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Left atrioventricular coupling index in hypertrophic cardiomyopathy and risk of new-onset atrial fibrillation

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ABSTRACT

Backgrounds: This study aimed to investigate the association between left atrioventricular coupling index (LACI) and the occurrence of atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy (HCM).
Methods: A total of 373 patients with HCM and no history of AF were evaluated by transthoracic echocardiography. LACI was defined by the ratio of left atrial (LA) end-diastolic volume divided by left ventricular (LV) end-diastolic volume. The cut-off value for LACI (≥40%) to identify LA-LV uncoupling was chosen based on the risk excess of new-onset AF described with a spline curve analysis.
Results: The median LACI was 37.5% (IQR: 24.4–56.7) and LA-LV uncoupling (LACI ≥40%) was observed in 171 (45.8%) patients. During a median follow-up of 11 (IQR 7–15) years, 118 (31.6%) subjects developed new-onset AF. The cumulative event-free survival at 10 years was 53% for patients with LA-LV uncoupling versus 94% for patients without LA-LV uncoupling ($p < 0.001$). Multivariable Cox regression analyses performed separately for each LA parameter showed an independent association between new-onset AF and LACI (hazard ratio [HR], 1.021; 95% CI, 1.017–1.026), LA maximum volume indexed (HR, 1.028; 95% CI, 1.017–1.039), LA minimum volume indexed (HR, 1.047; 95% CI, 1.037–1.060) and LA emptying fraction (HR, 0.967; 95% CI, 0.959–0.977, all $p < 0.001$). The inclusion of LACI in the multivariate model provided a larger improvement in the risk stratification for new-onset AF, as compared to conventional LA parameters.
Conclusion: In patients with HCM, LACI was more predictive of the occurrence of new-onset AF than conventional LA parameters.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in hypertrophic cardiomyopathy (HCM), occurring in about 20% of patients with an annual incidence of >2% [1–3]. Patients who develop AF are vulnerable to symptoms, hospitalization for heart failure or thromboembolic events, and, importantly, are known to have worse prognosis [1,2]. AF increases by 4-fold the risk of mortality in patients with HCM, independently from other risk factors, mainly due to heart failure and stroke-related death [1,2,4]. Thus, accurate risk stratification for new-onset AF is crucial and may have an impact on follow-up and treatment strategies.

Left atrial (LA) structural and functional remodeling strongly predicts AF development in patients with HCM [1–3,5–8]. Increased LA size and impaired LA function are common findings in HCM [5–8] and likely consequence of impaired left ventricular (LV) diastolic function, associated with LV hypertrophy and stiffness [1]. Indeed, LA and LV are directly connected during ventricular diastole and, in absence of mitral valve stenosis, their function and filling pressures are tightly coupled [9,10]. On this basis, it has been suggested that a single left atrioventricular parameter, which takes into account simultaneously LA and LV, may be a more sensitive marker of LA remodeling than individual LA parameters [11]. Hence, a novel left atrioventricular coupling index (LACI), defined by the ratio between LA and LV volumes measured in the

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ventricular end-diastole, has been introduced and investigated in a large cohort of patients without history of cardiovascular disease enrolled in the Multi-Ethnic Study of Atherosclerosis [11]. Among individuals free of clinically recognized heart failure and cardiovascular disease at baseline, LACI was independently associated with the incidence of AF, showing better predictive value for this end-point than individual LA and LV parameters [11].

We hypothesized that the use of this simple ratio may improve risk stratification for AF occurrence in patients with HCM, as compared to traditional LA measurements. Therefore, the objective of the present study was to investigate the association between LACI and new-onset AF in a large population with HCM and its incremental value over conventional LA parameters.

2. Methods

2.1. Study population

The population consisted of patients ≥18 years of age with HCM, defined according to current guidelines: a maximal LV wall thickness of ≥15 mm, in the absence of any other cardiac or systemic disease that could explain a similar degree of LV hypertrophy [12]. Patients were selected from an ongoing registry, excluding individuals with a history of AF at the time of the echocardiography or insufficient image quality to allow LACI assessment.

Demographic and clinical characteristics were collected from the departmental electronic patient information system (EPD Vision, Leiden University Medical Center, Leiden, The Netherlands).

