertrophy and volumetric remodeling, better diastolic function in addition to a trend toward lower resting LV outflow tract gradient, and mitral regurgitation severity (Table 1). Although such HCM patients with LA diameter $<45$ mm are generally considered to be at relatively low risk for new-onset AF, 59% (24 out of 41) of these events occurred in this subset of 185 patients (Figure 3), implicating a prevalence of 13% (24/185) versus 30% (17/57) in patients with LA diameter $\geq 45$ mm versus $\leq 45$ mm, respectively. Within the cohort of patients with LA diameter $<45$ mm, LA volume was larger and LA strain more impaired in patients who developed new-onset AF compared with patients who remained in sinus rhythm (Table 2). Again, no difference in LA remodeling parameters (diameter, volume, and strain) was noted between those patients with clinical versus silent AF, as demonstrated in Table 1 in the Data Supplement. Importantly, both LA parameters were able to further discriminate risk for new-onset AF in patients with LA diameter $<45$ mm, as illustrated by the survival curves free of new-onset AF in Figure 4. Patients with LA volume $\leq 37$ mL/m² and LA strain $\geq 23.4$% had better survival free of AF with cumulative 5-year survival of 93% versus 80% ($P=0.003$) and 98% versus 74% ($P=0.002$), respectively. C statistics indicated higher 5-year predictive value of new-onset AF for LA strain (0.83) compared with LA volume (0.73;
The sensitivity, negative 5-year predictive value and positive 5-year predictive value for new-onset AF in this subpopulation was higher for LA strain compared with volume, with similar specificity. Additionally, multivariable analysis after correction for age, E/e’, and MR grade (categorical) showed that both LA volume (HR, 4.3; 95% CI, 1.2–7.86; \( P=0.014 \)) and LA strain (HR, 3.77; 95% CI, 1.42–10.03; \( P=0.007 \)) were independently associated with the study end
point in this subpopulation. Likelihood ratio test in this subpopulation with LA diameter <45 mm indicated significant incremental predictive value when adding LA volume on top of a model containing LA diameter (R^2=0.100) to predict new-onset AF (P=0.011; R^2=0.131). Addition of LA strain tended to further improve the predictive value (P=0.126; R^2=0.142; Figure IIB in the Data Supplement).

Table 2.  LA Parameters for Prediction of New-Onset AF Using the Prespecified Cutoff Values

<table>
<thead>
<tr>
<th>Entire Study Population (N=242)</th>
<th>No AF (n=201)</th>
<th>AF (n=41)</th>
<th>P Value</th>
<th>Cutoff</th>
<th>C Statistics at 5 y</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA diameter, mm</td>
<td>40±6</td>
<td>44±6</td>
<td>&lt;0.001</td>
<td>≥45</td>
<td>0.63</td>
<td>28</td>
<td>80</td>
<td>86</td>
<td>20</td>
</tr>
<tr>
<td>LA volume, mL/m^2</td>
<td>37±13</td>
<td>47±15</td>
<td>&lt;0.001</td>
<td>≥37</td>
<td>0.71</td>
<td>70</td>
<td>58</td>
<td>92</td>
<td>23</td>
</tr>
<tr>
<td>LA strain, %</td>
<td>24.0±7.8</td>
<td>18.6±7.5</td>
<td>&lt;0.001</td>
<td>≤23.4</td>
<td>0.74</td>
<td>80</td>
<td>61</td>
<td>94</td>
<td>27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with LA diameter &lt;45 mm (N=185)</th>
<th>No AF (n=161)</th>
<th>AF (n=24)</th>
<th>P Value</th>
<th>Cutoff</th>
<th>C Statistics at 5 y</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume, mL/m^2</td>
<td>34±11</td>
<td>43±14</td>
<td>&lt;0.001</td>
<td>≥37</td>
<td>0.73</td>
<td>62</td>
<td>69</td>
<td>93</td>
<td>21</td>
</tr>
<tr>
<td>LA strain, %</td>
<td>25.3±7.4</td>
<td>19.5±7.7</td>
<td>&lt;0.001</td>
<td>≤23.4</td>
<td>0.83</td>
<td>87</td>
<td>68</td>
<td>98</td>
<td>27</td>
</tr>
</tbody>
</table>

Increased LA size, evaluated by unidimensional antero-posterior diameter assessment, has consistently been reported as one of the strongest correlates of AF in HCM patients. Increased LA strain, with LA strain yielding higher C statistics, sensitivity, NPV, and PPV compared with volume. Of note sensitivity, specificity, NPV, and NPV for AF at 5 y are depicted. AF indicates atrial fibrillation; LA, left atrium; NPV, negative predictive value; and PPV, positive predictive value.

