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RESEARCH ARTICLE

Cardiac magnetic resonance-derived left atrioventricular coupling index predicts outcome in reduced ejection fraction

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Abstract

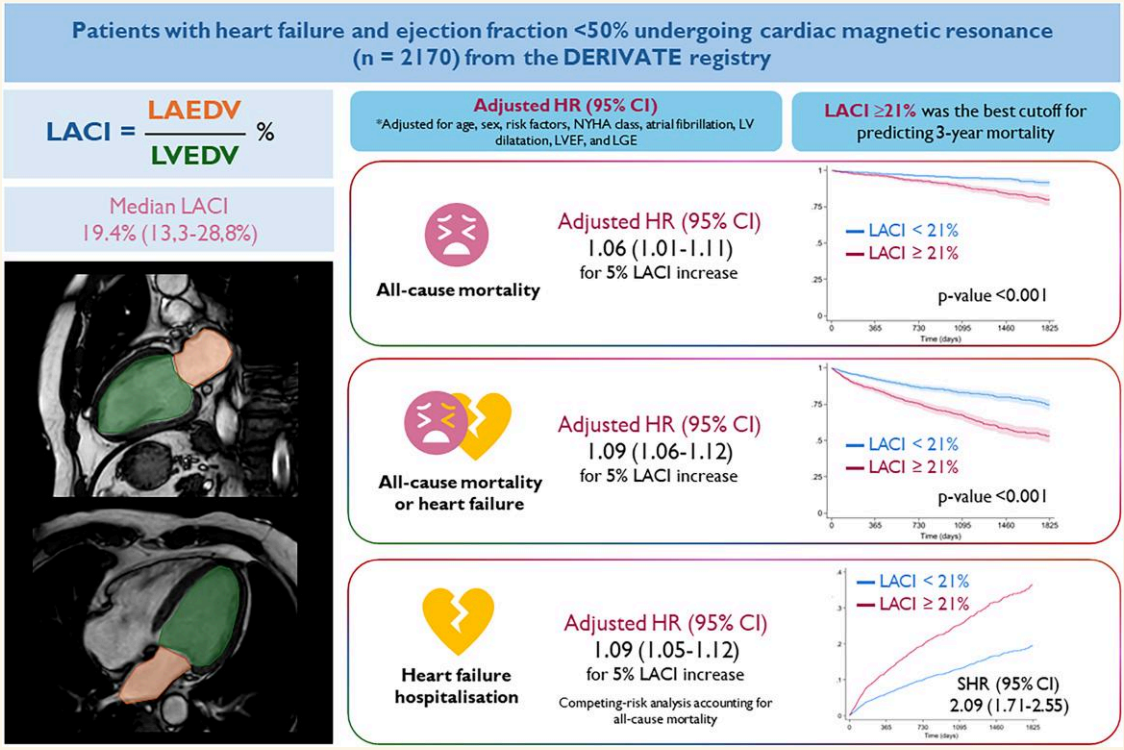
Introduction The left atrioventricular coupling index (LACI) has emerged as a potential prognostic marker in several clinical settings. This study evaluated the prognostic value of cardiac magnetic resonance (CMR)-derived LACI in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF).

Methods Patients from the multicentre DERIVATE registry with LVEF <50% who underwent CMR were included. LACI was calculated as the ratio between left atrial and left ventricular end-diastolic volumes. Univariable and multivariable Cox regression models estimated hazard ratios (HR) with 95% confidence intervals (CI) for predicting all-cause mortality (ACM), ACM or HF, and HF alone (competing-risk analysis). Time-dependent receiver operating characteristic analysis identified optimal cut-offs for 3-year outcomes.

Results A total of 2170 patients were included (mean age 59.8 ± 13.9 years; 24.7% women; mean LVEF 31.6 ± 11.3%). Median follow-up was 1016 days (580–1609). Median LACI was 19.4% (13.3–28.8). During follow-up, ACM occurred in 191 patients (8.8%), ACM or HF in 565 (26.0%), and HF in 442 (20.4%). After adjustment for clinical and CMR parameters, including LVEF and late gadolinium enhancement (LGE), each 5% increase in LACI was associated with higher risk of ACM (HR 1.06, 95% CI 1.01–1.11; $P = .016$), ACM or HF (HR 1.09, 95% CI 1.06–1.12; $P < .001$), and HF (HR 1.09, 95% CI 1.05–1.12; $P < .001$). The optimal cut-off for ACM was LACI ≥21% (AUC 0.617, 95% CI 0.561–0.673), identifying patients at higher risk of ACM, ACM or HF, and HF (log-rank $P < .001$ for all).

Conclusion CMR-derived LACI independently predicts ACM and HF in patients with reduced LVEF and provides incremental prognostic value beyond LVEF and LGE. A cut-off of ≥21% identifies higher-risk patients and may support clinical risk stratification.

Graphical Abstract



The left atrioventricular coupling index, derived from cardiovascular magnetic resonance as the ratio of left atrial to left ventricular end-diastolic volumes, independently predicts adverse outcomes in patients with reduced left ventricular ejection fraction, with values ≥21% identifying higher-risk patients.

Keywords Left atrioventricular coupling index • Cardiac magnetic resonance • Heart failure • Dilated cardiomyopathy • Ischaemic cardiomyopathy

Introduction

Patients with reduced ejection fraction (EF) are known to have an increased risk of major adverse cardiovascular events such as heart failure (HF), ventricular arrhythmias, and death.[1–3] Cardiac magnetic resonance (CMR) has a pivotal role in the diagnostic pathway and prognostic stratification in patients with reduced EF, being the gold standard in the evaluation of cardiac morphology, volumes, and function.[4,5] On top of that, several studies have highlighted the fundamental prognostic role of myocardial fibrosis or myocardial scar detected in late gadolinium enhancement (LGE) sequences as an important marker of long-term prognosis.[6–10]

Recently, many studies have emphasized how adverse cardiac events may also occur in the presence of a preserved left ventricle (LV) structure and function. In this setting, the role of the left atrium (LA) has been found to add prognostic information. Specifically, coupling between LV and LA has emerged as a key player in maintaining a normal global heart performance, especially in patients with known cardiovascular risk factors.[11–14] The evaluation of the left atrioventricular coupling index (LACI), defined as the ratio between left atrial end-diastolic volume (LAEDV) and left ventricular end-diastolic volume (LVEDV), has been found to be associated with outcome in different clinical settings.[15,16] Specifically, increased LACI indicates disproportionate atrial enlargement relative to ventricular volume, reflecting chronic elevation of filling pressures, atrial remodelling, and impaired ventricular compliance, all key mechanisms contributing to HF progression and adverse outcomes.[11–16] However, to date, the role of CMR-derived LACI has never been evaluated in a large cohort of patients with reduced EF.

The aim of the present study is to investigate the LACI in the setting of patients known for reduced EF and its long-term prognostic role.