At baseline, all patients with HCM had 12-lead ECG and 24-h ambulatory ECG Holter monitoring. As recommended, patients were followed-up on a yearly basis, including a clinical visit and 12-lead ECG [12]. Repeated 12-lead ECG or ECG Holter monitoring were performed at the discretion of the treating physician according to symptoms, presence of LA dilation, or for sudden cardiac death risk stratification. Device interrogation was performed every 3 to 6 months in patients with implantable cardioverter-defibrillators (ICDs).

As this study concerned a retrospective analysis of clinically acquired data, the institutional review board of the Leiden University Medical Center waived the need for written patient informed consent.

2.2. Echocardiographic analysis

Comprehensive transthoracic echocardiograms were performed using a commercially available system (VIVID 7, E9 and E95, GE-Vingmed, Horten, Norway) equipped with the MS5 and 4Vc-D 4D matrix cardiac probes. Two-dimensional, color, spectral continuous- and pulsed-wave Doppler images were obtained from the parasternal, apical and subcostal views. All images were digitally stored for offline analysis (EchoPAC version 203; GE-Vingmed, Horten, Norway).

From a short-axis view at basal, mid, and apical levels, the maximal LV end-diastolic wall thickness

was assessed. Septal and posterior wall thickness and LV diameters were measured from parasternal long-axis views, as recommended [13]. LV mass was then calculated according to the Devereux formula and indexed for body surface area (BSA) [14].

From the apical 2- and 4-chamber views, the LV end-diastolic and end-systolic volumes were measured and indexed for BSA and LV ejection fraction (LVEF) was calculated using the biplane Simpson's method [13]. Maximal and minimal LA volumes were obtained from the apical 2- and 4-chamber views, at end-systole and end-diastole respectively, using the biplane Simpson's method and then indexed for BSA (LAVImax and LAVImin, respectively). LA emptying fraction (LAEF) was calculated as follows: (LAVImax − LAVImin)/LAVImax, and expressed as percentage.

Diastolic parameters, including E/A and E/e' ratio,were assessed using pulsed wave Doppler at the tips of the mitral leaflets and tissue Doppler imaging at the level of the medial and lateral annulus, respectively [15].

The presence of systolic anterior movement of the mitral valve was assessed from parasternal long-axis and apical 3- and 5-chamber views. Resting LV outflow tract (LVOT) obstruction gradient was systematically explored by pulsed wave Doppler and quantified by continuous wave Doppler. Finally, the grade of mitral regurgitation was evaluated according to a multiparametric approach, as recommended [16].

2.3. Left atrioventricular coupling index

LACI was defined by the ratio between the LA end-diastolic volume (LAVmin) and the LV end-diastolic volume [11]. The LA and LV volumes were measured in the same end-diastolic phase defined by the mitral valve closure. LACI values were expressed as percentage with higher LACI indicating greater disproportion between the LA and LV volumes at ventricular end-diastole, reflecting greater impairment of left atrioventricular coupling [11].

2.4. Follow-up and clinical endpoints

New-onset AF at outpatient or emergency room visits, defined as an irregular heart rhythm without distinct P-waves documented on ECG, Holter ECG monitoring (if duration ≥30 s), or after expert analysis from device recordings in patients with implantable cardiac monitoring systems [17], comprised the primary study end-point. According to current recommendations, AF episodes were classified as clinical if documented by surface ECG or subclinical if they were asymptomatic and detected by implantable cardiac monitoring systems (duration ≥5 min) [17].

2.5. Statistical analysis

Normally distributed continuous variables are presented as mean ± standard deviation whereas non-normally distributed data are presented as median and interquartile range. Categorical variables are expressed as frequencies and percentages.

A spline curve analysis was performed to investigate the hazard ratio (HR) changes for new-onset AF across the range of LACI values. The cut-off value of LACI (≥40%) associated with increased risk of new-onset AF was estimated using the fitted spline curve (HR of the lower limit of the 95% confidence intervals [CIs] ≥1) and was used to define left atrioventricular uncoupling.

Cumulative event-free survival rates for the overall population, stratified by a specific LACI cut-off value (defined by the spline curve analysis) and LACI quartiles, were calculated using the Kaplan–Meier method. The log-rank test was used to compare the above defined groups.

