Left Atrioventricular Coupling Index: A Novel Diastolic Parameter to Refine Prognosis in Heart Failure

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Background: Left atrioventricular coupling index (LACI), an index coupling left atrial to left ventricular (LV) volume at end-diastole, has been shown to be associated with prognosis in different clinical settings. However, the relation between LACI and LV diastolic dysfunction (DD) remains to be established. The aims of the present study were to investigate the association between LACI and LV DD and to assess its prognostic value in patients with heart failure (HF).

Methods: A total of 1,158 patients with HF in stable condition, on optimal medical therapy, were retrospectively analyzed (derivation cohort). Clinical and echocardiographic features were characterized across LACI tertiles. The independent prognostic value of LACI (end point: all-cause death or HF hospitalization) was assessed using Cox regression. Results were validated in an external cohort of 242 patients with HF.

Results: In the derivation cohort, the median LACI value was 0.29 (interquartile range, 0.19-0.42). Patients in the third tertile (LACI > 0.36) were older and presented with more advanced HF symptoms. Although the prevalence of grade 1 DD (American Society of Echocardiography/European Association of Cardiovascular Imaging classification) progressively decreased across LACI tertiles, the prevalence of grade 3 DD significantly increased (8%, 23%, and 46%, respectively; $P < .0001$). A cutoff value of ≥0.26 identified moderate to severe DD with an area under the curve of 0.75. During follow-up (median, 28 months; interquartile range, 11-53 months), 407 patients (35%) reached the end point. On multivariable analysis, LACI was independently associated with outcomes (hazard ratio for a 1-SD increase, 1.16; 95% CI, 1.06-1.28; $P = .002$), showing incremental predictive value over the DD grading system (net reclassification improvement = 0.150, $P < .0001$). The prognostic value of LACI was consistent in the external validation cohort.

Conclusions: LACI is associated with DD severity and is an independent predictor of outcomes in patients with HF. (J Am Soc Echocardiogr 2024;37:1038-46.)

Keywords: Left atrium, Left ventricle, Heart failure, Diastolic function, Prognosis

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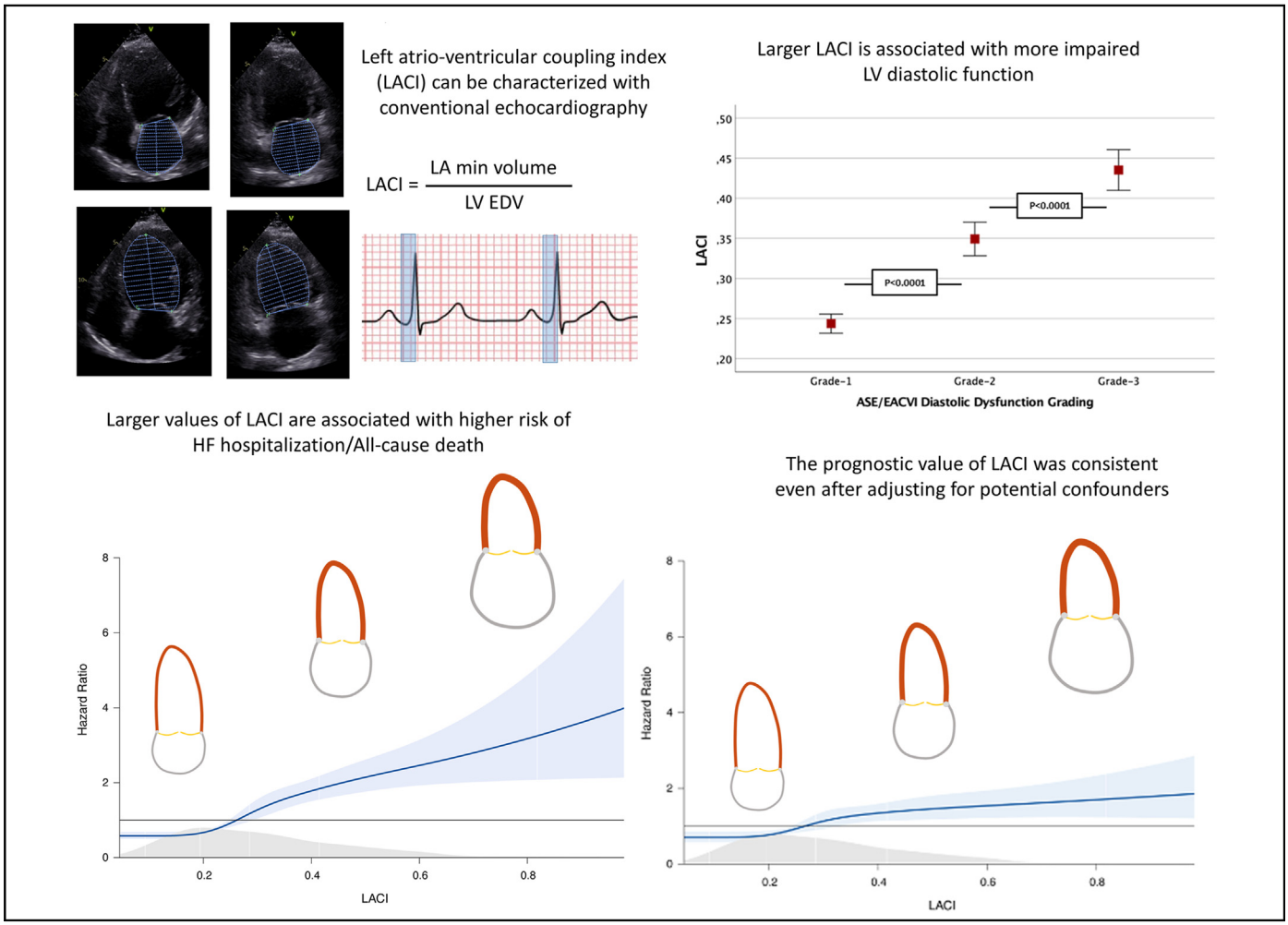
In recent years, because of advancements in echocardiography and other imaging modalities, as well as in pathophysiologic knowledge, there has been increasing interest in the left atrium in patients with heart failure (HF)[1,2] Both HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF) present left atrial (LA) structural and functional changes,[1,2] shown to be related to prognosis.[3,4] Although LA volume can be measured at different times during the cardiac cycle, LA maximal volume (LAVmax; measured at the end of left ventricular [LV] systole) has shown to be an independent marker of HF severity[2] and currently is the only LA echocardiographic parameter recommended by international guidelines to grade LV diastolic dysfunction.[5,6] However, LA minimal volume (LAVmin; measured at the end of LV diastole) has recently shown a stronger association with both invasively measured LV filling pressure and outcome in HF compared with LAVmax.[6-8]

