Cardiovascular Ultrasound

RESEARCH

Open Access

The role of left atrio-ventricular coupling index and left atrial ejection fraction in predicting onset of atrial fibrillation and adverse cardiac events in hypertrophic cardiomyopathy

Parisi Francesca[1*], La Franca Eluisa[1], Pistelli Lorenzo[2], Gentile Giovanni[3], Bellavia Diego[4], Nuzzi Vincenzo[1], Manca Paolo[1], Massimiliano Mulè[1], Zito Concetta[2], Di Bella Gianluca[2], Scipione Carerj[2], Cipriani Manlio[1] and Francesco F. Faletra[1]

Abstract

Background Several predictors of atrial fibrillation (AF) onset in patients with hypertrophic cardiomyopathy (HCM) have been proposed, however, all of them showed limited accuracy. This study aims to assess the role of new echographic parameters in predicting AF onset and major adverse cardiovascular outcomes (cardiovascular death or heart transplantation).

Methods Clinical and imaging data from 141 patients with HCM and without a history of AF were retrospectively analyzed over a 5-year period. Patients who developed AF during the study were compared to those who did not. The analysis focused on key atrial parameters, including the Left Atrial Contraction Index (LACI) and Left Atrial Ejection Fraction (LAEF). LACI was defined as the ratio of left atrial end-diastolic volume to left ventricular end-diastolic volume. Echocardiographic measurements were standardized using cardiac magnetic resonance (CMR) as the reference. Regarding statistical analysis, each significant continuous variable was categorized by identifying a cut-off value using the Youden index. Independent associations with outcomes and cumulative survival were assessed using Cox regression analysis.

Results Thirty-five patients developed AF, at a mean time of 4 years. The HCM-AF group had significantly higher values of LACI, left atrial diameter (LAD), and left atrial minimum volume (LAVmin). A LACI > 43% on echocardiography and LACI > 44% on CMR showed the best performance in identifying patients at risk for AF. In multivariate analysis, an echocardiographic LAEF < 43% was independently associated with the occurrence of AF (HR 2.9, 95% CI: 1.2–6.9). Additionally, a LAD > 40.5 mm was independently associated with AF onset, with a hazard ratio of 2.5 (95% CI 1.1–5.5). Eleven patients experienced the composite outcome of cardiovascular death or heart transplant, and a LACI > 60% was associated with this outcome.

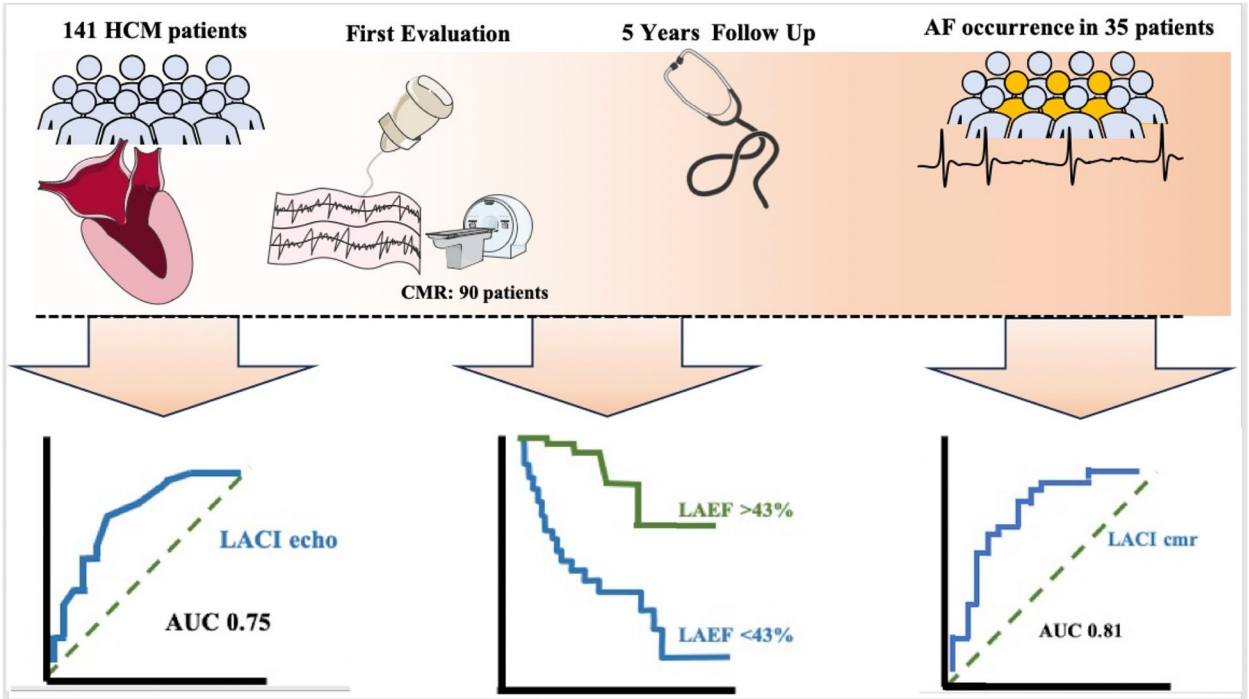
*Correspondence:
Parisi Francesca
fparisi@ismett.edu
Full list of author information is available at the end of the article

Conclusion In patients with HCM, both LACI and LAEF were significantly associated with the occurrence of AF over a 4-year period, demonstrating higher sensitivity and specificity compared to other parameters. A LACI > 60% was also found to be associated with cardiovascular death or heart transplant in this population.

Keywords Atrial fibrillation, Hypertrophic cardiomyopathy, Adverse outcome, Predictor, Imaging

Graphical Abstract

Evaluation of left atrial morpho-functionl parameter using multimodality imaging, and their association with atrial fibrillation in HCM patients. The figure summarizes the main findings of the present article. AF: atrial fibrillation; CMR: cardiac magnetic resonance; HCM: hypertrophic cardiomyopathy; TTE: transthoracic echocardiography; LACI: left atrioventricular coupling index; LAEF: left atrium ejection fraction.



Background

Atrial fibrillation (AF) is the most common arrhythmia in patients with hypertrophic cardiomyopathy (HCM), with an estimated prevalence of 25%, rising to over 40% in those older than 70 years [1]. A HCM patient has a 4 to sixfold increased lifetime risk of developing AF, with the first episode typically occurring at a younger age (around 55 years) compared to the general population [2]. Left ventricular (LV) diastolic dysfunction, mitral insufficiency, and left ventricular outflow tract obstruction (LVOTO) are key factors to atrial dilation and wall stress, promoting left atrial (LA) fibrosis and mechanical dysfunction, and finally creating a favorable substrate for AF [3]. In HCM, AF has significant prognostic implications, being associated with a threefold increased risk of heart failure (HF) and stroke [4]. Identifying patients at higher risk for AF is crucial to ensure early therapeutic intervention and prevent AF-related complications, ultimately improving their prognosis. Over the years, various indicators have been proposed to predict the development of AF, but none have demonstrated reliable sensitivity or specificity. Among these, the most commonly used is the anteroposterior left atrium diameter (LAD) ≥ 45 mm [5, 6]. Recently, the left atrio-ventricular coupling index (LACI) has been proposed as early marker of left atrium remodeling and impaired ventricular compliance. This parameter was defined as the ratio between left atrial end-diastolic volume and left ventricular end-diastolic volume (LVEDV) [7, 8].