Methods

Population of the study

The present study is a sub-analysis of the Cardiac Magnetic Resonance for Primary Implantable Cardioverter Defibrillator Therapy (DERIVATE) registry (NCT03352648).[17] The DERIVATE is an international, multicentre, prospective, observational registry that enrolled patients with HF who underwent transthoracic echocardiography (TTE) and CMR from 21 sites across Europe and the United States. The inclusion criteria are: (i) patients ≥18 years old affected with stage B or C HF according to the American College of Cardiology/American Heart Association (ACC/AHA) classification secondary to ICM or NICM, (ii) left ventricle ejection fraction (LVEF) <50%, and (iii) available clinical, TTE, and CMR data. Patients with poor-quality CMR images for the quantification of LACI were excluded. A complete list of inclusion and exclusion criteria is presented in Supplementary Table S1.

Demographic and clinical characteristics were collected, including age, sex, biometric parameters, cardiovascular risk factors, previous cardiac diseases, New York Heart Association (NYHA) class, left bundle branch block (LBBB), atrial fibrillation (AF), and medications. Furthermore, TTE principal findings were gathered, including left ventricle volumes, LVEF, and mitral regurgitation (MR) grading as per relevant guidelines.[18]

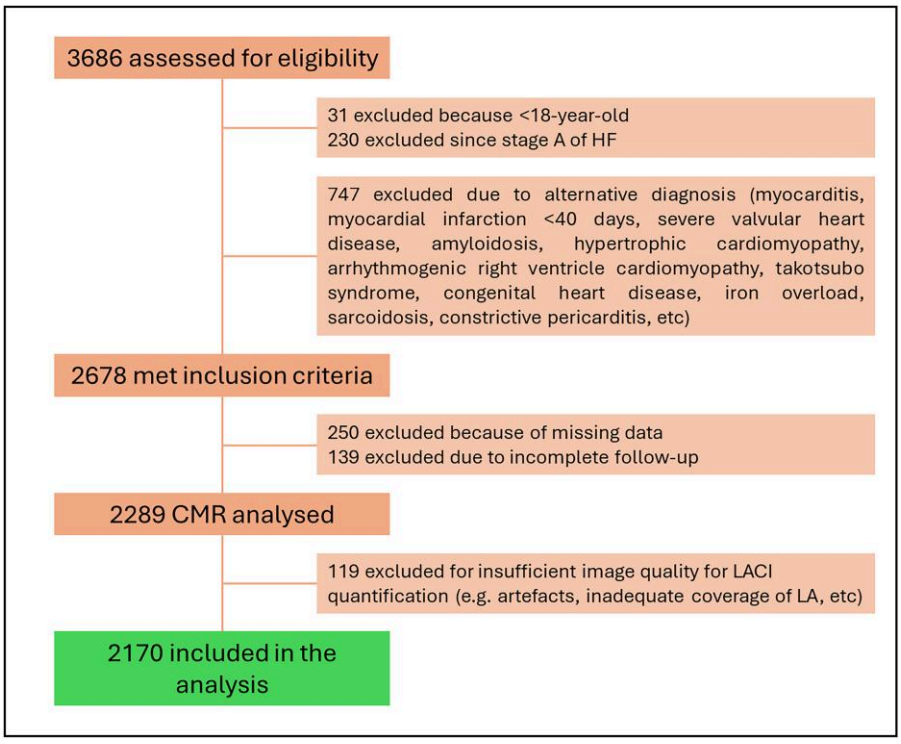


Figure 1 Flowchart of the study. CMR, cardiac magnetic resonance; HF, heart failure; LA, left atrium; LACI, left atrioventricular coupling index

CMR protocol

After the acquisition of localizers, breath-hold steady-state free precession (SSFP) sequences for functional analysis and quantification of ventricular volumes were acquired (spatial resolution of <2.0 mm × <2.0 mm, slice thickness ≤8 mm, gap 0–2 mm, temporal resolution 35–50 ms). Standard 2-, 3-, and 4-chamber long-axis views and a stack of short-axis images were obtained. LGE imaging was used for fibrosis assessment. Ten to 15 min after an intravenous bolus of 0.1–0.2 mmol/kg gadolinium-based contrast agent, segmented phase-sensitive gradient echo inversion recovery sequences were acquired by applying the same orientation as the SSFP. The inversion time was optimized to null normal myocardium.

CMR analysis

The CMR dataset was transferred and centrally evaluated by an experienced cardiac imager blinded to clinical and other instrumental characteristics of the patients. Circle CVI 4.2 (5.11.2) software was used for the automatic segmentation of cardiac chambers, followed by manual correction if needed. From short-axis cine LVEDV, LV end-systolic volume (LVESV), LV stroke volume (LVSV), LVEF, and LV mass were computed. Using 2-chamber and 4-chamber cine images, biplanar LAEDV, biplanar LA end-systolic volume (LAESV), and LA ejection fraction (LAEF)—defined as (LAESV-LAEDV)/LAESV * 100—were estimated. The biplanar area-length method was used to compute LA volumes.[19] The same phases were used for segmenting LA and LV, both in end-diastole and end-systole, based on mitral valve closure and opening. All parameters have been adjusted for body surface area (BSA). LACI was computed as LAEDV/LVEDV * 100, as previously described.[15] Visual assessment of LGE was performed. In ICM, LGE was also quantified as previously described.[20] The localization of LGE was reported according to the AHA 17-segment model, as in previous literature.[17]

Outcomes

Follow-up was performed at each local institution by direct interview during office visits or telephone contact with the patient or the patient's immediate family in case of death. All-cause mortality (ACM) was the main outcome. Two composite endpoints were also considered: (i) ACM or hospitalization for HF, and (ii) major arrhythmic adverse cardiac events (MAACE) defined as the combination of sudden cardiac death (SCD), aborted SCD event, or sustained ventricular tachycardia. HF alone was also considered as a separate outcome, accounting for the competing risk of all-cause mortality. Further details can be found in the published protocol of the DERIVATE.[17]

Statistical analysis

For continuous variables, the normality of the distribution was assessed with the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median (25th–75th percentile) as appropriate. Student's *t*-test or Mann-Whitney *U*-test were used as appropriate to compare continuous variables between patients with and without ACM. Discrete variables were expressed as absolute numbers and percentages and χ^2 test was performed to assess between-group differences. Univariable and multiple linear regression models were used to identify independent predictors of LACI. Univariate Cox proportional hazard models were used to identify predictors for study endpoints. Multiple variables regression Cox models were used to compute the adjusted hazard ratio (HR) and 95% confidence intervals (95% CI) considering significant predictors identified in the univariate analysis, clinically relevant parameters, and after exclusion of collinear predictors based on the variance inflation factor. A competing-risk analysis using the Fine-Gray sub-distribution hazard model to assess the risk of HF considering ACM as a competing event was performed. Time-dependent receiver operating characteristic (ROC) curves were drawn and the area under the curve (AUC) was calculated to evaluate the performance of LACI in predicting 3-year outcomes.[21] Bootstrap with 1000 resampling was used for the 95% CI of the AUC calculation and internal validation of Cox models. The optimal cut-off was identified using the Youden index. Sensitivity and specificity, according to the optimal cut-off were computed. The 'timeROC' package for R was used for the time-dependent ROC analysis for HF, accounting for the competing risk of ACM. Kaplan–Meier survival curves stratifying by the optimal LACI cut-off were drawn and the log-rank test was used for comparison. The