Discussion

The main study findings in this HCM population can be summarized as follows: (1) LA size (diameter and volume) and LA function (strain) are all related to new-onset AF; (2) the burden of new-onset AF is significant despite the relative young age, even in patients with LA diameter <45 mm; and (3) LA volume and LA strain assessment compared with LA diameter improves prediction of new-onset AF with both parameters yielding higher sensitivity, negative predictive value, and positive predictive value, even in the subset of patients with LA diameter <45 mm.

LA remodeling comprises structural and functional changes usually preceding atrial arrhythmias. In the current study, patients developing new-onset AF had larger LA size (diameter and volume) and more impaired LA function (strain), compared with HCM patients free of AF. HCM patients are particularly prone to adverse atrial remodeling for several reasons. Increased filling pressures because of LV diastolic dysfunction and hypertrophy, mitral regurgitation, and outflow tract obstruction are well-known determinants of increased LA size in HCM patients. Moreover, increased atrial fibrosis contributes to atrial enlargement and functional impairment. Although evidence is scarce, intrinsic atrial myopathy as part of the molecular disease has been suggested as well. Specific sarcomeric gene mutations have recently been described in atypical forms of HCM that relate to juvenile onset of AF in these patients. Even polymorphisms in nonsarcomeric genes, encoding for proteins involved in the renin-angiotensin-aldosterone system and collagen synthesis, have shown to act as HCM disease modifiers, increasing the likelihood of AF development. Therefore, it is not unexpected that AF often complicates the natural course of HCM, translating into a significant morbidity and mortality burden.
Current guidelines recommend intensification of diagnostic arrhythmia surveillance with 48-hour Holter 6-monthly once LA diameter is ≥45 mm. As atrial enlargement in the anteroposterior direction is restricted by the presence of the sternum and mediastinum (more specific), structural remodeling may be better described by evaluating atrial volume, often based on a 2D approach (more sensitive). Several reports demonstrate that increased LA volume heralds increased risk of AF and might be preferred over LA diameter. The current study confirms this hypothesis, indicating higher sensitivity and negative predictive value of LA volume versus diameter to identify patients at risk for new-onset AF.

Functional LA changes may coincide or even precede structural adaptations. Decreased LA ejection fraction, evaluated by echocardiography or cardiac MRI, has been linked to the occurrence of AF in HCM patients. 2-Dimensional speckle-tracking analysis allows angle-independent assessment of LA function by measuring magnitude (strain) or rate (strain rate) of atrial deformation. In particular, LA reservoir strain, referring to longitudinal deformation that occurs because of LA distention by pulmonary venous inflow during ventricular systole (reservoir phase), is a highly sensitive technique, able to identify atrial changes even in patients with normal LA size. Hence, impaired LA reservoir strain is often noted in HCM patients. A recent cross-sectional report in a limited number of patients indicated more impaired lateral reservoir Doppler-derived strain (rate) in HCM patients with versus without AF. One study in 50 HCM patients indicated that LA reservoir speckle tracking–derived strain independently predicts occurrence of AF requiring hospitalization (odds ratio, 0.85; 95%
CI, 0.75–0.97; \( P = 0.017 \). The present study, representing the largest cohort of HCM patients evaluated by LA strain to date, demonstrates higher sensitivity of LA strain compared with LA diameter to predict new-onset AF and confirms its independent predictive value for this end point.

Importantly, 59% of new-onset AF events in the HCM patients studied occurred despite a relatively preserved atrial diameter of <45 mm. This is of particular relevance because this subset of HCM patients is generally regarded as being at low risk to develop AF, and no additional follow-up measures are recommended.2 We showed that patients with LA diameter <45 mm who actually do develop AF have larger LA volume and more impaired LA function compared with patients free of atrial arrhythmia. In particular, patients with LA volume ≥37 mL/m² or LA strain ≤23.4% had worse survival free of AF. Presence of relatively preserved LA volume <37 mL/m² or LA strain >23.4% virtually excluded the risk of new-onset AF (negative predictive value of 93% and 98%, respectively). Not unexpectedly, additional assessment of LA volume and LA strain, therefore, conveyed a higher predictive value for new-onset AF in the subset of patients with LA diameter <45 mm.