Meucci et al., in a large population of patients with HCM, demonstrated that LACI is a promising predictor of AF [8]. However, to date, no previous study has compared LACI to other established and more commonly used indicators. Furthermore, the standardization of LACI echocardiographic measurements has yet to be evaluated. Additionally, while the prognostic implications of LACI have been investigated in other populations, they remain unexplored in the context of HCM [9].

Among other imaging parameters, left atrial ejection fraction (LAEF) has also been evaluated by Maron et al., who demonstrated that LAEF, assessed by cardiac magnetic resonance (CMR), was associated with a higher risk of developing AF. However, only a few other studies have investigated this correlation [10].

Our study aims to analyze the morpho-functional parameters of the left atrium and investigate their association with AF in HCM, compared to more commonly used parameters such as LAD. We also sought to enhance the objectivity and standardization of echocardiographic measurements by using CMR as a reference. Furthermore, we assessed the correlation between these parameters and major adverse cardiovascular outcomes, including heart transplantion (HTx) and cardiovascular death (CV death).

Materials and methods

Study population and design

The data of 141 HCM patients who underwent their first outpatient evaluation between 2011 and 2018 at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) were retrospectively retrieved from our digital archive and analyzed. Initially, the population consisted of 206 patients; however, 64 patients were excluded based on the following criteria: 1. Significant mitral valve disease that could influence the analysis of morpho-functional atrial parameters (defined as mitral regurgitation greater than moderate or the presence of mitral stenosis); 2. reduced ejection fraction (EF), defined as EF below 50%; 3. Initial LV dilation (LVEDV > 150 ml for males, > 106 ml for females); 4. History of AF or supraventricular tachycardia. The diagnosis of HCM was based on the presence of left ventricular hypertrophy, after excluding other possible cardiac and extracardiac causes [11]. Both obstructive and non-obstructive HCM patients were included. AF was defined according to guidelines [12]. Patients were followed up with annual continuous Holter monitoring and outpatient visits, including a 12-lead electrocardiogram (ECG) every 6 months or whenever symptoms occurred. Data from cardiac implantable devices were also included in the analysis. Indications for HTx were based on guidelines [13].

Echocardiographic data

All transthoracic echocardiograms (TTE) were analyzed offline with specialized software (EchoPAC). Conventional measurements were conducted in accordance with the recommendations of the European Society of Echocardiography and based on established reference values [14]. The end-systolic (LAVmax) and end-diastolic (LAVmin) volumes of the left atrium were measured in both the apical 4-chamber and 2-chamber views. LAEF was calculated as follows:

$$\mathrm{LAEF} = (\mathrm{LAVmax} - \mathrm{LAVmin})/\mathrm{LAVmax}$$

and expressed as a percentage. The LACI was defined as the ratio of LAVmin to left ventricular end-diastolic volume (LVEDV):

$$\mathrm{LACI} = \mathrm{LAVmin}/\mathrm{LVEDV}$$

and expressed as a percentage. Both volumes were measured during the same end-diastolic phase, at the time of mitral valve closure [7].

Cardiac magnetic resonance protocol

Ninety (90) patients from our cohort underwent CMR within 6 months of the indexed echocardiographic evaluation. CMR was performed using a 1.5 T scanner (Signa Excite HDxt platform, GE Healthcare, Milwaukee, WI, U.S.A.) with prospective ECG gating and surface coils positioned anteriorly and posteriorly on the patient's chest. In all patients, scout images were acquired in the transaxial, coronal, and sagittal planes, followed by breath-hold bSSFP (balanced steady-state free precession) cine images in long axis, and in the 4-, 3-, and 2-chamber views, as well as short-axis views covering the entire left ventricle from the atrioventricular plane to the apex. T2-weighted images were also obtained. Late gadolinium enhancement (LGE) images were acquired 10 min after intravenous infusion of gadolinium-based contrast medium (DTPA—diethylenetriaminepentaacetic acid) at a dosage of 0.1 mmol/kg, in the short axis and the 4-, 3-, and 2-chamber long-axis views, using the same orientations as the bSSFP cine images. The slice thickness was set to 8 mm with no inter-slice gap, a 224×224 matrix, a 50° flip angle, TI of 300 ms, and 30 cardiac phases. The acquired images were then analyzed.

Estimation of left ventricular volumes and mass was performed by manually tracing the endocardial and

epicardial borders in short-axis bSSFP cine sequences. Atrial volumes were evaluated using the 4- and 2-chamber long-axis cine bSSFP sequences, with the subendocardial border traced manually [15]. LAEF and LACI were calculated according to the same percentage ratios described for TTE. Finally, a comparison was made between the CMR data and those obtained from TTE to corroborate the results.

Statistical analysis

Continuous variables were tested for normality with the Shapiro–Wilk test, and subsequently analyzed with Student's t-test for independent samples or, when appropriate, with the Mann–Whitney test. The variance of the groups under analysis was found to be homogeneous with the Levene test. Results are reported as mean ± standard deviation. The discriminative capacity of the continuous variables found to be significant was tested through the analysis of the ROC curves. AUCs were compared between each other with the DeLong test to determine whether there was a significantly better performing indicator. Each significant continuous variable was made categorical by identifying a cut-off value with the Youden index. Categorical variables, reported as absolute count and percentage, were analyzed in contingency tables using the chi-square test. Categorical variables demonstrating a statistically significant association with the event in univariate analysis were subsequently included in multivariate Cox regression models to adjust for potential confounding factors. Only one variable per category (e.g., atrial dimensions: LAD, LAV, LAVi, LACI and LAEF) was chosen from those significant in the univariate analysis. The final model was selected based on the comparison of c-statistics for each model using the DeLong test. The strength of the association was reported as odds ratio (OR) or Hazard ration (HR) with a 95% confidence interval. For all analyses, statistical significance was defined as a two-sided p value < 0.05. To define whether there was concordance between echocardiographic and CMR measurements, Spearman correlation between echo and CMR measurements was performed. The statistical analysis was performed using IBM SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA), IBM SPSS Statistics version 29 (IBM Corporation, Armonk, NY, USA), and R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between 2011 and 2018, 141 consecutive patients with HCM and no history of AF (mean age 51 ± 17 years) were included in our registry. All patients underwent outpatient evaluations, including ECG and TTE, at our institution and were followed for a mean period of 5 ± 3 years. During follow-up, 35 patients developed AF and were assigned to the HCM-AF group, while the remaining 106 patients were assigned to the HCM-non-AF group. No statistically significant differences were observed between the two groups regarding age, comorbidities, or common cardiovascular risk factors. AF occurred after a mean period of 4 ± 3 years, at a mean age of 55 ± 17 years. Baseline characteristics of the two study groups are summarized in Table 1.