Table 1 Clinical and imaging characteristics according to all-cause mortality

	Total ($n = 2170$)	No ACM ($n = 1979$)	ACM ($n = 191$)	*P*-value
Age, years	59.8 ± 13.9	59.2 ± 13.9	66.3 ± 12.4	<.001
Female	537 (24.7)	490 (24.8)	47 (24.6)	.963
BSA, m²	1.91 ± 0.22	1.91 ± 0.22	1.87 ± 0.24	.024
CVD family history	674 (31.3)	617 (31.4)	57 (29.8)	.651
Smoking history	848 (39.2)	796 (40.4)	52 (27.2)	<.001
Hypertension	1088 (50.4)	975 (49.5)	113 (59.2)	.011
Dyslipidaemia	940 (43.5)	857 (43.5)	83 (43.5)	.995
Diabetes mellitus	466 (21.5)	403 (20.4)	63 (33)	<.001
NYHA class >II	486 (22.4)	415 (21)	71 (37.2)	<.001
ICM	844 (38.9)	741 (37.4)	103 (53.9)	<.001
Atrial fibrillation	446 (20.6)	390 (19.7)	56 (29.3)	.002
LBBB	555 (25.6)	507 (25.7)	48 (25.1)	.87
Beta-blockers	1838 (85.0)	1684 (85.4)	154 (80.6)	.075
Ivabradine	141 (6.9)	130 (7)	11 (6.2)	.687
ACE-I/ARBs	1822 (84.3)	1670 (84.7)	152 (79.6)	.062
Diuretics	1438 (68.4)	1281 (67)	157 (83.1)	<.001
Antiplatelets	1117 (53.2)	1004 (52.5)	113 (59.8)	.057
Statin	1043 (49.7)	942 (49.3)	101 (53.4)	.277
Amiodarone	315 (15.0)	276 (14.5)	39 (20.6)	.023
Cardiac magnetic resonance				
LVEDVI, mL/m²	128.1 ± 42.1	127.5 ± 41.8	134.4 ± 44.5	.028
LVESVI, mL/m²	89.9 ± 39.6	89.0 ± 39.2	99.2 ± 42.8	.001
LVSV, mL	61.0 ± 31.5	61.9 ± 31.5	51.6 ± 29.4	<.001
LVEF, %	31.6 ± 11.3	31.9 ± 11.2	28.1 ± 11.7	<.001
LV mass index, g/m²	79.0 ± 26.8	78.9 ± 26.8	80.62 ± 26.7	.489
LGE	1166 (53.7)	1045 (52.8)	121 (63.4)	.005
LGE segments, *n*	1 (0–4)	1 (0–4)	2 (0–5)	.001
LGE >3 segments	582 (26.8)	516 (26.1)	66 (34.6)	.012
LAEDVI, mL/m²	23.3 (15.5–36.2)	22.7 (15.1–35.5)	32.1 (21.4–49.5)	<.001
LAESVI, mL/m²	47.1 (36.8–60.0)	46.7 (36.5–59.5)	52.2 (41.0–66.8)	<.001
LAEF, %	43.9 ± 19.2	44.8 ± 19.0	35.0 ± 18.8	<.001
LACI, %	19.4 (13.3–28.8)	18.8 (13.0–28.2)	24.8 (17.1–37.6)	<.001
DERIVATE Scores				
NICM-DERIVATE[a]	3 (2–5)	3 (2–5)	3.5 (2–5)	.238
ICM-DERIVATE[b]	0.05 (−0.30; 0.37)	0.02 (−0.33; 0.35)	0.24 (−0.05; 0.48)	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ACM, all-cause mortality; ARBs, angiotensin receptors blockers; BSA, body surface area; CVD, cardiovascular diseases; DERIVATE, Cardiac Magnetic Resonance for Primary Implantable Cardioverter Defibrillator Therapy registry; ICM, ischaemic cardiomyopathy; LACI, left atrioventricular coupling index; LAEDVI, left atrium end-diastolic volume index; LAEF, left atrium emptying fraction; LAESVI, left atrium end-systolic volume index; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVI, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction; LVESVI, left ventricle end-systolic volume index; LVSV, left ventricle stroke volume; NICM, non-ischaemic cardiomyopathy; NYHA, New York Hearth Association.

[a]NICM-DERIVATE score is calculated as the sum of 2 points for male sex, 3 points if left ventricle end-diastolic volume index >120.5 mL/m², and 2 points for the presence of >3 segments of midwall fibrosis. Statistics are calculated in the population of 1326 patients with NICM.

[b]ICM-DERIVATE score is calculated as 0.005 * (left ventricle end-diastolic volume index [mL/m²])—0.029 * (left ventricle ejection fraction [%]) + 0.010 * (late gadolinium enhancement mass [g]). Statistics are calculated in the population of 844 patients with ICM.

cumulative incidence function curve was drawn to graphically show differences in HF cumulative incidence after competing risk analysis. The likelihood-ratio test or the Wald test was used, as appropriate, to evaluate the additive value of LACI over TTE-derived LVEF <35% and previously published CMR-based risk predictor scores, which considered parameters such as sex, LVEDV/BSA, LVEF, and LGE distribution and extension.[20,22] Subgroup analysis was performed to assess the prognostic role of the optimal cut-off in relevant subgroups (age, sex, aetiology of HF, AF, NYHA class, MR > mild, LVEF class, and LGE presence) using Cox models including interaction terms. Two-sided *P*-values <.05 were considered significant. All analyses were performed with Stata/SE 18.0 (Stata Corp LLC, College Station, TX) and RStudio 2024.12.1 (Posit Software PBC, Boston, MA).

Results

Characteristics of the population

The flowchart of the study is in *Figure 1*. According to the inclusion and exclusion criteria, 2289 patients were enrolled in the present study.

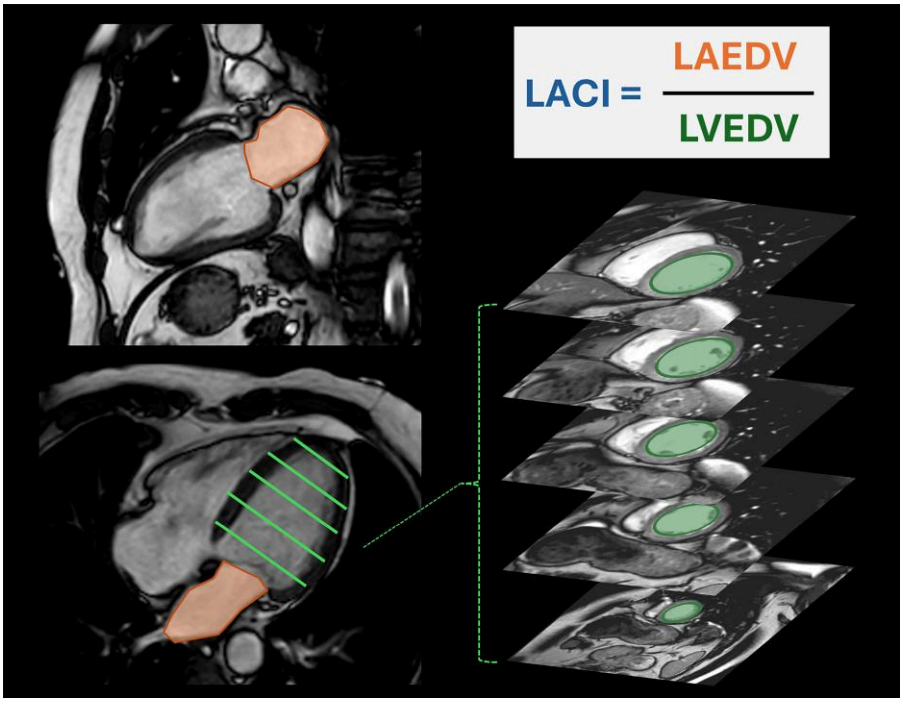


Figure 2 Schematic representation of left atrioventricular coupling index calculation (LACI). LVEDV, left ventricle end-diastolic volume; LAEDV, left atrial end-diastolic volume