Figure 2. Area under the curve (AUC)–based C statistics for new-onset atrial fibrillation at 5 y for different left atrial (LA) parameters. Top, Results for entire study population. Bottom, Restricted to patients with LA diameter <45 mm only. Note higher AUC for volume vs diameter with highest value for LA strain.

Table 4. Multivariable Cox Regression Analysis to Predict New-Onset AF for Different LA Parameters

<table>
<thead>
<tr>
<th></th>
<th>Multivariable LA Diameter</th>
<th>Multivariable LA Volume</th>
<th>Multivariable LA Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.03 (1.01–1.06)</td>
<td>0.012</td>
<td>1.04 (1.01–1.06)</td>
</tr>
<tr>
<td>E/e'</td>
<td>1.03 (0.99–1.07)</td>
<td>0.141</td>
<td>1.02 (0.98–1.06)</td>
</tr>
<tr>
<td>MR grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR grade 1</td>
<td>2.27 (0.83–6.22)</td>
<td>0.010*</td>
<td>2.17 (0.79–5.99)</td>
</tr>
<tr>
<td>MR grade 2/3/4</td>
<td>4.38 (1.51–12.70)</td>
<td></td>
<td>4.36 (1.50–12.69)</td>
</tr>
<tr>
<td>LA diameter ≥45 mm</td>
<td>1.67 (0.84–3.32)</td>
<td>0.145</td>
<td>...</td>
</tr>
<tr>
<td>LA volume ≥37 mL/m²</td>
<td>...</td>
<td>...</td>
<td>2.68 (1.30–5.54)</td>
</tr>
<tr>
<td>LA strain ≤23.4%</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Univariate predictors \( P < 0.05 \) in univariable model were included in the multivariable model. Separate models were created for each LA parameter to avoid collinearity. AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; LA, left atrium; and MR, mitral regurgitation.

*Median \( P \) value for MR grade across 100 imputations. Of note grades 2, 3, and 4 were collapsed to form one category.
HCM patients with LA diameter <45 mm. These findings probably reflect the previously reported higher sensitivity of LA volume and LA strain assessment in comparison with LA diameter.

**Clinical Implications**

Intensified monitoring to detect AF should indeed be offered to HCM patients with dilated LA ≥45 mm, as recommended. However, given the higher C statistics, sensitivity, negative predictive value, and positive predictive value of LA volume and strain as compared with LA diameter, both LA volume and strain assessment may be preferred over diameter. In addition, based on current findings, the intensified monitoring strategy should not be restricted to those patients with LA diameter ≥45 mm only, but LA volume and strain assessment should additionally be performed to rule out increased risk for AF. In those patients with LA volume >37 mL/m² and LA strain <23.4%, it might, therefore, be prudent to intensify follow-up aiming for detection of subsequent AF occurrence. In addition, observational data have indicated that patients with only one AF episode have similar risk for thromboembolism versus those with repeated episodes and oral anticoagulation using warfarin significantly decreased that likelihood. It has been suggested that prophylactic anticoagulation in HCM patients with increased LA size should be the focus of additional research. In light of current findings, it might prove valuable to consider additional assessment of LA volume or strain to facilitate such clinical decision making. Finally, ablation for AF in HCM patients is increasingly reported although the results seem less compared with non-HCM patients. The value of LA volume and strain rather than LA diameter to select candidates for ablation and predict success or recurrence of arrhythmia in HCM patients may be the scope of future investigation.

**Limitations**

Some limitations merit attention. First, this report is a retrospective longitudinal analysis of patients referred to a tertiary HCM center; therefore, selection bias cannot be fully excluded. Second, ICD recipients are submitted to continuous heart rhythm monitoring, increasing the likelihood of silent AF detection. Other patients were followed by annual ECG and Holter monitoring (at discretion of treating physician). Therefore, the true prevalence of new-onset AF may have been underestimated in our study population. No difference in LA remodeling was noted, however, between patients with clinical versus silent AF presentation.

**Conclusions**

Both LA size (diameter and volume) and function (strain) are related to new-onset AF in HCM patients. Overall, LA volume and strain outperform LA diameter and may be specifically useful to exclude increased risk for AF development based on their high negative predictive value. Furthermore, both parameters provide incremental predictive and discriminatory value also in the low-risk subset of patients with LA diameter ≤45 mm, still experiencing a significant proportion of AF events. Our findings, therefore, suggest that LA volume and strain may be preferred over LA diameter, and both might impact on provision and intensity of follow-up surveillance to detect AF in HCM, including in patients with preserved LA size.