Echocardiographic parameters

HCM-AF group showed thicker LV wall (maximum thickness 20 ± 5 vs. 18 ± 3 in the HCM-AF group vs HCM-non-AF group respectively, p = 0.04). LAD, LAVmax, LA area, LAVmin and LACI showed to be greater in HCM-AF compared to HCM-non-AF group, respectively: 41 ± 5 vs. 38 ± 5, $p = 0.01$; 86 ± 23 vs. 77 ± 27, $p = 0.01$; 25 ± 4 vs. 23 ± 5, $p = 0.004$; 55 ± 18 vs. 40 ± 20, $p < 0.001$; 62 ± 20 vs 43 ± 19%, $p < 0.001$. LAEF and A wave velocity were greater in the HCM-non-AF group (37 ± 9% vs. 49 ± 11% for HCM-AF and HCM-non-AF group, respectively; $p < 0.001$ and 0.61 ± 28 vs. 0.74 ± 30 for HCM-AF and HCM-non-AF group, respectively; $p < 0001$). No significant differences emerged regarding ventricular volumes and left and right ventricular function (Table 2).

Cardiac magnetic resonance

Ninety (90) patients, 74 male, mean age 53 ± 18 years, underwent CMR. The HCM-AF group had significantly greater values of LAVmax, LAVImax, LAVmin, LAVImin, and LACI (109 ± 25 vs. 87 ± 25, $p = 0.001$; 59 ± 13 vs. 47 ± 12, $p < 0001$; 69 ± 21 vs. 50 ± 17, $p < 0001$; 37 ± 11 vs. 27 ± 9, $p < 0001$; 56 ± 16 vs. 39 ± 13, $p < 0001$; respectively). LAEF was significantly higher in the HCM-non-AF group (35 ± 10 vs. 42 ± 8, $p = 0.001$). Table 3 illustrates in detail the CMR parameters analyzed in the two groups. Among the parameters analyzed, LACI showed the highest concordance between the two methods, while LVEF showed the lowest. Results are reported in Table 4.

Indicators comparison

In the ROC analysis, LACI, LAVmin, and LAD demonstrated the strongest discriminative ability. Specifically, a LACI greater than 43% on TTE demonstrated 85% sensitivity and 58% specificity (AUC 0.75) for identifying patients who would develop AF. On CMR, LACI > 44% showed 85% sensitivity and 70% specificity (AUC 0.81) in identifying the same patients.

LAD demonstrated its best performance with a cut-off value of 40.5 mm. Compared to a LAD cutoff of

Table 1 Baseline characteristics of the two HCM-AF and HCM-no-AF groups

	Total ($n=141$)	HCM-AF ($n=35$)	HCM-no-AF ($n=106$)	*P* value
Age (± sd)	51 (17)	52 (18)	51 (17)	0.63
Male (%)	74 (52)	11 (31)	63 (59)	**0.004***
BMI (± sd)	27.1 (4.8)	27 (5.4)	27.1 (4.5)	0.93
BSA (± sd)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	0.76
Family History of HCM	57 (40)	16 (46)	41 (39)	0.46
NSVT	7 (5)	3 (9)	4 (4)	0.26
Syncope	17 (12)	7 (20)	10 (11)	0.1
T2DM	19 (13)	4 (11)	15 (14)	0.68
AH	46 (33)	7 (20)	39 (37)	0.07
Dyslipidemia	21 (15)	4 (11)	17 (16)	0.51
CKD	4 (3)	1 (3)	3 (3)	0.99
COPD	8 (6)	2 (6)	6 (6)	0.99
CAD	7 (5)	0 (-)	7 (7)	0.12
PM	6 (4)	3 (9)	3 (3)	0.15
ICD	23 (16)	7 (20)	16 (15)	0.50
Myomectomy	27 (19)	8 (23)	19 (18)	0.52
Alcoholization	2 (1)	0 (-)	2 (2)	0.41
LVOTO	49 (35)	10 (4)	39 (37)	0.38
HCM Risk Score	1.9 (1)	2.1 (1.3)	2.2 (1.1)	0.86
AF				
Paroxymsal	24 (17)	24 (69)	-	
Persistent	7 (5)	7 (20)	-	
Permanent	4 (3)	4 (11)	-	

AH Arterial Hypertension, *BMI* Body Mass Index, *BSA* Body Surface Area, *CAD* Coronary Artery Disease, *CKD* Chronic Kidney Disease, *COPD* Chronic Obstructive Pulmonary Disease, *HCM* Hypertrophic Cardiomyopathy, *ICD* Implantable Cardioverter Defibrillator, *LVOTO* Left Ven-tricular Outflow Tract Obstruction, *NSVT* Non-sustained Ventricular Tachycardia, *PM* Pacemaker, *T2DM* Type 2 Diabetes Mellitus

*p values correspond to statistically significant result with $p < 0.05$

40.5 mm, LACI exhibited superior accuracy, with an AUC of 0.71 (Fig. 1A, B, C, D, E). Overall, LACI proved to be the parameter with the best performance (AUC 0.8 at TTE, and 0.79 at CMR) (Supplementary Table 1, Supplementary Fig. 1). However, no statistically significant differences were observed when the AUCs were compared using DeLong's Test. Detailed results of the DeLong Test are provided in the Supplementary Table 2. LAEF > 43% was instead associated with the non-occurrence of AF (sensitivity 76%, specificity 71%, AUC 0.81) (Fig. 1F).

The univariate analysis highlighted how female sex, LVThick > 19.5 mm, LAD > 40.5 mm, LAVmax > 35 ml, LAVmin > 43 ml, LAEF < 43%, and LACI > 43% were all factors significantly associated with the development of AF. The results of the univariate and multivariate analyses are reported in Table 5. After selecting only one variable per category, as previously described, four models were developed: (1) LV thick > 19.5 mm, sex, LAVmax > 35 ml, LAEF < 43%, LACI > 43%; (2) LV thick > 19.5, female sex, LAD > 40.5 mm, LAEF < 43%, LACI > 43%; (3) LV thick > 19.5 mm, female sex, LACI > 43%, LAEF < 43%, LAVmin > 43 ml; and (4) LV thick > 19.5 mm, female sex, LAVmin > 43 ml, LAEF < 43 ml, LAD > 40.5 mm. The discriminative ability of each model was compared using DeLong's test for C-statistics. Since no statistically significant differences were observed, the model with the highest C-statistic was selected: Model 2 (LV thick > 19.5 mm, female sex, LAD > 40.5 mm, LAEF < 43%, LACI > 43%). The C-statistic for each model and the details of the DeLong test are provided in Supplementary Materials.

