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Left Atrial Volumetric/Mechanical Coupling Index

A Novel Predictor of Outcome in Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Left atrial assessment is complex, particularly in heart failure with reduced ejection fraction due to interactions with functional mitral regurgitation (FMR). Pilot data suggest that left atrial volumetric/mechanical coupling index (LACI) may be useful, but large outcome data are lacking.

METHODS: We enrolled a comprehensively characterized cohort of patients in sinus rhythm with heart failure with reduced ejection fraction diagnosis at Mayo Clinic from 2007 to 2011. Routinely measured left atrial volume index and tissue-doppler-imaging a' allowed LACI calculation as (left atrial volume index)/(tissue-doppler-imaging a'). Survival was the outcome measured.

RESULTS: The cohort's 4196 patients (69 [58–77] years, ejection fraction 40 [31–45]%) had mild FMR in 1505 and moderate-severe FMR in 1068. LACI was overall 5.06 (3.50–8.10) and increased with each FMR grade (3.86 [2.94–5.29] without FMR, 5.38 [3.80–8.02] with mild, 5.45 [1.49–8.07] with moderate/severe FMR; $P<0.0001$). At diagnosis, higher LACI was independently determined by more severe FMR and by higher left ventricular mass index, lower ejection fraction, higher E/e', and lower glomerular filtration rate (all $P<0.0001$). During follow-up 1588 (38%) patients died. In spline modeling, excess mortality appeared around LACI=6 and steeply increased thereafter (5-year survival 72±1% with LACI<6 and 49±2% with LACI ≥6, $P<0.0001$). Multivariable comprehensive adjustment showed LACI strong association with excess mortality (adjusted hazard ratio, 1.41 [1.23–1.61], $P<0.0001$ for LACI ≥6). Independent link to mortality persistent across FMR grades (adjusted hazard ratio, 1.45 [1.13–1.86], $P=0.004$ without FMR, 1.42 [1.16–1.77], $P=0.0008$ with mild FMR, and 1.38 [1.01–1.66], $P=0.04$ with moderate/severe FMR) without interaction ($P=0.3$). LACI independent impact on outcome was incremental to that of left atrial volume index, tissue-doppler-imaging a', or any other characteristic including the Meta-Analysis Global Group in Chronic-score (least significant $P=0.02$).

CONCLUSIONS: In this large cohort, left atrial volumetric/mechanical coupling measured by LACI in routine practice integrates the influence of several morphological/hemodynamic determinants but displays progressive deterioration with increasing FMR severity in heart failure with reduced ejection fraction. About outcome, higher LACI is strongly, independently, and incrementally associated with excess mortality, irrespective of FMR grade and in all subsets. Hence, LACI is a novel and critical measure in heart failure with reduced ejection fraction, quantifiable in routine practice, which should be integrated in prognostication and decision-making.

Key Words: atrial function ■ functional mitral regurgitation ■ heart failure ■ left atrium ■ prognosis ■ secondary mitral regurgitation ■ ventricular dysfunction

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CLINICAL PERSPECTIVE

The results provide important information for clinicians. First, we propose a readily available approach to fully evaluate the left atrium by conventional echocardiography in patients with heart failure with reduced ejection fraction. As left atrial volumetric/mechanical coupling index is calculated as the ratio left atrial volume index/tissue-Doppler myocardial velocity at atrial contraction, clinicians do not need sophisticated software, but can use standard set of echocardiographic imaging. Second, we provide a framework for interpretation of this measurement seldomly studied. Indeed, using spline modeling, we demonstrate the steep and steady increase of mortality risk from lower to higher left atrial volumetric/mechanical coupling index values in an almost linear fashion with the value of 6 identified as the threshold of excess mortality. Third, as left atrial volumetric/mechanical coupling index modulates prognosis in all subset of heart failure with reduced ejection fraction, we think it represents a crucial information to help clinicians identify patients at higher risk of events. Hence, left atrial volumetric/mechanical coupling index should be calculated in routine practice and integrated into heart failure with reduced ejection fraction prognostication and clinical decision making.

The left atrium (LA) role in heart failure with reduced ejection fraction (HFrEF) is poorly understood. While it is the receptacle of filling-pressure elevation[1] and of the regurgitant volume of functional mitral regurgitation (FMR),[2] LA is often considered a passive bystander of these pathophysiologic alterations and is not included among measures integrated into prognostic scores such as the Meta-Analysis Global Group in Chronic score.[3] Recent renewed interest in LA yielded pilot studies of new LA assessment methods, suggesting that LA characteristics might modulate clinical consequences of HFrEF and FMR.[4–7] While the suggested mechanisms may involve buffering of elevated filling pressure or FMR,[6,7] these novel methods and pilot studies have not yet reached widespread applicability in routine clinical practice and limited follow-up does not allow outcome assessment.