While at the end of systole, the left atrium and left ventricle are separated by the closed mitral valve, at the end of diastole, the two



Central Illustration Association among LACI, DD, and prognosis in patients with HF. The figure summarizes the main findings of the present study. The *top left panel* illustrates how LACI can be assessed on conventional echocardiography. The *top right panel* shows the association between LACI and LV DD. The *bottom left panel* (unadjusted) and *bottom right panel* (adjusted) show the association between LACI and outcomes in patients with HF. *EDV*, End-diastolic volume.

chambers are directly connected and, in the absence of mitral stenosis, are tightly coupled. This makes LA dimension and function at this time point closely associated with LV remodeling and function.[9] Therefore, the assessment of LA and LV coupling could better reflect left atrioventricular dysfunction and might potentially be a better predictor of outcomes compared with independent assessment of the left atrium and left ventricle. This has led to the introduction of a novel imaging parameter that integrates the left atrium and left ventricle, the left atrioventricular coupling index (LACI),[7] defined by the ratio between LAVmin and LV end-diastolic volume (LVEDV). It is expected that LACI increases as LAVmin increases relative to LVEDV, suggesting more severe LV diastolic dysfunction. Although LACI has shown to be independently associated with cardiovascular outcomes in healthy individuals,[10] as well as in patients after acute myocardial infarction,[11] and in patients with hypertrophic cardiomyopathy,[12] its association with conventional echocardiographic parameters of LV diastolic function and its prognostic role in patients with chronic HF remain to be investigated.

Therefore, in the present study, we sought to evaluate the association between LACI and the severity of LV diastolic dysfunction across a broad spectrum of patients with chronic HF and to assess the independent and additive prognostic value of this index in patients with HF compared with the current guideline-based diastolic grading system.

METHODS

Study Population: Derivation Cohort

From January 2008 to December 2022, patients with chronic HF referred to the echocardiography laboratory of the Perugia HF outpatient clinic for comprehensive echocardiographic evaluation were retrospectively evaluated. Patients with any left ventricular ejection fraction (LVEF) value were eligible for this study if they were in sinus rhythm, and all diastolic function variables could be recorded as per guideline recommendations. Patients needed to be in stable clinical conditions and on optimal medical therapy for ≥3 months. At the time of the index clinical and echocardiographic examinations, demographic, clinical, laboratory,

Abbreviations

AF = Atrial fibrillation

ASE = American Society of Echocardiography

EACVI = European Association of Cardiovascular Imaging

eGFR = Estimated glomerular filtration rate

HF = Heart failure

HFpEF = Heart failure with preserved left ventricular ejection fraction

HFrEF = Heart failure with reduced left ventricular ejection fraction

HR = Hazard ratio

LA = Left atrial

LACI = Left atrioventricular coupling index

LAVmax = Left atrial maximal volume

LAVmin = Left atrial minimal volume

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

NT-proBNP = N-terminal pro–brain natriuretic peptide

NYHA = New York Heart Association

medication, and echocardiographic data were entered in a prospective database.

Exclusion criteria were (1) previous surgical or percutaneous treatment of mitral regurgitation or previous heart transplantation; (2) moderate or severe primary mitral and aortic valve disease, including any degree of mitral annular calcifications; (3) hospitalization for worsening HF, myocardial infarction, and revascularization in the previous 6 months; (4) malignancies or other noncardiac diseases that could affect short-term outcomes; and (5) HF due to a reversible cause, hypertrophic cardiomyopathy, untreated thyroid disease, pericardial disease, and amyloidosis.