**Sources of Funding**

No specific financial support for this work is involved. Dr Debonnaire was supported by a Sadra Medical Research Grant (Boston Scientific) and held a European Association of Cardiovascular Imaging (EACVI) Research Grant for 2013. Dr
LA Size and Function Versus AF Risk in HCM

Figure 4. Kaplan–Meier survival curves free of new-onset atrial fibrillation in patients with left atrial (LA) diameter <45 mm (n=185). Patients are stratified according to LA volume (A) and LA strain (B).

Delgado receives grants from St. Jude Medical. The Department of Cardiology of Leiden University Medical Centre received research grants from Biotronik, Medtronic, Boston Scientific, Lantheus Medical Imaging, Edwards Lifesciences, St. Jude Medical, and GE Healthcare.

Disclosures

None.

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Circ Arrhythm Electrophysiol. 2017;10:
doi: 10.1161/CIRCEP.116.004052

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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**Supplemental table 1. Clinical versus silent atrial fibrillation events: prevalence, diagnosis and left atrial remodeling comparison.** (Limited size of both groups compared may yield little power to detect differences.)

<table>
<thead>
<tr>
<th></th>
<th>Silent AF</th>
<th>Clinical AF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total study population (n=242)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AF events, n (%)</td>
<td>16/41 (39)</td>
<td>25/41 (61)</td>
<td>-</td>
</tr>
<tr>
<td>AF ECG diagnosis, n (%)</td>
<td>5/16 (31)</td>
<td>15/25 (60)</td>
<td>0.072</td>
</tr>
<tr>
<td>AF Holter diagnosis, n (%)</td>
<td>2/16 (13)</td>
<td>2/25 (8)</td>
<td>0.637</td>
</tr>
<tr>
<td>AF ICD/device diagnosis, n (%)</td>
<td>9/16 (56)</td>
<td>8/25 (32)</td>
<td>0.195</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>44 ± 6</td>
<td>43 ±6</td>
<td>0.492</td>
</tr>
<tr>
<td>LA volume, mL/m²</td>
<td>48 ± 15</td>
<td>47 ± 16</td>
<td>0.917</td>
</tr>
<tr>
<td>LA strain</td>
<td>19 ± 8</td>
<td>18 ± 7</td>
<td>0.641</td>
</tr>
<tr>
<td><strong>Patients with LA diameter &lt;45 mm only (n=185)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AF events, n (%)</td>
<td>10/24 (42)</td>
<td>14/24 (58)</td>
<td>-</td>
</tr>
<tr>
<td>AF ECG diagnosis, n (%)</td>
<td>2/10 (20)</td>
<td>6/14 (43)</td>
<td>0.388</td>
</tr>
<tr>
<td>AF Holter diagnosis, n (%)</td>
<td>1/10 (10)</td>
<td>1/14 (7)</td>
<td>1.000</td>
</tr>
<tr>
<td>AF ICD/device diagnosis, n (%)</td>
<td>7/10 (70)</td>
<td>7/14 (50)</td>
<td>0.421</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>41 ± 3</td>
<td>39 ± 4</td>
<td>0.150</td>
</tr>
<tr>
<td>LA volume, mL/m²</td>
<td>41 ± 11</td>
<td>45 ± 19</td>
<td>0.544</td>
</tr>
<tr>
<td>LA strain, %</td>
<td>22 ± 8</td>
<td>18 ± 7</td>
<td>0.174</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation, ECG: electrocardiogram, ICD: implantable automated cardiac defibrillator, LA: left atrium
Supplemental Figure 1. Visual representation of Cox regression linear base model versus non linear spline fit model of second (left panels) and third (right panels) degree. Panel A-B: left atrial (LA) diameter, Panel C-D: LA volume, Panel E-F: LA strain. No substantial deviation from a linear relation could be detected for all 3 LA parameters. Comparison between the non-linear and linear model fits using likelihood ratio testing in addition revealed no significant differences. In the absence of a clear step-up (non-linear) effect, the use of median value for LA volume (37 mL/m²) and LA strain (23.4%) as cut-off point is therefore justified.
Supplemental figure 2. Likelihood ratio test. Panel A: entire study cohort (n=242), Panel B: patients with left atrial diameter <45 mm (n=185). Subsequent addition of both left atrial (LA) volume (≥ 37mL/m²) and LA strain (≤23.4 %) on top of LA diameter (≥45 mm) assessment provides incremental value for prediction of new onset atrial fibrillation.