Conversely, diastolic tissue-Doppler myocardial velocity at atrial contraction (TDI-a') is an established measure of LA mechanics, highly correlated to complex measures of LA performance,[8,9] and is measurable in routine practice. Hence, TDI-a' allows calculation of the ratio of LA volume-index (LAVI) to TDI-a', that is, the LA volumetric/mechanical coupling index (LACI), which has been touted in various clinical contexts[10–12] and possibly in heart failure[13] as linked to clinical outcome. We aimed at verifying the dependent link between LACI and components of HFrEF, denoted by the severity of FMR and of diastolic filling alterations and to verify the hypothesis that independently of these determinants and of all markers of HFrEF severity, LACI carries strong and incremental prognostic significance for survival after the diagnosis of HFrEF. For the purpose, we gathered a large HFrEF cohort, comprehensively characterized clinically and by echocardiography and analyzed the end points of short- and long-term mortality.

METHODS

Eligibility Criteria of HFrEF Cohort

Eligible patients were diagnosed with HFrEF using clinical and echocardiographic assessment at Mayo Clinic, Rochester, MN, between 2007 and 2011. Inclusion criteria were the following: (1) age ≥18 years; (2) first diagnosis of heart failure stage B or C defined according to guidelines[14]; (3) left ventricular ejection fraction (LVEF) <50%; (4) sinus rhythm; (5) routinely measured LA volume index, TDI-a'; (6) comprehensive clinical characterization by electronic medical record within 3 months of diagnosis. Exclusion criteria were atrial fibrillation, organic mitral valve disease (defined as mitral prolapse, flail leaflet, prosthetic valve or more than trivial rheumatic or degenerative mitral valve thickening/calcification); greater than or equal to moderate aortic valve stenosis or regurgitation (aortic valve sclerosis was not excluded); greater than or equal to moderate mitral stenosis or organic tricuspid valve disease; pericardial, congenital, hypertrophic, or infiltrative (amyloidosis, hemochromatosis, sarcoidosis) heart disease; and previous valve surgery. The requirement for written informed consent was waived by the Mayo Clinic institutional review board that gave its approval for this study. Because of confidentiality issues, data sets and study materials safeguarded by the health science department of the Mayo Clinic cannot be made available to outside parties.

Clinical and Echocardiographic Data

Patients' medical history and clinical characteristics were documented by a physician at our institution and retrieved unaltered from the electronic records. Glomerular filtration rate (GFR) was estimated using Cockcroft-Gault formula.[15] Vital signs were measured at echocardiography. Comorbidities were evaluated by the Charlson index and the survival risk score developed by the Meta-Analysis Global Group in Chronic.[3] Heart failure related symptoms were identified by the physicians' and retrieved directly from the clinical notes.

All echocardiographic examinations were performed within routine clinical practice by multiple trained sonographers (>100) and reviewed by cardiologists (>30) at Mayo Clinic, Rochester, MN, using diverse commercially available machines. All echocardiographic measurements were guided by the American Society of Echocardiography recommendations. Mitral regurgitation was classified in grades: none/trivial, mild, moderate, and severe as per multiparametric assessment, according to recommendations.[16] The echocardiographic data

(qualitative and quantitative), including, when available, the effective regurgitant orifice area quantified by the proximal velocity surface area method, were retrieved unaltered from the original re-ports via electronic transfer. Diastolic filling assessed early (E) and late (A) inflow velocities, E/A ratio, E deceleration time, e' (septal and lateral) using tissue Doppler, and average E/e' ratio calculated. Systolic pulmonary artery pressure was derived from tricuspid regurgitation velocity and estimated right atrial pressure. Functional tricuspid and mitral regurgitation were graded as recommended.[16]

To calculate LACI, the LA volume was indexed for body surface area and then divided for a' measured by TDI at medial mitral annulus level. The unit of measurements is therefore mL×second/cm^{-1} per m^2 of body surface area.

Follow-Up Data

The primary end point was mortality under medical management (all cause), censoring patients at the time of cardiac surgery, defibrillator implant, or ventricular assist devices. Secondary end point was overall mortality irrespective of timing. The procedures performed during the follow-up time were electronically identified using clinical chart and by procedure codes. Occurrence and date of deaths were retrieved using Accurint, a proprietary resource gathering multiple national sources, at December 31, 2014.