Patients' functional status was determined according to the New York Heart Association (NYHA) classification. Ischemic etiology of HF was considered in the presence of a history of myocardial infarction, prior coronary revascularization, or evidence of significant (>70%) stenosis in at least one epicardial coronary artery on invasive coronary angiography.

The hemoglobin value closest to enrollment (<3 months) was used to define anemia (hemoglobin concentrations <13.0 g/dL in men and <12.0 g/dL in women).[13] Estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine value closest to clinical evaluation, using the Modification of Diet in Renal Disease study equation; chronic kidney disease was defined by an eGFR of <60 mL/min/1.73 m^2 during the past 3 months.[14] Venous blood samples for N-terminal pro–brain natriuretic peptide (NT-proBNP) assessment were drawn on the day of the index echocardiography.

The present study complied with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol, and informed consent was obtained from all included subjects.

Validation Cohort

The validation cohort consisted of 242 patients with chronic HF, with LVEFs <50%, in sinus rhythm, regularly followed at the Leiden University Medical Center. Similar inclusion and exclusion criteria used for the exploratory cohort were also applied to the validation group. Echocardiographic examinations were acquired using the same standardized protocol and performed by an investigator blinded to the exploratory group analyses.

Comprehensive Standardized Echocardiography

All patients underwent comprehensive transthoracic echocardiography using a Vivid 9 or a Vivid 7 ultrasound system (GE Medical Systems). LVEDV and LV end-systolic volume, LVEF, and LA end-systolic and end-diastolic volumes were calculated using the modified Simpson biplane method from apical imaging planes[15] and indexed to body surface area. A continuous-wave Doppler tracing of tricuspid regurgitation velocity was recorded to assess pulmonary arterial systolic pressure by combining tricuspid regurgitation velocity jet with an estimate of right atrial pressure on the basis of the diameter and collapsibility of the inferior vena cava. The severity of mitral regurgitation (grades I–IV) was determined by measuring the effective regurgitant orifice area or vena contracta width.[16]

Pulsed-wave peak early (E) and atrial (A) velocities of mitral inflow, their ratio (E/A), and early mitral inflow deceleration time were measured as recommended.[5] Using pulsed-wave Doppler tissue imaging, lateral and septal mitral annular early diastolic velocities (e') were measured and averaged. The ratio between transmitral E velocity and averaged e' velocity (E/e') was considered an index of mean LV filling pressure.[5] Diastolic function was graded using the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) algorithm for patients with reduced LVEFs or myocardial disease.[5] See the Supplemental Appendix for more details on how diastolic function was graded. According to the study protocol, all patients needed to have a complete data set of diastolic variables; therefore, there were no patients graded as indeterminate. All measurements were made over three consecutive cardiac cycles, and average values were used for the final analyses.

LACI

LACI was defined as the ratio between LAVmin and LVEDV.[10-12] LA and LV volumes were measured in the same end-diastolic phase defined by the mitral valve closure. As the long axes of the left ventricle and left atrium almost always lie in different planes, to optimize volume measurements, we took care to acquire dedicated acquisitions of the left atrium or focused views. In these views, care was taken to maximize the long-axis length and the base of the left atrium in both the apical four-chamber and two-chamber views to avoid foreshortening. LACI values were expressed as percentages, with higher values indicating greater disproportion between LA and LV volumes at ventricular end-diastole, reflecting greater impairment of left atrioventricular coupling.[10-12]

Clinical Follow-Up and Study End Points

Follow-up information was obtained during clinical visits and by phone call interviews with patients or their relatives. The primary study end point was a composite of all-cause death and hospitalization for worsening HF. The secondary end point was hospitalization for worsening HF. Events were ascertained from medical records of the patients and from direct contact with local physicians. For patients without events, the date of last contact was considered the end of follow-up.

Statistical Analysis

Continuous data are presented as mean ± SD if normally distributed or as median (interquartile range) in case of a skewed distribution. Discrete data are reported as number (percentage). NT-proBNP was logarithmically transformed for statistical analyses.

HIGHLIGHTS

- LACI can be calculated using conventional echocardiography.
- LACI is associated with LV DD.
- LACI is independently associated with prognosis in patients with HF.

To compare differences between tertiles of LACI, one-way analysis of variance (with Bonferroni correction), the Kruskal-Wallis test, and the χ^2 test were used for parametric continuous, nonparametric continuous, and categorical variables, respectively.