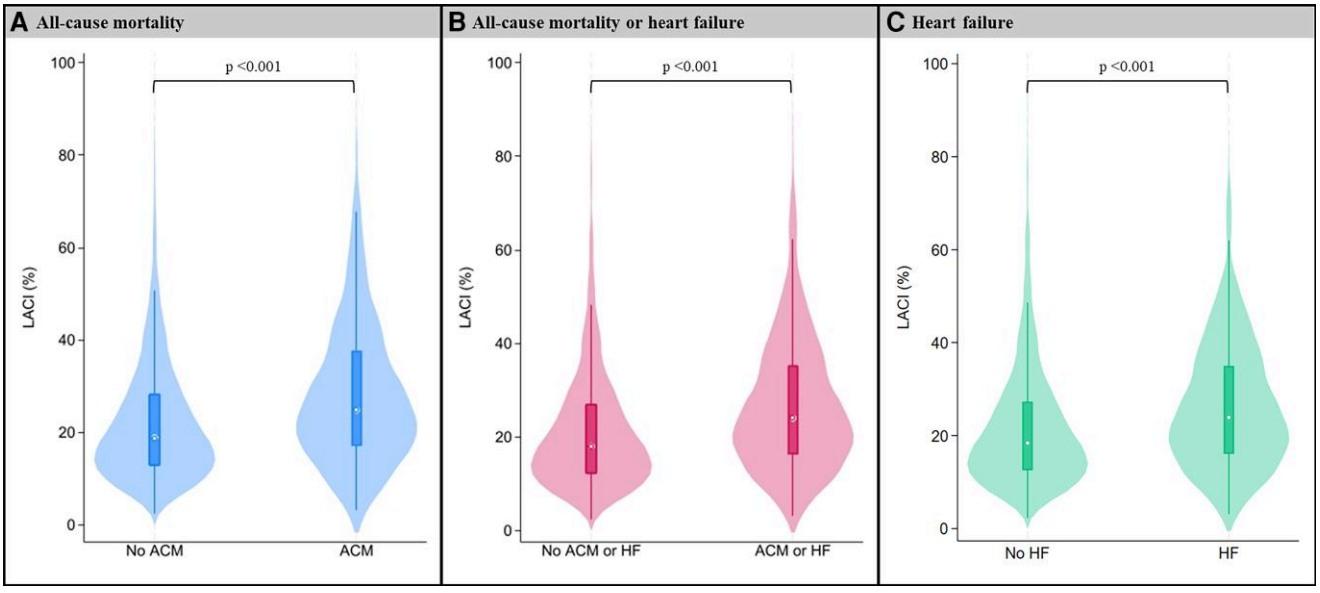


Figure 3 Violin plots illustrating the distribution of left atrioventricular coupling index (LACI) according to all-cause mortality (*A*), all-cause mortality or heart failure (*B*), and heart failure (*C*). ACM, all-cause mortality; HF, heart failure

119 (5.2%) were excluded because LA volumes cannot be computed for poor-quality images. The final population of the study consisted of 2170 patients, with a mean age of 59.8 ± 13.9 years, including 537 (24.7%) females. Ischaemic cardiomyopathy was the aetiology of the reduced EF in 844 (38.9%) patients. Mean LVEF by TTE was 34.1 ± 10.8%, with 1286 (59.3%) patients having a LVEF ≤35%. MR > mild was

Table 2 Predictors of LACI by univariable and multivariable linear regression

	Coeff (95% CI)	*P*-value	Coeff (95% CI)[a]	*P*-value
Age, years	0.284 (0.243; 0.324)	<.001	0.132 (0.099; 0.165)	<.001
Female	−0.099 (−1.447; 1.249)	.886		
BSA, m^2	−1.010 (−3.687; 1.666)	.459		
CVD family history	−0.565 (−1.825; 0.695)	.379		
Smoking history	−0.675 (−1.869; 0.519)	.268		
Hypertension	4.100 (2.946; 5.254)	<.001		
Dyslipidaemia	2.978 (1.808; 4.148)	<.001		
Diabetes mellitus	4.562 (3.157; 5.967)	<.001	1.228 (0.239; 2.217)	.015
NYHA class >II	5.849 (4.475; 7.222)	<.001	2.567 (1.543; 3.590)	<.001
ICM	5.993 (4.827; 7.160)	<.001		
Atrial fibrillation	8.825 (7.434; 10.216)	<.001	4.308 (3.304; 5.312)	<.001
LBBB	−2.422 (−3.753; −1.092)	<.001	−1.522 (−2.471; −0.574)	.002
Beta-blockers	−0.868 (−2.503; 0.767)	.298		
Ivabradine	−1.178 (−3.512; 1.156)	.322		
ACE-I/ARBs	−4.565 (−6.157; −2.973)	<.001	−3.092 (−4.219; −1.966)	<.001
Diuretics	2.539 (1.263; 3.814)	<.001		
Antiplatelets	2.514 (1.326; 3.702)	<.001		
Statin	2.061 (0.874; 3.248)	.001		
Amiodarone	3.082 (1.420; 4.743)	<.001		
MR > mild	2.951 (1.732; 4.171)	<.001		
Cardiac magnetic resonance				
LVEDVI, mL/m^2	−0.068 (−0.081; −0.054)	<.001	−0.146 (−0.158; −0.134)	<.001
LVESVI, mL/m^2	−0.040 (−0.054; −0.025)	<.001		
LVSV, mL	−0.135 (−0.153; −0.118)	<.001		
LVEF, %	−0.168 (−0.219; −0.117)	<.001	−0.197 (−0.242; −0.153)	<.001
LV mass index, g/m^2	−0.079 (−0.101; −0.057)	<.001	−0.032 (−0.049; −0.015)	<.001
LGE	1.970 (0.806; 3.134)	.001		
LGE segments, *n*	0.288 (0.107; 0.469)	.002		
LGE >3 segments	1.735 (0.424; 3.046)	.010		
LAEDVI, mL/m^2	0.650 (0.631; 0.670)	<.001		
LAESVI, mL/m^2	0.445 (0.418; 0.471)	<.001	0.487 (0.463; 0.511)	<.001
LAEF, %	−0.491 (−0.514; −0.467)	<.001		