The association between clinical and echocardiographic variables with the occurrence of new-onset AF was investigated using univariable and multivariable Cox proportional hazard regression models. Variables with a significant association in the univariable analysis ($p < 0.05$) were included in the multivariable regression models, using multiple imputation to account for missing data (E/e', $n = 64$). We generated 100 multiple imputed data sets and the results were combined using Rubin rules. For collinearity reasons, multivariable testing was performed separately for each LA parameter (LAVImax, LAVImin, LAEF and LACI). A minimum tolerance level of 0.5 and a maximum correlation coefficient of 0.7 were established to avoid collinearity between covariates. The proportional hazards assumption was verified based on Schoenfeld residuals. Model discrimination was evaluated by calculating the Harrell's C-statistic and its 95% CIs.

The incremental prognostic value of LACI over conventional LA parameters was investigated using the likelihood ratio X^2 test for nested models and the receiver operating Characteristic (ROC) curve analysis for the categorical endpoint of AF occurrence at 10-years. The comparison between areas under the curve (AUCs) of different LA

parameters was performed by the DeLong's method [18]. Finally, the risk stratification value of LACI cut-off (defined by the spline curve) was evaluated after stratification for mitral regurgitation (MR) grade and LAVImax (using the guidelines-based threshold of LAVImax to define LA dilation).

Two-sided *p*-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient population

After excluding patients with history of AF ($n = 49$) and insufficient image quality for LACI assessment ($n = 8$), 373 patients with HCM were included in the present study. Baseline demographic, clinical, and echocardiographic characteristics are provided in Table 1. The study cohort exhibited typical features of HCM including increased LV wall thickness, small LV cavities and preserved LVEF, together with LA dilation. In addition, the presence of systolic anterior movement of the mitral valve or resting LVOT obstruction (peak gradient ≥30 mmHg) was observed in one third of the population. The median value of LACI in the overall population was 37.5% (IQR: 24.4–56.7). No gender-based differences were present in LACI values. Patients were divided according to quartiles of LACI, being ≤24.4% the first quartile (best left atrioventricular coupling), 24.4% to 37.5% the second quartile, 37.5% to 56.7% the third quartile and ≥ 56.7% the fourth quartile (worst left atrioventricular coupling).

Table 1
Baseline characteristics of the study population.

Clinical characteristics	Population ($n = 373$)
Age (years)	48 ± 17
Male gender (n,%)	245 (65.7)
Hypertension (n,%)	130 (35.0)
Diabetes (n,%)	42 (11.3)
Dyslipidemia (n,%)	126 (33.8)
NYHA class (n,%)	
I/II	359 (96.2)
III/IV	14 (3.8)
ICD (n,%)	33 (8.9)
Primary prevention	23(6.2)
Secondary prevention	10 (2.7)
Medications (n,%)	
Beta-blockers	164 (44.0)
Calcium-antagonists	104 (28.0)
Diuretics	40 (10.7)
Echocardiographic Characteristics	
Maximum LV wall thickness (mm)	18 (16–22)
LVEDD (mm)	44 (40–48)
LV mass index (g/m^2)	135 (112–174)
LVEDVI (ml/m^2)	46 (40–54)
LVEF (%)	66 (59–72)
LAVImax (ml/m^2)	36 (29–45)
LAVImin (ml/m^2)	18 (11–26)
LAEF (%)	51 (36–65)
LACI (%)	37.5 (24.4–56.3)
E/A	1.1 (0.8–1.4)
E/e'	11.2 (8.5–15.5)
Systolic anterior motion of MV (n,%)	139 (37.3)
Rest LVOT gradient >30 mmHg (n,%)	68 (18.2)
Moderate or severe MR (n,%)	76 (20.4)

Values are expressed as n (%), mean ± SD or median (IQR).
Abbreviations. ICD: implantable cardioverter defibrillator; LA: left atrial; LACI: left atrioventricular coupling index; LAEF: LA emptying fraction; LAVImax: indexed maximal LA volume; LAVImin: indexed minimal LA volume; LV: left ventricular; LVEDD: LV end-diastolic diameter; LVEDVI: indexed LV end-diastolic volume; LVEF: LV ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association.

3.2. Follow-up and clinical endpoints

During a median follow-up of 11 (7–15) years, 118 (32%) patients experienced new-onset AF. The majority of the events were classified as clinical AF (84% versus 16% episodes of subclinical AF).