The association between LACI and the outcome of interest (time to event for the composite event of either all-cause mortality or HF hospitalization) were modeled using Cox proportional-hazards models, adjusting for baseline characteristics that were significant at the univariable analysis (see Supplemental Table 1), and providing

Table 1 Clinical and echocardiographic characteristics according to LACI tertiles

Variable	Total (n = 1,158)	Tertiles of LACI <0.22 (n = 387)	0.22-0.36 (n = 385)	>0.36 (n = 386)	P
Age, y	66 ± 12	63 ± 12	66 ± 11	69 ± 12	<.001
Gender, male	867 (74.9)	292 (75.5)	295 (76.6)	280 (72.5)	.404
BMI, kg/m^2	27 ± 4	27 ± 4	27 ± 4	26 ± 5	.104
NYHA functional class III/IV	340 (29.4)	85 (22.0)	104 (27.0)	151 (39.1)	<.001
Diabetes	330 (28.9)	107 (28.1)	110 (28.9)	113 (29.9)	.859
Hypertension	718 (63.0)	211 (55.4)	244 (64.0)	263 (69.6)	<.001
Ischemic etiology	459 (39.6)	143 (37.0)	143 (37.1)	173 (44.8)	.039
HF phenotype					<.001
HFrEF	812 (70)	266 (69)	287 (75)	259 (67)	
HFmrEF	158 (14)	64 (17)	56 (15)	38 (10)	
HFpEF	188 (16)	57 (15)	42 (11)	89 (23)	
CKD	468 (40.4)	126 (32.6)	162 (42.1)	180 (46.6)	<.001
eGFR, mL/min	67.9 ± 27.6	73.8 ± 28.6	65.6 ± 27.4	64.3 ± 25.8	<.001
NT-proBNP, pg/mL	1,349 (643-2,950)	1,036 (457-2,632)	1,341 (638-2,840)	1,600 (867-3,429)	<.001
Loop diuretic daily dose	25 (25-75)	25 (0-50)	25 (0-50)	50 (25-75)	<.001
RAS inhibitors*	913 (85.5)	306 (86.2)	312 (88.6)	295 (81.7)	.029
β-blockers	853 (79.9)	285 (80.3)	282 (80.1)	286 (79.4)	.957
MRAs	525 (49.2)	173 (48.7)	173 (49.1)	179 (49.7)	.965
LVEDV index, mL/m^2	96 ± 37	102 ± 39	99 ± 36	86 ± 34	<.001
LVESV index, mL/m^2	65 ± 34	68 ± 36	68 ± 33	58 ± 31	<.001
EF, %	36 ± 12	36 ± 11	34 ± 11	37 ± 14	.255
E/A ratio	1.5 ± 1.2	1.0 ± 0.8	1.4 ± 1.1	2.1 ± 1.3	<.001
DT, msec	191 ± 79	205 ± 72	193 ± 80	175 ± 82	<.001
E/e′ ratio	15 ± 8	12 ± 6	15 ± 8	18 ± 9	<.001
DD by ASE/EACVI					<.001
Grade 1	480 (41)	258 (67)	152 (39)	70 (18)	
Grade 2	380 (33)	97 (25)	146 (38)	137 (35)	
Grade 3	298 (26)	32 (8)	87 (23)	179 (46)	
Severe MR	140 (12.1)	27 (7.0)	39 (10.1)	74 (19.2)	<.001
LAVmax index, mL/m^2	48 ± 19	36 ± 12	48 ± 15	60 ± 19	<.001
LAVmin index, mL/m^2	29 ± 16	16 ± 8	28 ± 11	43 ± 16	<.001
LACI	0.29 (0.19-0.42)	0.16 (0.13-0.19)	0.29 (0.25-0.32)	0.49 (0.42-0.58)	<.001
TAPSE, mm	20 ± 5	20 ± 4	20 ± 5	19 ± 5	<.001
PASP, mm Hg	35 ± 14	30 ± 10	34 ± 13	41 ± 16	<.001

BMI, Body mass index; *CKD*, chronic kidney disease; *DT*, deceleration time; *EF*, ejection fraction; *GLS*, global longitudinal strain; *HFmrEF*, HF with mildly reduced ejection fraction; *LVESV*, LV end-systolic volume; *MR*, mitral regurgitation; *MRA*, mineral receptor antagonist; *PASP*, pulmonary artery systolic pressure; *RAS*, renin-angiotensin system; *TAPSE*, tricuspid annular peak systolic excursion.

P values by one-way analysis of variance for continuous variables and χ^2 test for binary and categorical variables.

*RAS inhibitors stands for renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers or angiotensin-receptor-neprilisin inhibitors - ARNI).

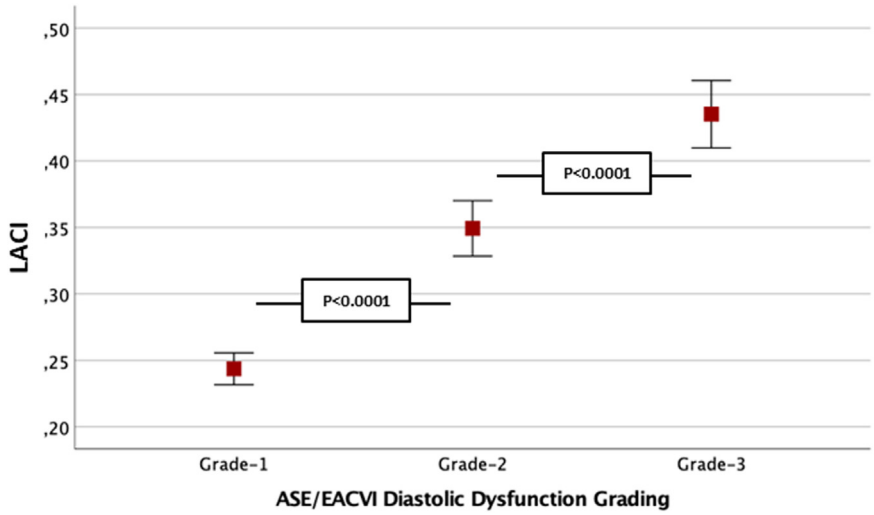


Figure 1 LACI according to LV DD grades. The *red boxes* display the mean values of LACI, while the *lines* illustrate the 95% CIs of LACI (y axis) in the three groups defined according to the grade of LV DD (x axis).