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptors blockers; BSA, body surface area; CI, confidence intervals; CVD, cardiovascular diseases; ICM, ischaemic cardiomyopathy; LACI, left atrioventricular coupling index; LAEDVI, left atrium end-diastolic volume index; LAEF, left atrium emptying fraction; LAESVI, left atrium end-systolic volume index; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVI, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction; LVESVI, left ventricle end-systolic volume index; LVSV, left ventricle stroke volume; MR, mitral regurgitation; NICM, non-ischaemic cardiomyopathy; NYHA, New York Hearth Association

[a]R^2 of the model is equal to 0.607.

present in 743 (34.2%) of patients. Baseline characteristics are listed in *Table 1*. The median follow-up time was 1016 days (25th-75th percentiles: 580–1609 days). ACM affected 191 (8.8%) patients during follow-up. A total of 565 patients (26.0%) experienced ACM or HF, while 442 (20.4%) had HF and 199 (9.2%) had a MAACE. Median LACI was 19.4% (13.3–28.8%). A schematic representation of LACI is shown in *Figure 2*. LACI was higher in patients experiencing ACM, ACM or HF, and HF during follow-up ($P < .001$ for all), as shown in *Figure 3*.

Clinical and instrumental predictors of LACI

Several clinical and instrumental predictors of LACI were identified by univariable and multiple linear regression (*Table 2*). Multiple linear regression with stepwise forward selection model identified as independent predictors of LACI: age, diabetes mellitus, NYHA class >2, AF, absence of LBBB and no therapy with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARB), and CMR-derived LVEDV/BSA, LVEF CMR derived, LV mass index, and LASVI/BSA ($P < .05$ for all). A sensitivity analysis (Supplementary Table S2) excluding LV and LA dimensions from the multivariable model identified as an additional predictor of increased LACI hypertension and MR > mild.

LACI as an independent predictor of adverse outcomes

The predictors of ACM, ACM or HF, and HF identified by univariable Cox regression are summarized in Supplementary Table S3. The multiple Cox regression models with and without bootstrapping confirmed CMR-derived LACI as an independent predictor of outcomes after

Table 3 Hazard ratios adjusted for age, sex, cardiovascular risk factors, aetiology of heart failure, New York Heart Association class, atrial fibrillation, and cardiac magnetic resonance characteristics

	ACM		ACM or HF		HF[a]	
	HR (95% CI)*	*P*-value*	HR (95% CI)*	*P*-value*	HR (95% CI)*	*P*-value*
Age, years	1.03 (1.01–1.04)	<.001	1.00 (0.99–1.01)	.416	1.00 (0.99–1.01)	.539
Female	1.12 (0.78–1.60)	.542	0.91 (0.74–1.13)	.384	0.76 (0.59–0.98)	.031
Smoking history	0.61 (0.44–0.85)	.003	0.76 (0.63–0.91)	.003	0.83 (0.68–1.02)	.079
Hypertension	1.10 (0.81–1.50)	.545	0.99 (0.82–1.20)	.950	0.98 (0.79–1.22)	.866
Dyslipidaemia	0.72 (0.53–0.99)	.045	0.97 (0.81–1.17)	.766	1.07 (0.87–1.32)	.508
Diabetes mellitus	1.42 (1.03–1.97)	.035	1.45 (1.19–1.76)	<.001	1.26 (1.01–1.58)	.044
NYHA class >II	1.85 (1.36–2.52)	<.001	1.67 (1.38–2.01)	<.001	1.54 (1.25–1.91)	<.001
ICM	1.44 (1.03–2.01)	.034	1.11 (0.91–1.36)	.287	1.02 (0.82–1.27)	.852
Atrial fibrillation	1.23 (0.88–1.71)	.235	1.18 (0.97–1.43)	.100	1.12 (0.89–1.40)	.323
LVEDVI, mL/m^2	1.00 (0.99–1.01)	.111	1.00 (1.00–1.01)	.001	1.00 (1.00–1.01)	.018
LVEF, %	1.00 (0.98–1.02)	.705	0.99 (0.98–0.99)	.016	0.98 (0.97–0.99)	<.001
LGE segments, n	1.05 (1.01–1.10)	.015	1.04 (1.01–1.07)	.003	1.02 (0.99–1.05)	.113
LACI, 5%	1.06 (1.01–1.11)	.016	1.09 (1.06–1.12)	<.001	1.09 (1.05–1.12)	<.001

Confidence intervals and *P*-values were obtained with bootstrap resampling for internal validation of Cox regression models
Abbreviations as in *Table 2*.
*Bootstrapped hazard ratios with 95% confidence intervals using 1000 bootstrap samples. Bootstrapped *P*-valued using 1000 bootstrap samples.
[a]Competing-risk analysis considering all-cause mortality as a competing event.

Table 4 Area under the curve (AUC) with 95% confidence intervals (95% CI) of left atrioventricular coupling index (LACI) for prediction of 3-year all-cause mortality (ACM), ACM or heart failure (HF), and HF

Outcome	AUC (95% CI)[a]	Optimal LACI cutoff	Sensitivity	Specificity
ACM	0.617 (0.561–0.673)	21.0	63.7	56.0
ACM or HF	0.627 (0.597–0.657)	21.0	61.4	59.5
HF[b]	0.606 (0.571–0.641)	N/A	62.2	56.6

[a]Bootstrapped 95% confidence intervals using 1000 bootstrap samples.
[b]Competing-risk analysis considering all-cause mortality as a competing event. Sensitivity and specificity are calculated applied the ACM-derived cut-off of 21%.

adjustment for age, sex, cardiovascular risk factors, NYHA class, ischaemic aetiology of HF, AF, LVEDV/BSA, LVEF, and number of LGE-positive segments (*Table 3* and Supplementary Table S4). The adjusted HRs and 95% CI with bootstrap resampling for 5% increase in LACI were 1.06 (1.01–1.11) for ACM, 1.09 (1.06–1.12) for ACM or HF, and 1.09 (1.05–1.12) for HF. As shown in Supplementary Table S5, higher LACI was also associated with a higher risk of MAACE (adjusted HR = 1.08 with 95% CI 1.03–1.13 for 5% increase in LACI).

The AUC of the ROC curves is reported in *Table 4*. In particular, the AUC with 95% CI was 0.617 (0.561–0.673) for 3-year ACM, 0.627 (0.599–0.655) for 3-year ACM or HF, 0.606 (0.571–0.641) for 3-year HF accounting for competing risk of ACM, and 0.613 (0.558–0.668) for 3-year MAACE. The optimal cut-off for LACI in the prediction of 3-year ACM selected with the Youden index was 21%. On the contrary, as shown in Supplementary Table S6, LVEF, both TTE- and CMR-derived, LVEDV/BSA by CMR, and number of positive LGE segments had a very limited discriminatory ability for the prediction of ACM (AUC <0.600 for all), ACM or HF (AUC <0.600 for all except for CMR-derived LVEF, which had an AUC = 0.615), and HF (AUC <0.600 for all). Only CMR-derived LVEF and LVEDV/BSA were comparable with LACI in the discrimination between patients with low and high risk of MAACE (AUC = 0.623 and 0.646, respectively).