Cox regression analysis revealed that LAD > 40.5 mm, LAEF < 43%, and female sex were independently associated with the occurrence of AF, with HR of 2.5 (95% CI: 1.1–5.5), 2.9 (95% CI: 1.2–6.9), and 2.3 (95% CI: 1.1–5.0), respectively.

These factors were also linked to reduced AF-free survival (Fig. 2). The cumulative risk of AF was as high as 5% at two years and 24% after 10 years.

Figure 2A and B represent AF free survival in patients with and without LAEF<43% and LAD>40.5mm.

Eleven patients (5 males, mean age at event 53 ± 20 years) either underwent HTx (6) or died for

Table 2 Evaluation of the echocardiographic variables of the two groups

	Total ($n=141$)	HCM-AF ($n=35$)	HCM no-AF ($n=106$)	*P* value
LVEDV, ml (± sd)	94 (21.9)	92.8 (24.8)	94.4 (21)	0.70
LVEDD, mm (± sd)	42.2 (4.6)	42 (5)	42.3 (4.4)	0.77
LVESV, ml (± sd)	32.9 (10.2)	33.5 (12.9)	32.8 (9.3)	0.71
LVEF, % (± sd)	64.4 (5.4)	63.8 (6.5)	64.(5)	0.47
LVthick, mm(± sd)	18.7 (4.4)	20.1 (5.5)	18.1 (3.8)	**0.004***
LAD, mm (± sd)	39.2 (5.5)	41.9 (5.1)	38.3 (5.4)	**0.001***
LAVmax, ml (± sd)	79.7 (27.1)	86.6 (23.7)	77.3 (27.8)	**0.013***
LAA, cmq (± sd)	23.7 (5.2)	25.7 (4.8)	23.1 (5.3)	**0.004***
LAVmin, ml (± sd)	44 (21.2)	55.3 (19)	40.3 (20.8)	**< 0.001***
LAEF, % (± sd)	46 (12)	37 (10)	49 (11)	**< 0.001***
LACI (± sd)	48 (21)	62 (20)	43 (19)	**< 0.001***
E vel, cm/s (± sd)	81 (25)	81 (24)	82 (25)	0.82
A vel, cm/s (± sd)	70 (30)	61 (28)	74 (30)	**0.042***
DT, ms(± sd)	213 (71.9)	211 (75)	214 (71)	0.84
E/e' (± sd)	14.1 (7.4)	16.2 (8.6)	23.5 (6.8)	0.08
TAPSE, mm (± sd)	22 (3.4)	22 (2.7)	22 (3.6)	0.46
SPAP, mmHg (± sd)	32 (10.8)	33 (10.2)	31 (11.1)	0.44
LVOT grad, mmHg (± sd)	25 (29.8)	24 (30)	26 (29.9)	0.79
MR -/1 + /2 +	56/64/21	12/14/10	44/50/11	0.15
AR -/1 + /2 + /3 + /4 +	122/15/4/-/-	28/6/1/-/-	94/9/3/-/-	0.35
TR -/1 + /2 + /3 + /4 +	89/44/8/-/-	25/7/3/-/-	64/37/5/-/-	0.22

AR aortic regurgitation, *DT* deceleration time, *LAA* left atrium area, *LACI* left atrioventricular coupling index, *LAD* left atrium diameter, *LAEF* left atrium ejection fraction, *LAVmax* maximal left atrium volume, *LAVmin* minimal left atrium volume, *LVEDD* left ventricular end-diastolic diameter, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *LVOT* left ventricular outflow tract, *LVthick* left ventricular thickness, *MR* mitral regurgitation, *SPAP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation

*p values correspond to statistically significant result with $p < 0.05$

Table 3 Evaluation of variables at cardiac magnetic resonance

	Total ($n=141$)	HCM-AF ($n=35$)	HCM no-AF ($n=106$)	*P* value
LVEDV (± sd)	128 (28.1)	125.6 (34.8)	128.8 (25.8)	0.64
LVESV (± sd)	40 (12.2)	38 (12.6)	41.2 (12)	0.27
LVEF (± sd)	68.5 (7.2)	69.4 (9.7)	68.2 (6.2)	0.15
LVthick(± sd)	19.3 (4.8)	20 (5.6)	19 (4.5)	0.36
LAVmax (± sd)	93.2 (26.8)	109 (25.7)	59.5 (13.5)	**0.001***
LAVImax (± sd)	50.9 (13.9)	69.5 (21.5)	50.5 (17.4)	**< 0.001***
LAA	25.3 (8)	30.7 (7.4)	23.8 (7.7)	0.06
LAVmin (± sd)	55.4 (20.2)	69,5 (21.5)	50.5 (17.4)	**< 0.001***
LAVImin(± sd)	30.3 (10.9)	37.6 (11.9)	27.7 (9.5)	**< 0.001***
LAEF(± sd)	40 (9.4)	35 (10.3)	42 (8.3)	**0.001***
LACI(± sd)	44 (16)	57 (17)	40 (13)	**< 0.001***
LVmass (± sd)	158.9 (64.7)	163.7 (80.7)	157.4 (58.9)	0.68
LGE in gr (± sd)	13.2 (20.7)	15.9 (23.3)	12.4 (20)	0.21
LGE in % (± sd)	8.8 (14)	10.3 (13.3)	8.4 (14.3)	0.23

LAA left atrium area, *LACI* left atrioventricular coupling index, *LAD* left atrium diameter, *LAEF* left atrium ejection fraction, *LAV max* maximal left atrium volume, *LAV min* minimal left atrium volume, *LAVI max* indexed maximal left atrium volume, *LAVI min* indexed minimal left atrium volume, *LGE in gr* late gadolinium enhancement in grams, *LGE in %* late gadolinium enhancement in percentage, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *LV mass* left ventricular mass

*p values correspond to statistically significant result with $p < 0.05$

Table 4 Correlation between TTE and CMR parameters

	Spearman's Rho	95% CI	*P* value
LACI	0.84	0.76–0.89	< 0.001
LAEF	0.52	0.35–0.66	< 0.001
LAVmax	0.72	0.59–0.81	< 0.001
LVEF	0.33	0.12–0.50	0.002

LACI left atrioventricular coupling index, *LAEF* left atrium ejection fraction, *LAVmax* maximal left atrium volume, *LVEF* left ventricular ejection fraction

CV causes (5). The events occurred at a mean time of 3 ± 2 years from recruitment. Only three of them had AF onset prior to HTx or death. There was no statistically significant association between LVEF and the composite outcome of HTx or CV death. Conversely, higher values of LACI, LAVmin, and lower values of LAEF, and E wave deceleration time (DecT) were found to be associated with the composite outcome of HTx or death (Supplementary Table 3). LACI revealed good accuracy in identifying patients who would have met the composite outcome of HTx or CV death (AUC 0.74) (Fig. 3). More specifically, a LACI > 60% showed the best discriminative accuracy (sensitivity 64%, specificity 78%). In contrast, a LAEF > 45% and a DecT > 170 ms showed sensitivity of 55% and specificity of 91% (AUC 0.71), and sensitivity of 75% and specificity of 81% (AUC 0.79), respectively, in identifying patients who would be free from HTx or CV death at 5 year (Supplementary Table 4).