In order to investigate the relationship between LACI and the occurrence of new-onset AF, a spline curve was fitted, demonstrating that higher values of LACI were associated with an increased probability of new-onset AF at 10-years follow-up (Fig. 1). A cut-off value for LACI of ≥40% identified left atrioventricular uncoupling based on the risk excess of new-onset AF. Left atrioventricular uncoupling was observed in 171 (45.8%) patients.

Patients with left atrioventricular uncoupling (LACI ≥40%) had a lower cumulative event-free survival compared to those without left atrioventricular uncoupling (LACI <40%): 85% versus 99% at 1 year, 68% versus 98% at 5 years, 53% versus 94% at 10 years (all log-rank $p < 0.001$; Fig. 2A). Furthermore, survival free from new-onset AF was progressively lower when the population was stratified according to LACI quartiles (99%, 90%, 67% 37% at 10 years for quartiles 1, 2, 3 and 4 respectively; log-rank $p < 0.001$; Fig. 2B).

On the univariable Cox regression analysis (Table S1), LACI was significantly associated with incident AF, either expressed as continuous variable (HR of 1.019 [95% CI: 1.016–1.023]; p < 0.001) or as dichotomous variable, LACI≥40% (HR of 8.175 [95% CI: 5.049–13.236]; p < 0.001). In addition, age, the use of beta-blockers, LV mass index, LVEF, E/e', resting LVOT obstruction, moderate or severe MR, LAVImax, LAVImin and LAEF were also associated with the occurrence of new-onset AF. Several multivariable Cox regression models were built including significant clinical and echocardiographic variables (age, the use of beta-blockers, LV mass index, LVEF, E/e' and resting LVOT obstruction) and alternatively one of LA parameters (LACI, LAVImin, LAVImax and LAEF) (Table 2). These multivariable models demonstrated an independent association between each LA parameter and AF occurrence (all $p < 0.001$). Notably, the multivariable models incorporating LACI, either as continuous or categorical variable, yielded higher C-statistic, as compared to those including LAVImax, LAVImin or LAEF (Table 2).

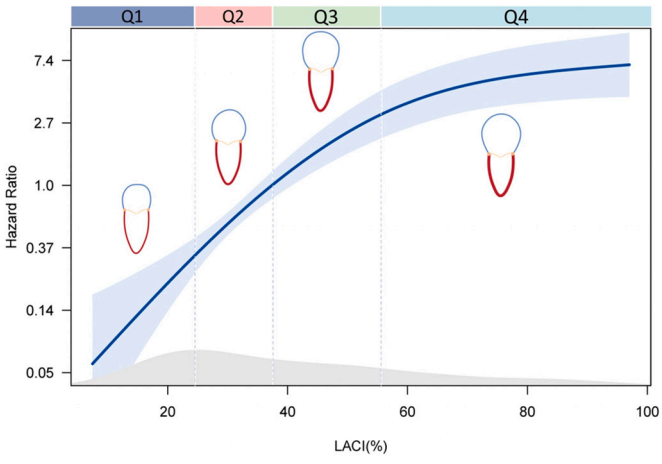

Fig. 1. Spline curve analysis for incident AF according to LACI values.
Penalized spline curve shows the hazard ratio changes for new-onset AF with 95% confidence intervals (shaded blue areas) across the range of LACI values.
Abbreviations. AF: atrial fibrillation; LACI: left atrioventricular coupling index; Q: quartile. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