estimated hazard ratios (HRs) with 95% CIs. Incidence rates (per 100 patients/y) were also calculated. Restricted cubic splines with four knots were used to evaluate the shape of the relationship between the hazard for event and LACI modeled as a continuous variable. The cutoff value associated with increased hazard for the primary end point (the point at which the spline curve crossed the identity line) was also confirmed by time-dependent receiver operating characteristic analysis (Youden index). LACI was also modeled dichotomously instead of continuously on the basis of the previously defined cutoff value (i.e., ≥0.32 vs <0.32) and as a three-level categorical variable (tertiles of LACI). Kaplan-Meier event-free curves were plotted stratified by both LACI tertiles and LACI as categorical variable (i.e., ≥0.32 vs <0.32), with the composite end point of all-cause death or HF hospitalization as the event. Unadjusted group comparisons for the Kaplan-Meier curves were made using the log-rank test. Similar analyses were done on the validation cohort. Calibration was assessed using the Hosmer-Lemeshow test; the proportional-hazards assumption was verified by inspecting the log-log plot of survival and using Schoenfeld residuals.

A fractional polynomial was constructed for LVEF and entered into the model as an interaction term with LACI as categorical variable (≥0.32 vs <0.32) to assess the prognostic impact of LACI < 0.32 across the wide range of LVEF. The results of the interaction were displayed graphically using the mfpi command in Stata (StataCorp).[17] Finally, the incremental predictive value of LACI over guideline-based DD grading and other significant predictors by the multivariable Cox model was assessed by calculating the improvement in the C statistic, in the likelihood ratio χ^2 statistic, and in the continuous net reclassification index for survival data (R package survNRI). Analyses were performed with Stata version 17 and R version 4.3 (R Foundation for Statistical Computing).

Table 2 Multivariable Cox regression analysis for the composite end point of all-cause mortality and/or HF hospitalization

	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per 10 y)	1.29 (1.16-1.43)	<.0001	1.28 (1.16-1.42)	<.0001
eGFR (per 10 mL/min)	0.92 (0.88-0.96)	<.0001	0.92 (0.88-0.96)	<.0001
Loop diuretic daily dose	1.06 (1.03-1.09)	<.0001	1.06 (1.03-1.09)	<.0001
LVESV index (per 10 mL/m^2)	1.09 (1.06-1.12)	<.0001	1.09 (1.06-1.12)	<.0001
LACI (per 1-SD increase)	1.16 (1.06-1.28)	.002		
LACI second tertile vs first tertile			1.35 (1.02-1.78)	.033
LACI third tertile vs first tertile			1.73 (1.29-2.33)	<.0001
LV DD grade II vs I	1.67 (1.28-2.18)	<.0001	1.59 (1.22-2.08)	.001
LV DD grade III vs I	2.16 (1.63-2.87)	<.0001	1.94 (1.43-2.62)	<.0001

LVESV, LV end-systolic volume.
Other significant univariable predictors (male gender, NYHA functional class, diabetes, previous HF hospitalization, therapy with renin-angiotensin system inhibitors and β-blockers, NT-proBNP, LVEF, severe functional mitral regurgitation, tricuspid annular plane systolic excursion, and pulmonary artery systolic pressure) did not enter the equation.