Discussion

Several studies have focused on identifying parameters capable of predicting AF in patients with HCM, but despite numerous proposals, there is a lack of strong evidence supporting any parameter, except for LAD, which remains the most commonly used. In our analysis, we evaluated the association between AF and the morpho-functional parameters of the left atrium. The main findings were: (i) LACI strongly correlates with onset of AF; this result is confirmed by CMR data. (ii) LAEF is independently associated with the development of AF. (iii) LACI was significantly associated with a worse prognosis.

LACI and LAEF in the development of AF

LACI was first evaluated by Pezel et al. in individuals free of clinically recognized HF and cardiovascular disease at baseline, using CMR. They found that LACI provided incremental prognostic value for predicting

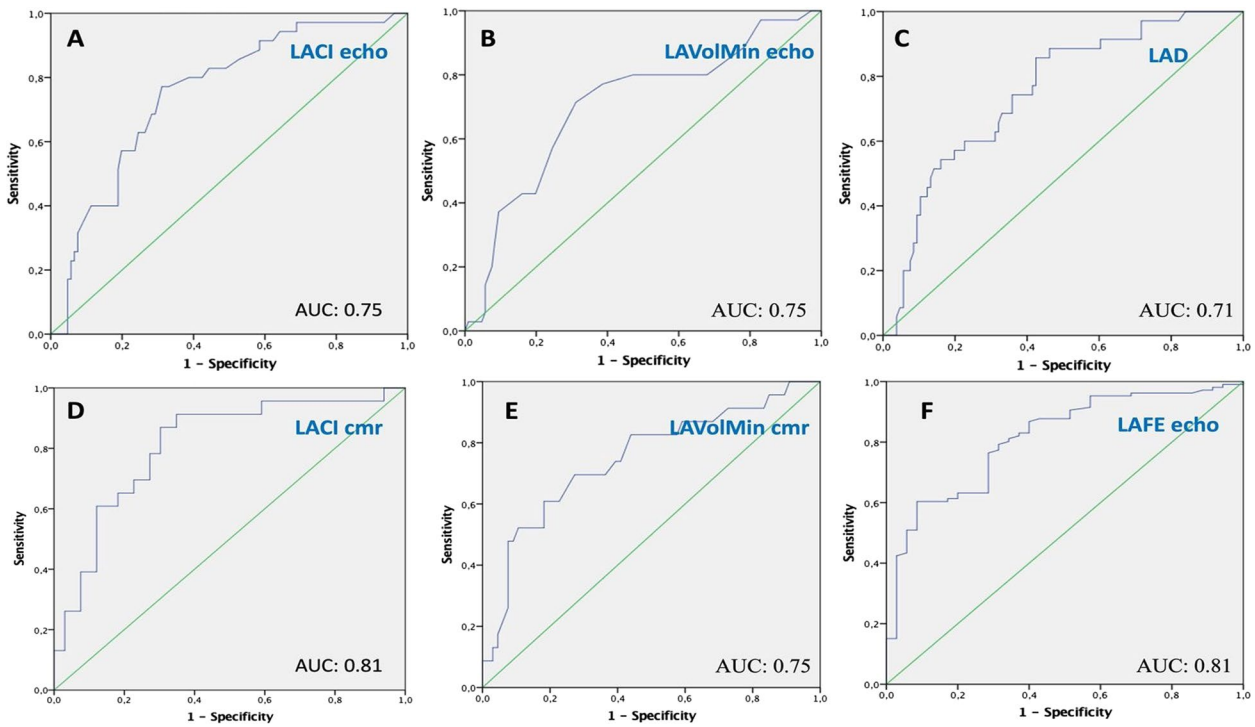
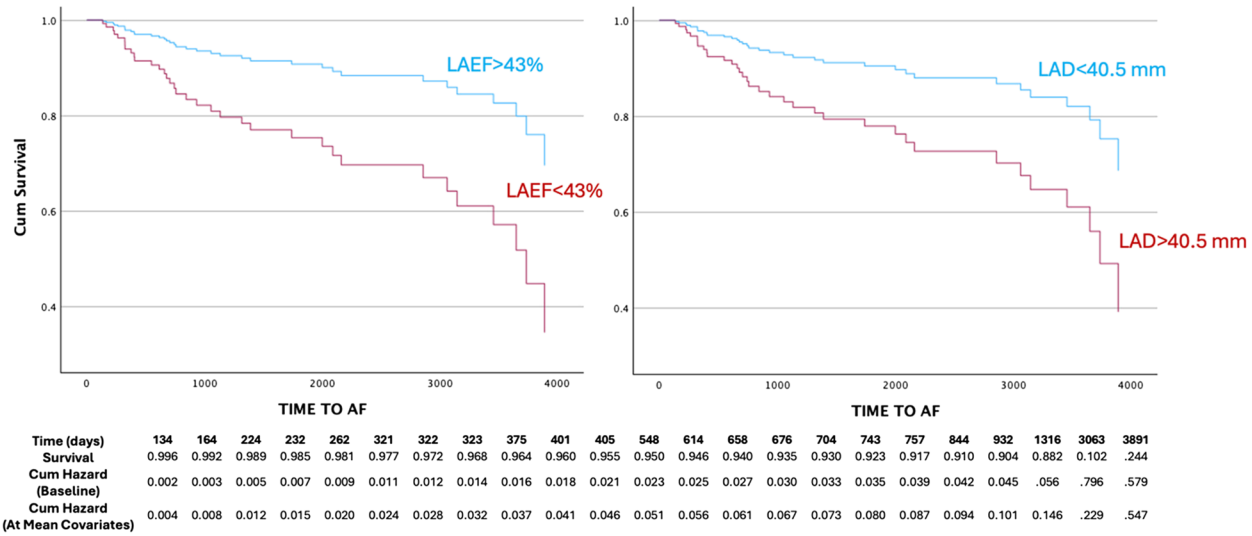