Kaplan–Meier curves stratifying the population according to LACI cut-off of 21% are shown in *Figure 4* and confirmed the worse prognosis in terms of ACM and ACM or HF if LACI ≥21% (log-rank test *P*-value < .001 for both). The cumulative incidence function after competing-risk analysis for HF occurrences stratified by LACI ≥21% shows similar results (*Figure 5*).

The additive value of LACI in prognostic stratification over TTE-derived LVEF and risk stratification through previously published DERIVATE scores is depicted in *Figure 6*. The population of the study was divided according to HF-aetiology since two different DERIVATE scores were developed for NICM and ICM. In NICM, stratifying according to LACI ≥21% provided a significant increase in the model fit for all the outcomes ($P < .001$). In ICM, LACI had an additive value over LVEF and ICM-DERIVATE score for ACM, ACM or HF, and HF alone prediction ($P < .05$). For the prediction of MAACE, LACI granted a better stratification over LVEF ($P < .001$), but not on top of the ICM-DERIVATE score ($P = .051$).

Finally, the subgroup analysis (Supplementary Figure S1) identified a quantitative interaction between LACI cut-off of 21% and

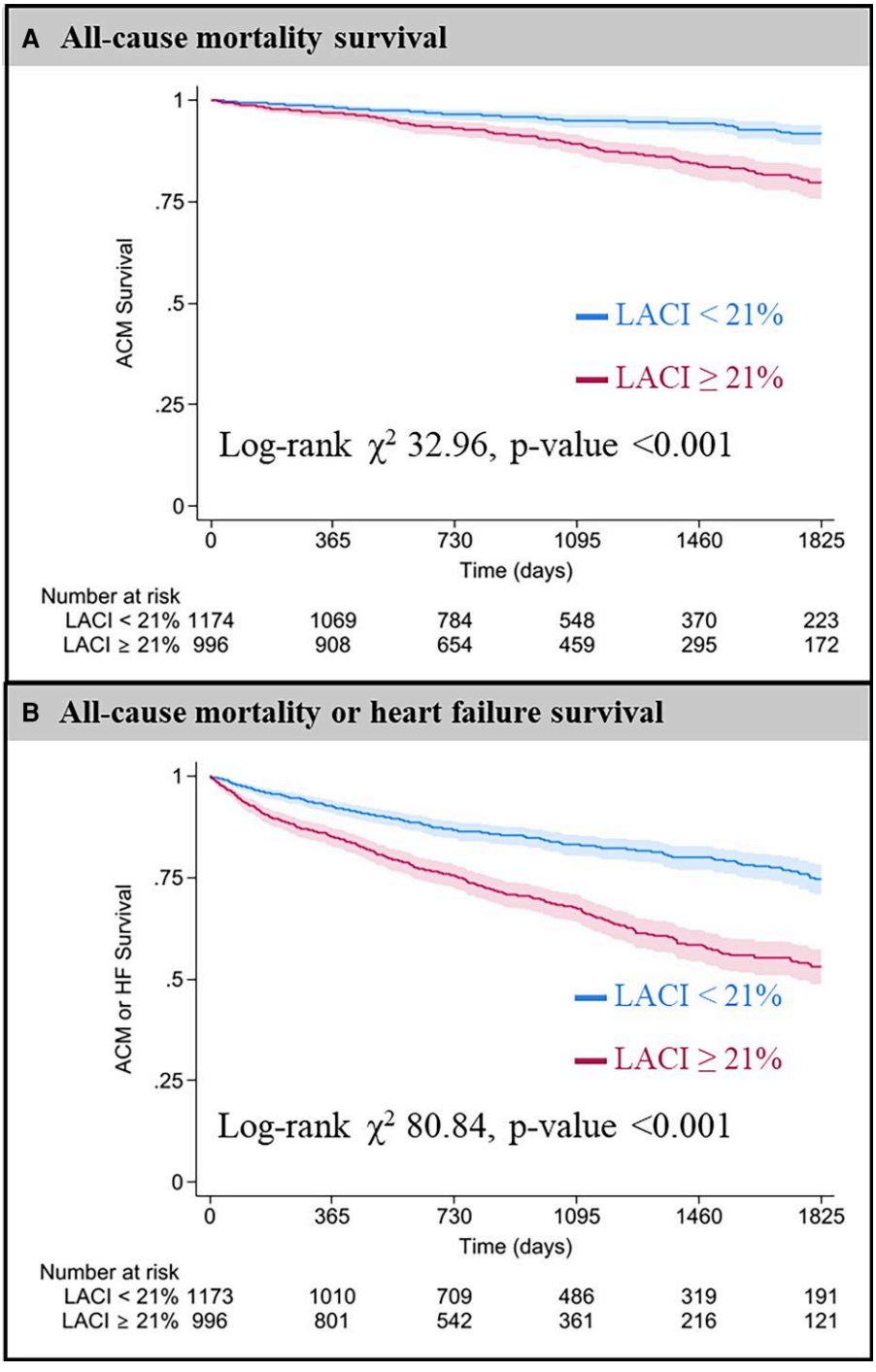


Figure 4 Kaplan–Meier curves showing event-free survival rates according to left atrioventricular coupling index (LACI) ≥21% for all-cause mortality (*A*) and all-cause mortality or heart failure (*B*)

LVEF (*P* for interaction = .03) in the prediction of ACM or HF, but not for ACM, HF, and MAACE. In particular, LACI ≥21% conferred a higher risk of ACM or HF in patients with LVEF >40% (HR 3.40, 95% CI 2.17–5.34) than in those with LVEF ≤40% (HR 1.97, 95% CI 1.64–2.37). No other significant interaction between LACI cut-off of 21% and age, sex, aetiology of HF, NYHA class, AF, MR > mild, and LGE for the prediction of the outcomes was found.

Discussion

To the best of our knowledge, this is the first study to evaluate the additional prognostic value of the LA and LV coupling in a broad cohort of patients with reduced EF. The main findings are:

(a) LACI was identified as an independent predictor of all-cause mortality, heart failure, and arrhythmic events during long-term follow-up. This