Statistical Analysis

Group Statistics for the continuous variables were expressed as mean±SD or median and interquartile range, depending on the normalcy of distribution. The distribution of the variables were assessed visually as well as with Shapiro-Wilk and Kolmogorov-Smirnov-Lillefors test. *P* value for trends were obtained through Cochran-Armitage trend test or regression analysis as appropriate.

A restricted cubic spline was produced to analyze the risk of mortality under medical management associated with LACI. The patients with LACI value that exceeded the average mortality of the cohort (risk ratio of 1) were labeled as having increased LACI; others were considered patients with low LACI.

Association between risk factors and outcome (LACI) were assessed using univariable /multivariable logistic regression with odds ratios (ORs) reported. Determinants of increased LACI were selected based on pathophysiologic links to atrial function: age, sex, left ventricular mass, systolic (LVEF) and diastolic (E/e′) measures of left ventricular dysfunction, MR severity, other clinical characteristics. Pulmonary hypertension, which may be a determinant or a consequence of increased LACI, was not used in the primary model but was introduced in secondary model as adjustment for other determinants of LACI. Potential consequences of increased LACI were evaluated by logistic regression using LACI as a predictor of other clinical and biological outcomes. Consequences of increased LACI were identified based on clinical and biological plausible link (dyspnea, pulmonary hypertension, right ventricular dysfunction).

Survival rates were estimated using the Kaplan-Meier method. Survival distribution across mitral regurgitation severity grades were compared using the log-Rank test. The Cox-proportional hazards regression model was used to assess the effect of LACI adjusted for other clinically relevant variables on survival differences. Three models were created: the unadjusted model, the core model: adjusted for age, sex, ejection fraction, Charlson-index, and the comprehensive model: adjusted for age, sex, ejection fraction, dyspnea, comorbidities by means of Charlson index, and GFR. In the subgroup of patients with available measurement, FMR quantification was added to the comprehensively adjusted model. Furthermore, alternative end points were also explored: the first censoring only at the time of left ventricular assist device and transplant; the second, using left ventricular assist device and transplant as events.

To test whether impact of LACI on survival under medical management was affected by other variables, interaction terms were included in the unadjusted Cox proportional hazard model.

Analyses were performed using JMP v.14, SAS version 9.4 (SAS Institute, Inc, Cary, NC) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed a priori alpha level of <0.05 was considered significant.

RESULTS

Study Cohort

The cohort included 4196 patients with first diagnosis of HFrEF. Overall clinical characteristics (Table 1, left column) were typical of HFrEF: age 69 (58–77) years, mostly male, left ventricular dimensions markedly enlarged and ejection fraction 40 (31%–45%). FMR was present in 61% of patients, mild in 36% (N=1505) and moderate or severe in 25% (N=1068). Cardiovascular risk-factors were frequent and comorbidity burden was high (Charlson Index 3.08±2.65). Patients were intensely treated with the following: 84% received β-blockers, 77% received angiotensin inhibitors, and 62% received diuretics. LA was frequently enlarged with overall LA volume index 38 (30–48) mL/m^2 while TDI-a' was 7 (6–9) cm/second. Hence, LACI overall was calculated at 5.06 (3.50–8.10). Hence divided by quartiles LACI ranged from ≤3.5 for the lowest quartile, from 3.5 to 5.0 for the second quartile, 5.0 to 8.1 for the third quartile, and >8.1 for the highest quartile, all with 1049 patients.

Baseline characteristics stratified by LACI quartiles are presented in the right part of Table 1 (the characteristics stratified by LACI < or ≥6 are presented in Table I in the Data Supplement). This stratification shows that higher LACI values occurred with concomitant LAVI increase (from 27 [23–31] to 53 [45–62] mL/m^2, *P*<0.0001) and TDI-a' decrease (from 10 [9–11] to 4 [3–5] cm/s, *P*<0.0001) with LACI increasing from 2.81 (2.32–3.15) to 12.24 (9.75–16.76) mL/m^2 per cm/second, *P*<0.0001. Concomitant to the LACI increase, there were multiple clinical and echocardiographic differences between LACI quartiles (Table 1): slightly older age, more symptoms, diabetes, and generally more

Table 1. Clinical and Echocardiographic Characteristics of HFrEF Cohort According to LACI Quartiles