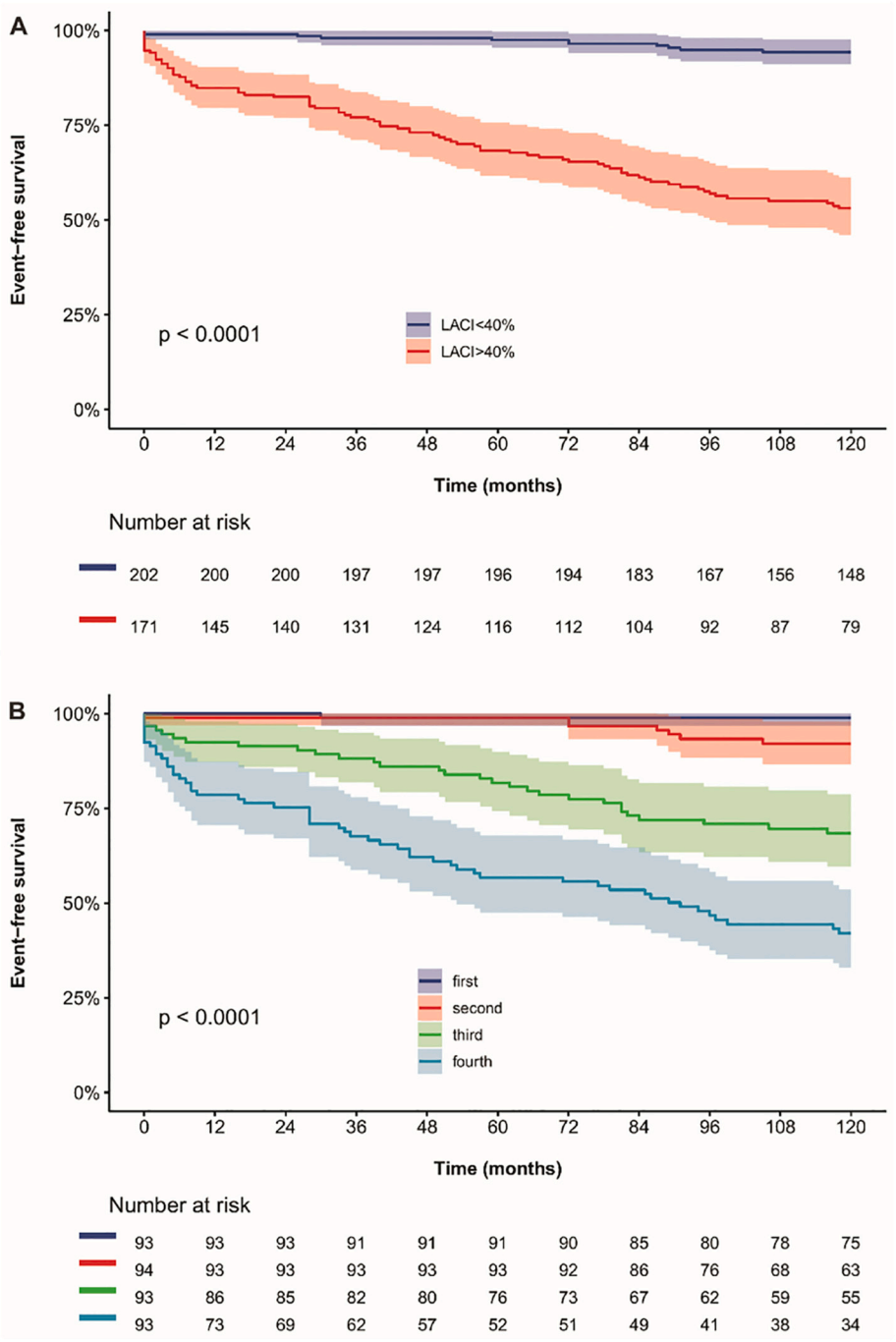

Fig. 2. Kaplan-Meier curves at 10 years for new-onset AF stratified by LACI ≥40% (A) and LACI quartiles (B).
Abbreviations. AF: atrial fibrillation; LACI: left atrioventricular coupling index; Q1: first quartile (LACI≤24.4%); Q2: second quartile (24.4%<LACI>37.5%); Q3: third quartile (37.5% ≤ LACI>56.7%); Q4: fourth quartile (LACI>56.7%).

3.3. Incremental value of LACI assessment

The likelihood ratio X^2 test demonstrated an incremental value of LACI to predict new-onset AF on top of the multivariate model including LAVImin or LAVImax ($p = 0.017$ and $p < 0.001$, respectively), while the addition of LAVImin or LAVImax did not improve the risk discrimination of the model including LACI ($p = 0.135$ and $p = 0.635$, respectively).

On ROC curve analysis (Fig. S1), LACI showed higher discrimination power to identify patients at risk of AF at 10 years, as compared to LAVImin, LAEF and LAVImax (AUC of 0.850 vs 0.830, $p = 0.068$; 0.850 vs 0.783, $p = 0.002$ and 0.850 vs 0.715, $p < 0.001$; respectively).