Fig. 1 ROC curves of echocardiographic variables in predicting AF occurrence (**A**-**E**) or non AF occurrence during the study period (**F**). **A** ROC curve LACI echo, **B** ROC curve LAVmin echo, **C** ROC curve LAD, **D** ROC curve LACI cmr, **E** ROC curve LAVmin cmr, **F** ROC curve LAEF echo. LACI: left atrioventricular coupling index, LAD: left atrium diameter, LAEF: left atrium ejection fraction; LAV min: minimal left atrium volume

Table 5 Univariate and multivariate analysis of variables associated with the development of AF

Univariate					
	Total (*n*=141)	**HCM-AF (*n*=35)**	**HCM no-AF (*n*=106)**	**OR (IC 95%)**	***P* value**
Sex M (%)	74 (52)	11 (31)	63 (59)	0.31 (0.14-0.7)	**0.004***
LVthick(%)	94 (67)	16 (46)	78 (74)	3.3 (1.5-7.3)	**0.002***
LAD (%)	58 (41)	25 (71)	33 (31)	5.53 (2.39-12.8)	**<0.001***
LAVmax (%)	102 (72)	31 (89)	71 (67)	3.8 (1.2-11.7)	**0.013***
LAVmin (%)	60 (43)	27 (77)	33 (31)	7.47 (3.07-18.17)	**<0.001***
LAEF<43% echo (%)	50 (35)	25 (71)	25 (24)	8.1 (3.4-19.1)	**<0.001***
LACI>43% echo (%)	75 (53)	30 (86)	45 (42)	9.13 (2.92-22.6)	**<0.001***
Multivariate					
	***P* value**		**HR**	**95% CI**	
LVthick>19.5 mm	0.52		1.9	0.9-3.9	
LAD>40.5 mm	0.03		2.5	1.1-5-5	
LAEF<43%	0.014		2.9	1.2-6.9	
LACI>43%	0.38		1.6	0.6-4.5	
Female Sex	0.22		2.38	1.11-5.00	

LAEF left atrium ejection fraction, *LAV* max maximal left atrium volume, *LAV* min minimal left atrium volume, *LVthick* left ventricular thickness



Time (days)	134	164	224	232	262	321	322	323	375	401	405	548	614	658	676	704	743	757	844	932	1316	3063	3891
Survival	0.996	0.992	0.989	0.985	0.981	0.977	0.972	0.968	0.964	0.960	0.955	0.950	0.946	0.940	0.935	0.930	0.923	0.917	0.910	0.904	0.882	0.102	.244
Cum Hazard (Baseline)	0.002	0.003	0.005	0.007	0.009	0.011	0.012	0.014	0.016	0.018	0.021	0.023	0.025	0.027	0.030	0.033	0.035	0.039	0.042	0.045	.056	.796	.579
Cum Hazard (At Mean Covariates)	0.004	0.008	0.012	0.015	0.020	0.024	0.028	0.032	0.037	0.041	0.046	0.051	0.056	0.061	0.067	0.073	0.080	0.087	0.094	0.101	0.146	.229	.547

Fig. 2 Survival Curve free from AF for LAEF (on the left) and for LAD (on the right). LAD: left atrium diameter; LAEF: left atrium ejection fraction

cardiovascular events, beyond left atrial or left ventricular parameters alone [8].

In our study, LACI, assessed by both TTE and CMR, demonstrated superior performance in identifying patients at risk of developing AF at univariate analysis, superior to LAD, which is the current reference parameter recommended by the European Society of Cardiology (ESC) [5]. Our results are consistent with those of Meucci et al., who identified a similar cut-off (LACI > 40%) in HCM patients with AF, further supporting the reliability of our findings [8].

The strength of LACI in the context of HCM likely lies in its intrinsic ability to reflect early impairment of left ventricular diastolic function and atrial remodeling. Indeed, left atrial emptying is closely associated with left ventricular filling pressures; pathological atrioventricular coupling affects left atrial pressure, contributing to the development and worsening of atrial myopathy (Fig. 4).

In Fig. 5, we show two patients from our cohort: one from the HCM no AF group, exhibiting a low LACI, and the other from the HCM AF group, who developed arrhythmia after 18 months, showing a high LACI. This

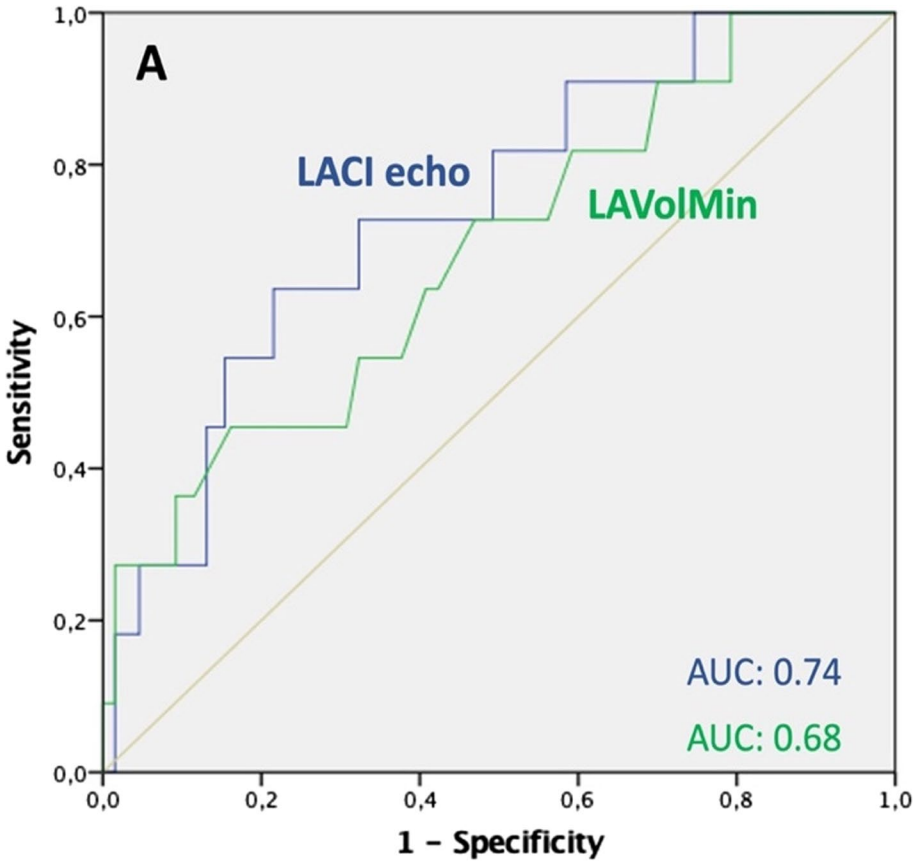


Fig. 3 ROC Curves for LACI and LAVmin in predicting HTx or death. LACI: left atrioventricular coupling index, LAV min: minimal left atrium volume

illustration highlights the differences in atrial function and atrioventricular coupling, which are clearly observed on TTE (Fig. 5).