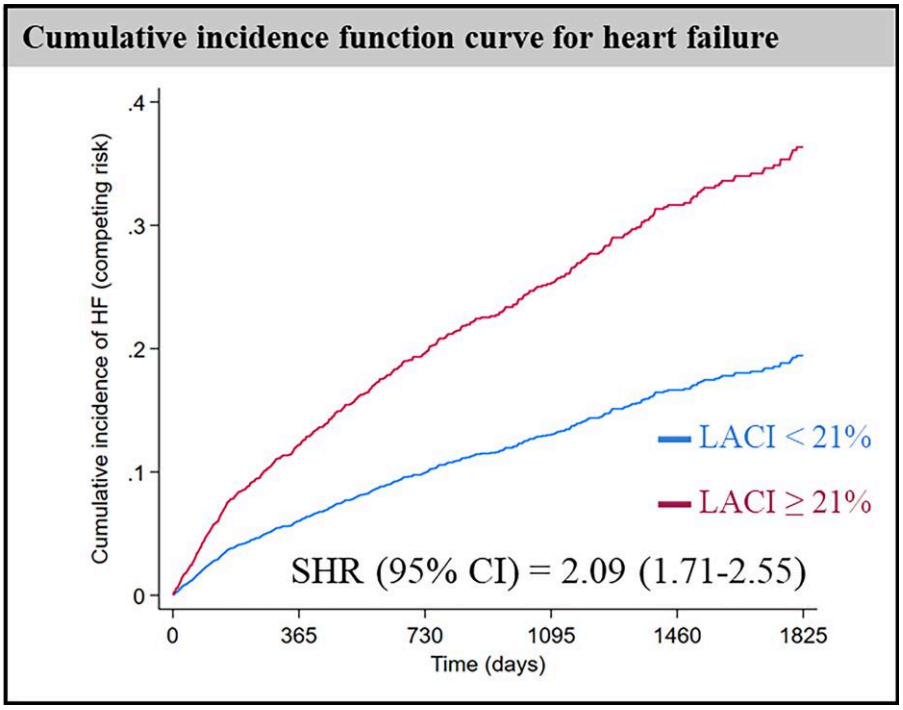


Figure 5 Cumulative incidence function curve for HF occurrence and accounting for competing risk of all-cause mortality according to left atrioventricular coupling index (LACI) ≥21%. 95% CI, 95% confidence intervals; SHR, subhazard ratio

predictive role is independent of traditional features such as NYHA class, HF aetiology, AF, and LGE.

(b) Predictors of elevated LACI included clinical factors (including age, DM, and AF, LBBB) and CMR parameters (such as LVEF and LV mass index).

(c) A cut-off of 21% for LACI was found to be the best in identifying patients at high risk of adverse events during follow-up in our cohort.

The role of LA-LV coupling in the cardiac performance

Efficient LV performance is essential for maintaining cardiac output, ensuring proper tissue perfusion, and supporting overall cardiovascular health. However, accumulating evidence is showing that the LA also has an important role in maintaining the correct cardiac functioning.[23] Moreover, an intricate relationship between the LA and the LV exists and the loss of LA-LV coupling is a key feature in determining outcomes. LACI represents an indirect measure of the interplay between the LA and LV.[16,24]

Our analysis identified older age, diabetes mellitus, and AF as clinical predictors of elevated LACI. These findings are in accordance with what has been suggested by previous studies, including apparently healthy subjects or other cardiomyopathies.[25–28] Additionally, higher LACI values have been correlated with the development of AF and microvascular disease.[29–31] Taken together, these findings could indicate that some patients with reduced EF have worse atrial adverse remodelling because of the coexistence of risk factors for a primary atrial cardiomyopathy, such as diabetes, AF, and older age.[32] Moreover, the presence of LBBB was independently associated with lower LACI. It is possible that in most patients in our cohort with LBBB, the ventricular dyssynergy is the first determinant of reduced LVEF, mainly affecting LV dimensions but with no or minimal effect on LA. Furthermore, in our analysis, the use of ACE-I/ARB is protective against high LACI. The importance of the renin-angiotensin-aldosterone system in atrial remodelling is well known.[33,34] However, the observational design of this study prevents evaluating the potential beneficial role of medications on LACI. Nevertheless, LACI could serve as an interesting marker of atrial reversal remodelling for therapies, such as ACE-I/ARB, sacubitril/valsartan, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Specific studies with this aim are warranted. Finally, hypertension and more than mild MR resulted as independent predictors of LACI, but not when adjusting for LV and LA dimensions. This could indicate that these conditions may similarly affect LV and LA, resulting in a pseudo-normalization of LACI. Further studies in these settings may elucidate the specific role of LACI. Finally, we observed a limited discriminatory ability of LGE-positive segments for predicting ACM, which may be explained by population heterogeneity, the semi-quantitative nature of segment-based assessment, and the high prevalence of LGE in patients with reduced ejection fraction, potentially reducing its incremental prognostic value.

LACI as prognostic index

The possible prognostic role of the LACI was first described in the Multi-Ethnic Study of Atherosclerosis (MESA), where LACI was found to be an independent predictor of HF, AF, and cardiovascular death among healthy subjects.[15] Furthermore, a higher increment of LACI after 10 years can predict HF development independently from other clinical and instrumental risk factors for HF.[35] In a cohort of 478 patients with HF and LVEF <50%, higher LACI values were associated with a higher risk of all-cause mortality or HF.[36] In patients after acute myocardial infarction, higher CMR-derived LACI could predict adverse outcomes, even if its predictive ability was only borderline when