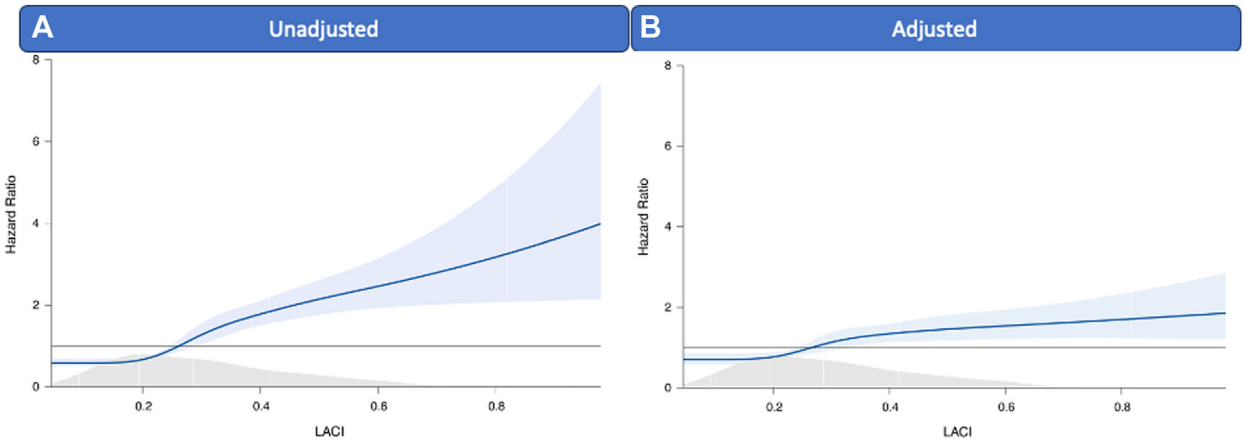


Figure 2 Unadjusted and adjusted spline curve analysis for the combined end point of HF hospitalization and death. The figure shows the unadjusted **(A)** and adjusted **(B)** HRs *(blue line)* with their 95% CIs *(light blue area)* for the composite end point across the baseline values of LACI (x axis). The *gray histogram* indicates the cohort distribution according to LACI.

RESULTS

Patient Population

Derivation Cohort. Overall, 1,158 patients met the inclusion criteria and were included in the present study (derivation cohort; Supplemental Figure 1). Table 1 shows the baseline characteristics of the entire study population and according to LACI tertiles. The mean age was 66 ± 12 years, 75% were men, and 29% were in NYHA functional class III or IV. Ischemic etiology was present in about 40% of patients. Overall, 812 patients (70%) had HFrEF, 158 (14%) had HF with mildly reduced LVEF, and 188 (16%) had HFpEF.

Patients in the third tertile of LACI (>0.36) were significantly older ($P < .0001$), presented with more advanced NYHA functional class ($P < .0001$), and showed increased prevalence of hypertension ($P < .0001$), ischemic etiology ($P = .039$), and chronic kidney disease ($P < .0001$) compared with patients with lower values of LACI (Table 1). Furthermore, patients in the third tertile of LACI showed significantly greater values of NT-proBNP ($P < .0001$), received higher daily doses of loop diuretics, and were less likely to be treated with renin-angiotensin system inhibitors than patients with lower values of LACI (Table 1).

Regarding echocardiographic characteristics, the mean LVEF was 36 ± 12%, which did not differ across the LACI tertiles (Table 1).

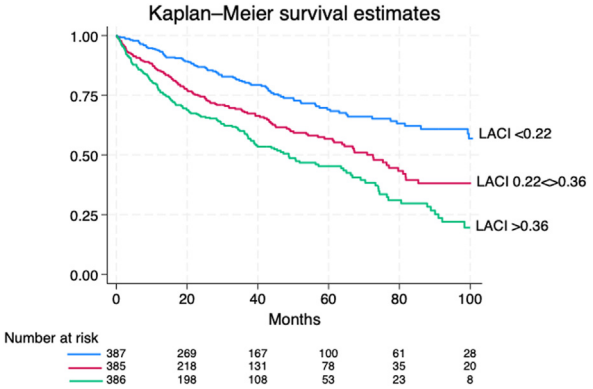


Figure 3 Kaplan-Meier curves for survival according to LACI tertiles.

The median LACI was 0.29 (interquartile range, 0.19-0.42). Patients with higher values of LACI had smaller LV volumes ($P < .0001$) but greater LA volumes ($P < .0001$, at both end-systole and end-diastole), a higher prevalence of severe functional mitral regurgitation ($P < .0001$), worse right ventricular systolic function, and higher pulmonary artery systolic pressure ($P < .001$) than patients with lower LACI values (Table 1).

Validation Cohort. The characteristics of the external validation cohort ($n = 242$) are shown in Supplemental Table 2. Compared with the derivation cohort, these patients were younger, with a higher prevalence of ischemic etiology of HF, smaller average LV volumes, lower mean LVEF, and greater average LACI ($P < .0001$).

LACI and Diastolic Dysfunction

Patients in the third tertile of LACI (>0.36) had increased E/A ratios ($P < .0001$), lower deceleration time of E-wave velocity ($P < .001$), and greater E/e′ ratios ($P < .0001$) than patients in the lower tertiles of LACI (Table 1). When categorized according to the ASE/EACVI classification, the prevalence of grade 1 DD progressively decreased across LACI tertiles (67%, 40%, and 18% in the first, second, and third tertiles, respectively; $P < .0001$), whereas the prevalence of grade 3 DD significantly increased (8%, 23%, and 46%, respectively; $P < .0001$; Table 1). Figure 1 and Supplemental Table 3 show that LACI significantly increased with worsening of LV diastolic dysfunction as graded according to ASE/EACVI algorithm. A cutoff value for LACI of ≥0.26 identified moderate to severe LV DD with diagnostic accuracy of 0.75 (Supplemental Figure 2).