To further confirm the additive prognostic value of LACI, the population was stratified according to the LAVImax guidelines-based threshold to define LA dilation (LAVImax>34 ml/m^2) (13). The risk of developing new-onset AF at 10 years of follow-up was significantly higher in patients with left atrioventricular uncoupling (LACI≥40%) versus patients without left atrioventricular uncoupling (LACI<40%), irrespective of the presence of LA dilation (log-rank $p < 0.001$) (Fig. S2 A-B). Similarly, when the population was stratified according to the MR grade (no-mild MR and moderate-severe MR), left atrioventricular uncoupling was consistently associated with an increased risk of developing new-onset AF (log-rank $p < 0.001$) (Fig. S3 A-B).

Table 2
Association between left atrial parameters and the occurrence of AF: Multivariable Cox regression models.

Multivariable models	Adjusted HR (95% CI)	P-value	C-statistic (95% CI)
Baseline model + LACI (%)	1.021 (1.017–1.026)	<0.001	0.806 (0.801–0.809)
Baseline model + LACI, cutoff >40%	7.229 (4.373–11.950)	<0.001	0.801 (0.797–0.804)
Baseline model + LAVImin (ml/m^2)	1.047 (1.037–1.060)	<0.001	0.788 (0.784–0.792)
Baseline model + LAVImax (ml/m^2)	1.028 (1.017–1.039)	<0.001	0.750 (0.746–0.754)
Baseline model + LAEF (%)	0.967 (0.959–0.977)	<0.001	0.772 (0.768–0.776)

Legend. Each LA parameter was separately added to the baseline multivariable model. The baseline model comprises the following variables: age, the use of beta-blockers, LV mass index, LVEF, E/e' and the presence of resting LVOT obstruction. The adjusted hazard ratio of LA parameters and the C-statistic are illustrated.
Abbreviations. CI: confidence intervals; HR: hazard ratio; LA: left atrial; LACI: left atrioventricular coupling index; LAEF: LA emptying fraction; LAVImax: indexed maximal LA volume; LAVImin: indexed minimal LA volume; LV: left ventricular; LVEF: LV ejection fraction; LVOT: left ventricular outflow tract.

4. Discussion

In the present study, we demonstrated that LACI, a novel left atrioventricular coupling index, is significantly associated with new-onset AF in a large cohort of patients with HCM. Of note, LACI showed a stronger risk stratification power for new-onset AF than conventional LA parameters.

AF is commonly observed in patients with HCM and is a key determinant of symptoms and long-term outcomes [1–4]. Thus, accurate risk stratification for new-onset AF is of crucial importance and may have an impact on follow-up strategies and therapeutic decisions.

The association between LA structural and functional remodeling and AF development in HCM has been consistently reported [1–3,5–8]. LA dilation, assessed by an increase in LA antero-posterior diameter [1,3] or volume [5–7], is an independent predictor of AF occurrence. Additionally, parameters of LA function, including LAEF evaluated by echocardiography or cardiac magnetic resonance [7,8] and LA reservoir strain measured by speckle-tracking echocardiography [4], demonstrated an incremental value over LA size for the prediction of new-onset AF.

Although LA antero-posterior diameter has been traditionally considered the strongest AF correlate in patients with HCM, several reports demonstrated a higher sensitivity of LAVImax to identify HCM patients at risk of new-onset AF [5–8]. In addition, recent investigations suggested that measuring LAVImin may be more robust than LAVImax to predict cardiovascular events [19–23]. LA can be stretched by LV longitudinal systolic function through systolic displacement of the mitral annular plane toward the LV apex, which may influence LAVImax. On the other hand, LAVImin is measured at end-diastole, when the LA is more directly exposed to LV pressure. Accordingly, it has been shown that LAVImin is more closely related to invasively measured LV filling pressure and NT-proBNP levels, than LAVImax [19,20]. A rise in LAVImin may also better reflect the reduction of LA pump function, which has been proposed as an independent predictor of incident AF [24]. Among patients without previous history of cardiovascular disease, LAVImin was superior to LAVImax for predicting newly developed AF [25–27]. Consistent with those data, the present study shows a stronger association of LAVImin with new-onset AF, as compared to LAVImax, in patients with HCM.