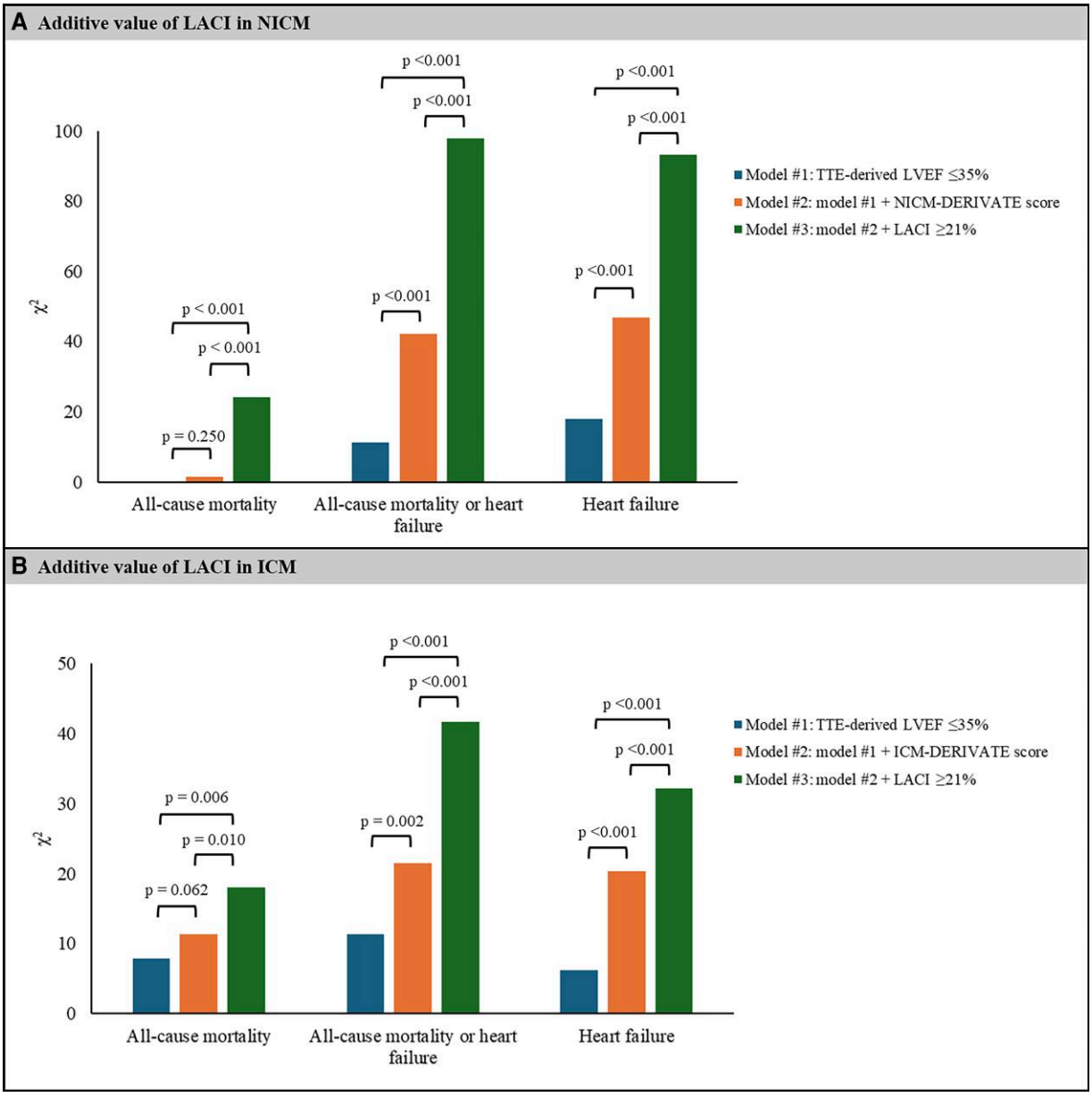


Figure 6 Incremental value of left atrioventricular coupling index (LACI) on top of previously developed DERIVATE scores for (*A*) non-ischaemic (NICM) and (*B*) ischaemic cardiomyopathy (ICM) and echocardiography-derived left ventricle ejection fraction (TTE-derived LVEF). NICM-DERIVATE score is calculated as the sum of 2 points for male sex, 3 points if left ventricle end-diastolic volume index >120.5 mL/m^2, and 2 points for the presence of >3 segments of midwall fibrosis. ICM-DERIVATE score is calculated as 0.005 * (left ventricle end-diastolic volume index [mL/m^2])—0.029 * (left ventricle ejection fraction [%]) + 0.010 * (late gadolinium enhancement mass [g]). The likelihood-ratio test was used for comparison of all-cause mortality and the composite of all-cause mortality and heart failure. The Wald test was used for comparison of models predicting heart failure with competing risk

adjusted for clinical parameters and LVEF (adjusted HR with 95% CI 3.1 (1.0–9.4), $P = .049$).[37,38] In patients undergoing cardiac computed tomography (CCT), CCT-LACI ≥25% predicted all-cause and cardiovascular death even after adjustment for cardiovascular risk factors, LVEF, and obstructive CAD detection by CCT.[39]

Our study expands these results by considering a large population of patients with reduced EF. Also, in this group of patients, LACI was found to be an independent predictor of all-cause death, HF, and major arrhythmic events on top of LVEDV/BSA, LVEF, and LGE. Furthermore, we were able to identify the cut-off of LACI ≥21% as the best predictor of ACM or HF and MAACE in our population. This is in line and expands previous results; even if evaluated on transthoracic echocardiography, a LACI ≥20% as predictor of adverse outcomes (all-cause death, heart transplant, nonfatal cardiac arrest, or hospitalization for HF) in a small cohort of patients with dilated cardiomyopathy.[40] Similarly, in patients undergoing cardiac computed tomography (CCT), a CCT-LACI

≥25% was also found predictor of all-cause and cardiovascular.[39] In our study, the prognostic ability of LACI appears modest. However, it should be considered that it is a single parameter which does not require additional CMR sequences or calculation since ventricular and atrial volumes are generally obtained in all scans. Moreover, it must be noted also that LACI ≥21% appears to be more effective in predicting ACM or HF in the subgroup of patients with LVEF >40%. This can be attributed to the fact that, with a higher LVEF, other factors beyond the EF alone come into play when determining patient prognosis. In this context, the LACI, which reflects the interplay between the LA and LV, becomes an important prognostic tool. Specific studies should aim to assess the utility of LACI in prognostic stratification of patients with HF with preserved or mildly reduced LVEF. Conversely, we found no significant interaction between the prognostic predictive ability of LACI ≥21% and age, sex, or the presence of MR. Therefore, this favours the applicability of this cut-off across different age and sex categories. From a practical perspective, LACI may represent a readily implementable parameter in routine CMR reporting, as it can be derived from standard cine acquisitions without additional imaging sequences or post-processing. In clinical practice, LACI could support baseline risk stratification, particularly in patients with moderately reduced LVEF where traditional markers may be less discriminative. Furthermore, longitudinal assessment of LACI may help identify progressive atrial remodelling and worsening ventricular–atrial coupling. When integrated with established parameters such as LVEF and LGE, LACI may contribute to a comprehensive multiparametric approach to guide follow-up intensity and clinical management.

Limitations of the study

The main limitation of this study is its retrospective design, implicating the risk of referral bias. However, to adjust for differences, multivariable analyses were performed to identify the independent predictors of outcomes. Even if an internal validation with bootstrap has been performed, an external validation cohort is needed. However, the multicentric origin of the data in the DERIVATE registry favours the possibility of generalizing the results. Data for calculating LACI and evaluating diastolic dysfunction by echocardiography were not available, hence a direct comparison and possible assumption on diastolic dysfunction could not be made. Nevertheless, CMR-derived LACI has already been validated using invasive assessment of filling pressures.[24] Left atrial volumes were assessed using the biplanar area–length method, although widely used in clinical practice, which relies on geometric assumptions and may be less accurate in patients with markedly dilated or asymmetric atria, potentially leading to under- or over-estimation of left atrial volumes. Therefore, cases in which the LA was not appropriately covered were excluded. The use of segment-based LGE assessment, particularly in non-ischaemic cardiomyopathy, may have limited the accuracy of fibrosis quantification, as patchy distribution and small areas of enhancement could lead to potential over- or underestimation compared with quantitative LGE mass measurements. The protocol of the DERIVATE registry was first published in 2018, therefore the use of some therapies, such as SGLT2 inhibitors, vericiguat, and cardiac resynchronization therapy, was not widespread and its impact cannot be analysed. Finally, in our analysis, novel CMR-derived parameters, such as parametric mapping, were not included, thus the additive prognostic value of LACI over these parameters remains unknown.

Conclusions

CMR-derived LACI, calculated as the ratio between LA end-diastolic volume and LV end-diastolic volume, is an independent predictor of all-cause death, HF, and MAACE in both ICM and NICM. A cut-off of LACI ≥21% can discriminate patients with a higher risk of all-cause death, HF, and MAACE. Although its prognostic value may appear modest, LACI has an additive prognostic value over TTE-derived LVEF and other clinical and CMR-derived parameters, including LGE. Moreover, LACI is an easily derived CMR parameter that does not require specific additional sequences and contrast agent administration. In clinical practice, the implementation of LACI when reporting a CMR has proven to add relevant prognostic information. Future studies should evaluate whether LACI could prompt a more aggressive follow-up strategy and guide the management and diuretic and anti-remodelling therapy of patients.

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Supplementary data

Supplementary data are available at *ESC Heart Failure* online.

Declarations

Disclosure of Interest

Dr. Anna Giulia Pavon received the support of the Swiss Heart Foundation for the analysis of the study. The other authors declare that they have no competing interests.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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