Prognostic Relevance of LACI

During a median follow-up period of 28 months (interquartile range, 11-53 months), there were 236 deaths and 296 HF hospitalizations. Overall, 407 patients (35%) reached the primary composite end point with an incidence rate of 12.1 (95% CI, 11.0-13.4) per 100 patients/y. By univariable analysis (Supplemental Table 1), in the whole population, LACI was significantly associated with the composite end point (HR per 1-SD increase, 1.257; 95% CI, 1.169-1.350; $P < .001$). This association remained significant after adjustment for other significant covariates (age, male gender, NYHA functional class, diabetes, previous HF hospitalization, eGFR, loop diuretic daily dose, therapy

Table 3 Comparison of predictive value of the different multivariable prognostic models

Primary composite end point: all-cause death or HF hospitalization				*P*		
	Model 1	Model 2	Model 3	Model 2 vs model 1	Model 3 vs model 1	Model 3 vs model 2
Likelihood ratio χ^2	172.4	222.6	235.2	<.0001	<.0001	.0001
NRI				0.133 (0.062-0.214) <.0001	0.174 (0.092-0.243) <.0001	0.150 (0.069-0.223) <.0001

Model 1: age, eGFR, loop diuretic daily dose, LV end-systolic volume index, and LVEF. Model 2: model 1 plus guideline-based DD grading. Model 3: model 2 + LACI.

with renin-angiotensin system inhibitors and β-blockers, NT-proBNP, LVEF, LV end-systolic volume index, severe functional mitral regurgitation, tricuspid annular plane systolic excursion, pulmonary artery systolic pressure, and severity of diastolic dysfunction) when LACI was expressed either as a continuous variable or in tertiles (Table 2). The adjusted model yielded a Harrell's C index of 0.74. After adjusting for potential confounders, LACI showed a consistent independent association with the composite end point also in the external validation cohort (Supplemental Table 4).

Figure 2 shows unadjusted and adjusted HRs for the composite end point across the spectrum of LACI modeled as restricted cubic splines: risk for events increased progressively over a wide range starting at about 0.32. Similar results were obtained in the external validation cohort (Supplemental Figure 3). Figure 3 shows the Kaplan-Meier survival curves for patients stratified by tertiles of LACI (log-rank $\chi^2 = 59.4$, $P < .0001$), confirming the ability of this parameter to stratify patient prognosis. Furthermore, in a subgroup analysis, the ability of LACI to identify high-risk patients increased from the HFrEF to the HFpEF group (Supplemental Figure 4). The addition of LACI to a basal model including age, renal function, loop diuretic daily dose, LV end-systolic volume index, LVEF, and ASE/EACVI diastolic dysfunction grading provided a significant improvement in the net reclassification index and likelihood ratio χ^2 of the model (Table 3), suggesting improvement in risk stratification.

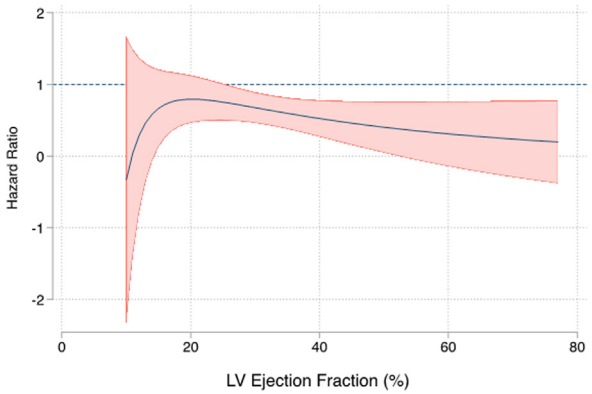


Figure 4 Spline curve analysis stratified according to LVEF. HR of being in the first tertile of LACI vs the second and third LACI tertiles *(blue solid line)* with its 95% CI *(red shaded area)* for the composite end point of all-cause death or HF hospitalization across the baseline values of LVEF (x axis). The neutral effect (HR, 1.0) is indicated by the *black horizontal dotted line*. An HR of <1.0 favors the first LACI tertile vs the second and third tertiles. The figure shows that the prognostic value of LACI is blunted for values of LV ejection fraction <20%.

Figure 4 graphically shows the HR of the first LACI tertile compared with the second and third LACI tertiles for the end point described earlier using fractional polynomial analysis across the whole range of LVEF treated as a continuous variable. Although no significant interaction between LVEF and LACI was founded (*P* for interaction = .199), the protective effect of having LACI in the first tertile compared with second and third tertiles was blunted for values of LVEF <20%, indicating limited prognostic value of this index in patients with very severe LV systolic dysfunction. Moreover, no interaction was found between LACI and sex or between LACI and DD severity.

DISCUSSION

The main findings of the present study are the following: (1) in patients with HF, LACI is associated with the severity of LV diastolic dysfunction as defined by the current international echocardiographic guidelines; 2) LACI is independently associated with outcomes in patients with HF; and 3) it provides incremental prognostic value over conventional clinical and echocardiographic prognostically relevant parameters in patients with HF.