Notably, in our study, the findings from TTE and CMR imaging are consistent. A strong concordance was observed in the LACI measured with the two different methods, further supporting the standardization of this parameter. Regarding the identification of patients at risk of developing AF, we demonstrated the superior performance of LACI measured with CMR compared to TTE, likely due to CMR's superior precision in volume assessment (LACI CMR AUC 0.8 vs. LACI TTE AUC 0.75).

It is important to note that our cohort presented with early-stage atrial disease, characterized by only mildly dilated atria. Therefore, we can conclude that the superiority of LACI was evident even before severe atrial dilation and arrhythmia occurred, making it a sensitive parameter in the early stages.

On the other hand, LAEF was the parameter independently associated with the development of AF in multivariate analysis. An LAEF < 43% identified patients with a 2,ninefold increased risk of developing AF compared to other HCM patients, who already have an inherent 4- to sixfold higher risk of AF than the general population [2]. In these patients, given the very high risk of AF and the elevated stroke risk, more intensive arrhythmic monitoring may be warranted. This could include periodic 48-h Holter ECG or even the implantation of a loop recorder. Furthermore, an LAEF > 43% suggests a lower risk of developing AF. Several previous studies have already explored the role of LAEF as a potential predictor of AF in patients with HCM. Our results are consistent with those of Tuluce et al., who demonstrated that LAEF, assessed by TTE, was associated with a higher risk of arrhythmia, and that a cut-off value of 49% predicted its development with good specificity [16]. Compared to LACI, LAEF is a more direct marker of intrinsic atrial disease, which explains its stronger association with the development of AF at multivariate analysis.

In our study, LAD was found to have a good diagnostic accuracy for development of AF compared to the other variables. Our results are consistent with the literature, which identifies LAD as current reference parameter for screening the development of AF, although it is often criticized for its relatively low specificity [5, 16, 17].

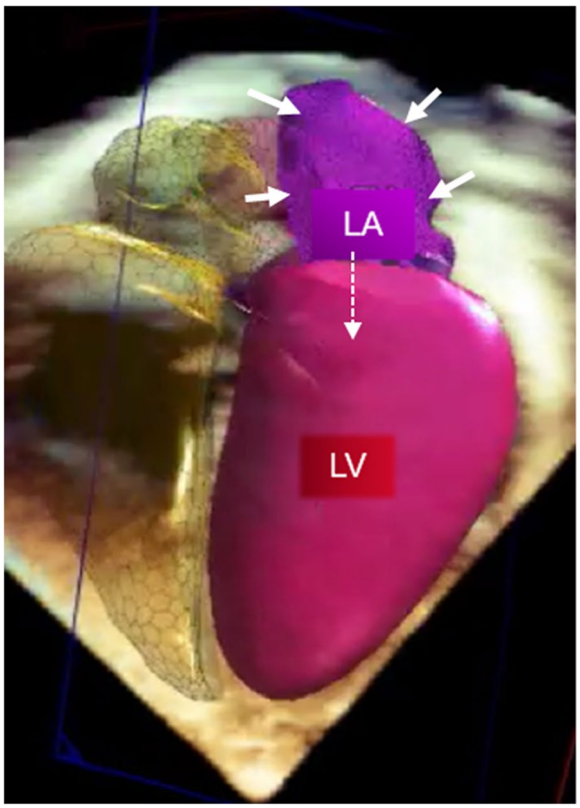


Fig. 4 Booster pump phase illustration. In this phase, the LA emptying (white dashed arrow) depends mainly on the strength of LA contraction (white arrows) and atrial afterload. These elements are sensibly expressed in the LACI

The role of LA strain may also provide additional insights, as suggested by Debonnaire et al. In a cohort of 242 patients, a strain < 23% was shown to be associated with an increased risk of AF, even in cases with non-dilated LA [18]. However, despite its elegant approach, LA strain analysis requires specialized software and is time-consuming, which limits its applicability in routine clinical practice. Therefore, we opted to focus on parameters that are more feasible for everyday use, providing a more practical approach to arrhythmia screening.

LACI and LAEF as predictors of HTx and death

In our study, we found that LACI was significantly associated with HTx or CV death. Previous studies have reported an association between LACI and worse outcomes in patients with heart failure and reduced LVEF [8, 11, 19]. To the best of our knowledge, we are the first to report this association in the context of HCM. In this setting, where LVEF remains preserved until the later stages of the disease, LACI plays an even more critical role in early prognostic stratification. Atrioventricular uncoupling appears to be a subclinical marker of disease progression toward LVEF reduction and LV dilation. Identifying patients who are more susceptible to this progression may enable closer follow-up and help prevent future hospitalizations.

In our analysis, no statistically significant correlation was found between LAEF and major adverse cardiovascular outcomes. This is likely due to the fact that LAEF is a parameter that primarily reflects atrial function.

Limitations

The main limitations of our study are its retrospective design and small sample size. A prospective registry with a larger population is needed to confirm and strengthen our preliminary findings. Moreover, due to the retrospective nature of the study, advanced echocardiographic parameters were often unavailable, preventing their

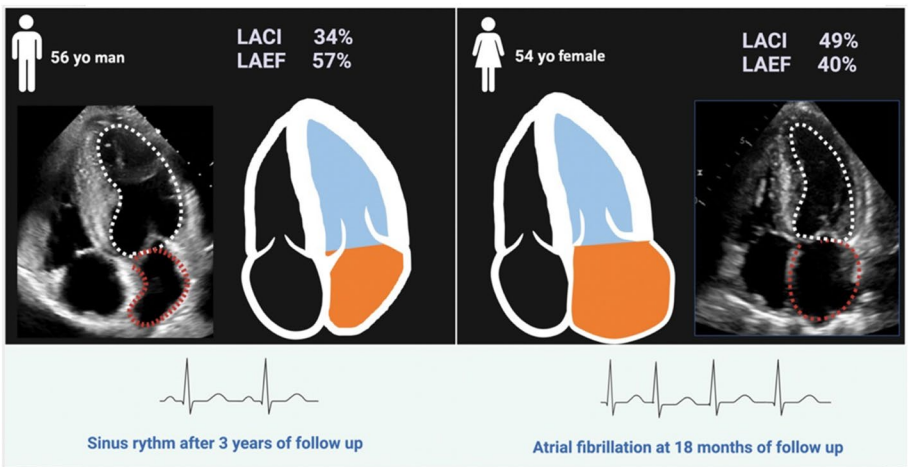


Fig. 5 Comparison of two patients from our cohort. On the left, a 56-year-old male with obstructive HCM, who remained free of AF until the most recent follow-up (3 years). His LACI was low, at 34%. On the right, a 54-year-old female with non-obstructive HCM, who developed her first episode of AF 18 months after baseline TTE. Her LACI was elevated, at 49%

inclusion in our analysis. Finally, AF detection was based solely on clinical evaluation, which may have led to the underdiagnosis of asymptomatic and subclinical episodes.