Multiple determinants of LA remodeling in HCM have been described, including resting LVOT obstruction, mitral regurgitation and an intrinsic atrial myopathy associated with specific HCM-causing mutations [1,28,29]. However, LA remodeling is more typically caused by LV diastolic dysfunction and increased LV filling pressure, related to myocardial hypertrophy and interstitial fibrosis [1,28].

Considering the close interaction between LA and LV structure and function, LACI may represent a next step in order to further optimize the AF risk stratification using conventional echocardiography. An increase in LA volume relative to that of the LV at end-diastole directly reflects the impairment of LV compliance. Therefore, the assessment of LACI may allow to detect earlier stages of LA remodeling, in comparison to conventional LA parameters [11]. In the context of HCM, a rise in LACI may also account for the decrease of LV size that can occur with the progression LV hypertrophy. Of remarkable importance for clinical practice, LACI can be easily calculated from standard echocardiographic images, without the need of additional acquisition or postprocessing software. This novel index was recently introduced in a large multiethnic population of 4124 patients, free of cardiovascular disease at enrollment, using cardiac magnetic resonance data [11]. LACI was an independent predictor for the incidence of new-onset AF, heart failure and cardiovascular disease, showing better prognostic value than individual LA and LV parameters (including strain parameters) [11]. Similarly, we found that LACI was strongly associated with AF occurrence in patients with HCM and exhibited better risk stratification power for this end-point as compared with conventional LA parameters, including LAVImin, LAVImax and LAEF.

Of interest, the concept of left atrioventricular coupling has gained increasing attention in the recent years [30–32]. Particularly, Benfari et al. suggested an index of left atrioventricular coupling, defined by ratio between LAVImax and tissue-Doppler myocardial velocity at atrial contraction (TDI-a'), as predictor of survival in patients with heart failure with reduced LVEF [30]. This alternative parameter may be particularly valuable for the assessment of left atrioventricular coupling in the presence of LV dilation. Conversely, the prognostic value of LACI for the prediction of clinical outcomes in patients with heart failure and preserved LVEF may be the object of further studies.

4.1. Clinical implications

Given the substantial risk of stroke associated with AF development, periodic surveillance with ambulatory ECG Holter registration in high-risk patients may allow early intervention with anticoagulants. Accordingly, current guidelines of HCM recommend intensified monitoring to detect AF in patients with LA dilation, as well as patients with advanced age and New York Heart Association class III-IV heart failure symptoms (class IIa recommendation) [12]. In the light of the better and incremental risk stratification power of LACI as compared to indexed LA volumes, the assessment of left atrioventricular coupling may be a useful additional tool for the selection of patients at higher risk of AF, who should be candidates for intensified follow-up.

Considerable debate exists regarding the threshold of AF duration for initiation of anticoagulation in patients with subclinical AF [12,17]. At the current state, the decision should be tailored for each patient, taking also into account the total AF burden and the underlying substrate [12,17]. Thus, it might be valuable to consider the assessment of left atrioventricular coupling to facilitate such clinical decision making.

4.2. Limitations

Some limitations should be acknowledged. First, this is a retrospective longitudinal analysis of patients referred to a tertiary center and, therefore, selection bias cannot be fully excluded.

Moreover, implantable cardiac monitoring system recipients had continuous heart rhythm monitoring, increasing the likelihood of AF detection. However, only a minority of events detected during follow-up were subclinical (16%).

Other potentially relevant factors for AF prediction such as ECG features, the presence of symptoms or inducible myocardial ischemia

were not considered, being the main purpose of our study to investigate the predictive value of LACI in comparison to conventional LA parameters.

Further prospective studies are required to confirm our findings and to assess how LACI can optimize clinical decision making in patients with HCM.

4.3. Conclusions

A higher LACI, indicative of LA-LV uncoupling, was independently associated with the occurrence of AF in patients with HCM, demonstrating a stronger and incremental value in comparison to conventional LA parameters.

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CRediT authorship contribution statement

Maria Chiara Meucci: Data curation, Investigation, Formal analysis, Writing – original draft. **Federico Fortuni:** Software, Validation. **Xavier Galloo:** Data curation, Investigation. **Marianne Bootsma:** Resources. **Filippo Crea:** Supervision. **Jeroen J. Bax:** Supervision, Visualization. **Nina Ajmone Marsan:** Methodology, Visualization. **Victoria Delgado:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

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Appendix A. Supplementary data

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