The left atrium plays a fundamental role in HF.[18,19] In the initial stages of HF, a compensatory increase in LA active end-diastolic emptying contributes to maintaining LV filling, cardiovascular hemodynamics, and cardiac output.[18] With progressive LV diastolic and systolic dysfunction, LA preload and afterload increase, leading to an elevation of LA pressure, which is the driving force of LA dilatation.[20] LA remodeling, which consists mainly of LA dilatation, is usually accompanied by LA dysfunction, which can manifest with a decrease in LA active emptying in patients in sinus rhythm or with the onset of atrial fibrillation (AF) and the complete loss of the LA contribution to LV filling.[21] Therefore, when assessing LA remodeling and function in HF, the left ventricle should be taken into account. Current echocardiographic guidelines to grade LV diastolic dysfunction recommend measuring LAVmax at the end of LV systole.[5] Nevertheless, although strongly associated with outcome, LAVmax is affected not only by LV filling pressures but can also be significantly influenced by LV longitudinal systolic function, which stretches the left atrium through the systolic displacement of the mitral annular plane toward the LV apex. Conversely, LAVmin is measured at the end of LV diastole, when the left atrium is directly exposed to LV pressures. Accordingly, LAVmin has been shown to be more closely related to invasively measured LV filling pressures compared with LAVmax.[6,7] Considering the deep interaction between the left atrium and the left ventricle, the use of LACI, which is the ratio between LAVmin

and LVEDV, measured at the same cardiac phase, could improve the characterization of LA remodeling and its coupling with the left ventricle in HF. Moreover, LACI offers the opportunity to characterize LA remodeling in relation to LV remodeling by identifying proportionate LA dilatation (smaller LACI values) in contrast to disproportionate LA dilatation (marked by larger LACI values), opening the possibility of a novel framework to assess LA remodeling using various imaging modalities.

Lately, the concept of LA-LV coupling has gained increasing attention.[10-12,22] In particular, Benfari *et al.*[22] proposed estimating it as the ratio between LAVmax and tissue Doppler myocardial velocity at atrial contraction. They described an association between this parameter and survival in a large retrospective cohort of patients with HFrEF,[22] although the association between this index and the severity of LV diastolic dysfunction (as defined in current guidelines[5]) remained to be investigated. More recently, the novel LA-LV coupling index, defined as the ratio between LAVmin and LVEDV (measured on cardiac magnetic resonance), was introduced and, in a large cohort of patients free from cardiovascular diseases, showed better prognostic value compared with individual LA and LV parameters (including feature-tracking strain parameters).[10] LACI evaluated on echocardiography also showed a higher predictive value for new-onset AF in a cohort of patients with hypertrophic cardiomyopathy compared with conventional LA parameters.[12]

To our knowledge, the present study is the first to show an association between LACI and LV diastolic dysfunction grades in a large cohort of patients across the whole range of HF. We showed that LACI significantly increased as LV diastolic dysfunction worsened. Although the prognostic value of LACI was blunted for patients with very severe LV systolic dysfunction (i.e., LVEF < 20%), this index showed additional prognostic value over conventional parameters, including DD severity, normally assessed in patients with HF. The blunted prognostic value of LACI in patients with very severe LV systolic dysfunction can be related to the very advanced LV remodeling, which could decrease the prognostic importance of the left atrium and LA-LV coupling in this particular patient category. The stronger prognostic value of LACI in patients with more preserved LVEFs (Figure 4, Supplemental Figure 4) could make this index of particular clinical interest in patients with HFpEF. However, dedicated studies would be needed to verify this hypothesis.

LACI is based on conventional volumetric echocardiographic parameters and might be easily implemented in clinical practice. Compared with LA speckle-tracking parameters,[3,19,23] it does not require postprocessing analysis and is not dependent and influenced by specific vendor-related variability.[24] Moreover, it is a ratio that can also be assessed on cardiac magnetic resonance imaging and could be useful to investigate LV diastolic function, LA remodeling in relation to LV remodeling, and LA-LV coupling also with this imaging modality, which traditionally can provide very limited information on LV diastolic function. Future research might also investigate whether HF therapies and interventions affect LA-LV coupling and if LACI changes during patient follow-up have an impact on HF symptoms and patient prognosis.

Limitations

The limitations of this study are inherent to its retrospective design. Only patients with all echocardiographic diastolic function parameters available were included, and this might represent a source of selection bias; therefore, we are unable to assess the usefulness of LACI to characterize patients with indeterminate diastolic function according to current guidelines.[5] Moreover, as AF itself can cause atrial remodeling and confound the assessment of LV diastolic function with echocardiography, patients with AF were specifically excluded. However, LACI might have the potential to refine the assessment of diastolic function also in patients with AF, and this needs further investigation. The percentage of patients with HFpEF was relatively low (16% of the total cohort) in the present study; therefore, our results need to be confirmed in dedicated studies including a larger cohort of patients with HFpEF. Although this study was focused on the use of conventional echocardiographic parameters, future studies might compare LACI with advanced echocardiographic indices (such as LA strain) both for assessing LV diastolic function and for risk stratification in HF.

CONCLUSION

LACI can be assessed on conventional echocardiography, is associated with LV diastolic dysfunction severity, is an independent predictor of outcomes in patients with HF, and provides additional prognostic value compared with conventional echocardiographic and clinical parameters (Central Illustration).

REVIEW STATEMENT

Given her role as *JASE* Associate Editor, Nina Ajmone Marsan, MD, PhD, and given her role as *JASE* Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Sheldon E. Litwin, MD.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2024.06.013.

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