Conclusions

In HCM patients, both LACI and LAEF were functional indices associated with a higher risk of AF, a finding further confirmed by CMR data. Additionally, in HCM patients, LACI was associated with the composite outcome of HTx or CV death.

Abbreviations

AF	Atrial fibrillation
CMR	Cardiac magnetic resonance
CV	Cardiovascular
EF	Ejection fraction
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HTx	Heart transplant
LA	Left atrial
LAA	Left atrium area
LACI	Left atrioventricular coupling index
LAD	Left atrium diameter
LVEDV	Left ventricular end-diastolic volume
LAEF	Left atrium ejection fraction
LAVmax	Maximal left atrium volume
LAVmin	Minimal left atrium volume
LGE	Late gadolinium enhancement
LV	Left ventricular
LVOTO	Left ventricular outflow tract obstruction
TTE	Transthoracic echocardiograms

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12947-025-00343-5.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

This study is winner of Award Attilio Maseri, Fondazione per il Tuo cuore.

Authors' contributions

FP,FF,LP,ELF,MC, GG conceptualization, methodology, validation, data curation, writing-original draft, writing-review & editing, supervision; LP,DB: formal analysis, validation; CZ,GDB,SC,VN,MM,PM: validation, writing-review & editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This research was approved by the Ethical Committee of IRCCS ISMETT and all patients enrolled gave written informat consense.

Competing interests

The authors declare no competing interests.

Author details

[1]Clinical Cardiology and Heart Failure Unit, Mediterranean Institute for Transplantation and Advanced Therapies (ISMETT), IRCCS, Palermo, Italy. [2]Department of Clinical and Experimental Medicine, Cardiology Unit, University of Messina, Messina, Italy. [3]Radiology Unit, Mediterranean Institute for Transplantation and Advanced Therapies (ISMETT), IRCCS, Palermo, Italy. [4]Department of Research, Mediterranean Institute for Transplantation and Advanced Therapies (ISMETT), IRCCS, Palermo, Italy.

Received: 10 November 2024 Accepted: 26 February 2025
Published online: 28 March 2025

References

1. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial Fibrillation in Hypertrophic Cardiomyopathy: Prevalence, Clinical Correlations, and Mortality in a Large High-Risk Population. J Am Heart Assoc. 2014;3(3):e001002. https://doi.org/10.1161/JAHA.114.001002.
2. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104(21):2517-24. https://doi.org/10.1161/hc4601.097997.
3. Garg L, Gupta M, Sabzwari SRA, et al. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical impact, and management. Heart Fail Rev. 2019;24(2):189–97. https://doi.org/10.1007/s10741-018-9752-6.
4. Arunachalam K, Maan A, Chu A. Atrial Fibrillation in Hypertrophic Cardiomyopathy: Evidence-based Review About Mechanism, Complications and Management. Crit Pathw Cardiol J Evid-Based Med. 2020;19(2):87–9. https://doi.org/10.1097/HPC.0000000000000210.
5. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79. https://doi.org/10.1093/eurheartj/ehu284.
6. Fortuni F, Morroni S, Biagioli P, et al. Echocardiographic assessment of patient hemodynamics in heart failure. Minerva Cardiol Angiol. Published online 1 Jul 2024. https://doi.org/10.23736/S2724-5683.24.06471-8.
7. Pezel T, Ambale Venkatesh B, Kato Y, et al. Left Atrioventricular Coupling Index to Predict Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis. Front Cardiovasc Med. 2021;8:704611. https://doi.org/10.3389/fcvm.2021.704611.
8. Meucci MC, Fortuni F, Galloo X, et al. Left atrioventricular coupling index in hypertrophic cardiomyopathy and risk of new-onset atrial fibrillation. Int J Cardiol. 2022;363:87–93. https://doi.org/10.1016/j.ijcard.2022.06.017.
9. Maron BJ, Haas TS, Maron MS, et al. Left Atrial Remodeling in Hypertrophic Cardiomyopathy and Susceptibility Markers for Atrial Fibrillation Identified by Cardiovascular Magnetic Resonance. Am J Cardiol. 2014;113(8):1394–400. https://doi.org/10.1016/j.amjcard.2013.12.045.
10. Writing Committee Members, Ommen SR, Mital S, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020;142(25). https://doi.org/10.1161/CIR.0000000000000937.
11. Fortuni F, Biagioli P, Myagmardorj R, et al. Left Atrioventricular Coupling Index: A NovelDiastolic Parameter to Refine Prognosis in Heart Failure. J Am Soc Echocardiogr. 2024;37(11):1038–46. https://doi.org/10.1016/j.echo.2024.06.013.
12. Van Gelder IC, Rienstra M, et al. ESC Scientific Document Group, 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the

ESC. Endorsed by the European Stroke Organisation (ESO). Eur Heart J. 2024;45(36):3314–414. https://doi.org/10.1093/eurheartj/ehae176.
13. Saeed D, Feldman D, et al. The 2023 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support: A 10- Year Update. J Heart Lung Transplant. 2023;42(7):e1–222. https://doi.org/10.1016/j.healun.2022.12.004.
14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. https://doi.org/10.1016/j.echo.2014.10.003.
15. Maceira AM, Cosín-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2010;12(1):65. https://doi.org/10.1186/1532-429X-12-65.
16. Tuluce K, Yakar Tuluce S, Kahya Eren N, et al. Predictors of Future Atrial Fibrillation Development in Patients with Hypertrophic Cardiomyopathy: A Prospective Follow-Up Study. Echocardiography. 2016;33(3):379–85. https://doi.org/10.1111/echo.13093.
17. Tani T, Tanabe K, Ono M, et al. Left atrial volume and the risk of paroxysmal atrial fibrillation in patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr. 2004;17(6):644–8. https://doi.org/10.1016/j.echo.2004.02.010.
18. Debonnaire P, Joyce E, Hiemstra Y, et al. Left Atrial Size and Function in Hypertrophic Cardiomyopathy Patients and Risk of New-Onset Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2017;10(2):e004052. https://doi.org/10.1161/CIRCEP.116.004052.
19. Benfari G, Essayagh B, Nistri S, et al. Left Atrial Volumetric/Mechanical Coupling Index: A Novel Predictor of Outcome in Heart Failure With Reduced Ejection Fraction. Circ Cardiovasc Imaging. 2021;14(1):e011608. https://doi.org/10.1161/CIRCIMAGING.120.011608.

Publisher's Note