	Overall cohort	LACI I q (≤3.5)	LACI II q (3.5–5)	LACI III q (5.0–8.1)	LACI IV q (>8.1)	*P* value for trend
	N=4196	N=1049	N=1049	N=1049	N=1049	
Age, y	69 (58–77)	64 (54–73)	67 (56–77)	71 (63–79)	70 (60–80)	<0.0001
Female, N (%)	1319 (31)	307 (29)	329 (36)	373 (36)	310 (30)	0.4
Heart rate, bpm	70 (61–80)	73 (64–83)	69 (62–78)	68 (60–77)	70 (61–80)	<0.0001
Systolic blood pressure, mm Hg	119 (106–134)	118 (106–132)	120 (108–132)	122 (108–136)	117 (102–134)	0.8
Diastolic blood pressure, mm Hg	70 (60–78)	70 (62–80)	70 (60–78)	68 (60–78)	68 (60–77)	<0.0001
NYHA III-IV, n (%)	1392 (33)	206 (15)	280 (20)	364 (26)	542 (39)	<0.0001
MAGGIC score	20.4±7.3	17.1±6.9	19.0±7.0	21.5±6.8	24.3±6.7	<0.0001
Decompensated heart failure, n (%)	1242 (30)	172 (17)	256 (24)	331 (31)	483 (46)	<0.0001
Charlson-index	3.08±2.65	2.60±2.45	2.92±2.69	3.34±2.77	3.45±2.60	<0.0001
Glomerular filtration rate, mL/min per mq	74 (50–103)	87 (62–117)	80 (56–111)	70 (46–95)	60 (39–82)	<0.0001
Systemic hypertension, n (%)	2424 (58)	538 (22)	597 (24)	673 (28)	616 (25)	<0.0001
Diabetes, n (%)	1093 (26)	194 (18)	265 (24)	322 (29)	312 (28)	<0.0001
Dyslipidemia, n (%)	2263 (54)	572 (25)	564 (25)	592 (26)	535 (23)	0.2
Previous myocardial infarction, n (%)	1406 (34)	331 (24)	366 (26)	384 (27)	325 (23)	0.9
Chronic obstructive pulmonary disease, n (%)	563 (13)	158 (28)	135 (24)	138 (25)	132 (23)	0.1
Cardiac resynchronization therapy, n (%)	125 (3%)	15 (1%)	26 (2%)	22 (2%)	62 (6%)	<0.0001
Echocardiographic characteristics						
LV end-diastolic diameter, mm	56 (51–61)	53 (49–57)	55 (51–60)	57 (52–63)	59 (53–66)	<0.0001
LV end-systolic diameter, mm	44 (39–51)	41 (37–45)	43 (39–48)	45 (40–51)	49 (42–57)	<0.0001
LV mass index, g/m^2	121 (101–146)	106 (89–125)	116 (100–137)	129 (109–153)	140 (115–166)	<0.0001
LV ejection fraction, %	40 (31–45)	43 (37–47)	41 (34–45)	39 (31–45)	32 (23–41)	<0.0001
LV forward stroke volume, mL	80 (66–95)	81 (69–95)	83 (69–97)	83 (69–97)	72 (58–87)	<0.0001
E/A	1.00 (0.69–1.50)	0.75 (0.60–1.00)	0.83 (0.67–1.18)	1.00 (0.71–1.40)	1.75 (1.20–2.60)	<0.0001
E/e'	14 (10–20)	10 (7.5–12.5)	12.5 (10–16)	16 (12–20)	22.5 (16–30)	<0.0001
LA volume-index, mL/m^2	38 (30–48)	27 (23–31)	35 (30–39)	43 (37–49)	53 (45–62)	<0.0001
TDI-a', cm/s	7 (6–9)	10 (9–11)	8 (7–9)	7 (6–8)	4 (3–5)	<0.0001
LACI (LA volume-index/TDI-a')	5.06 (3.50–8.10)	2.81 (2.32–3.15)	4.20 (3.85–4.58)	6.23 (5.61–6.98)	12.24 (9.75–16.76)	<0.0001
No/trivial FMR, n (%)	1623 (39)	663 (41)	510 (31)	302 (19)	148 (9)	<0.0001
Mild FMR, n (%)	1505 (36)	294 (20)	398 (26)	444 (30)	369 (24)	
Moderate/severe FMR, n (%)	1068 (25)	92 (9)	141 (13)	303 (28)	532 (50)	
SPAP, mm Hg	35 (28–46)	30 (26–36)	32 (26–39)	36 (30–46)	46 (36–56)	<0.0001
Moderate/severe RV dysfunction, n (%)	524 (12)	57 (11)	75 (14)	101 (19)	291 (56)	<0.0001

FMR indicates functional mitral regurgitation; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LACI, left atrial volumetric/mechanical coupling index; LV, left ventricular; MAGGIC, Meta-Analysis Global Group in Chronic; NYHA, New York Heart Association class; RV, right ventricular; SPAP, systolic pulmonary artery pressure; and TDI-a', tissue-Doppler myocardial velocity at atrial contraction.

comorbidities with lower GFR, while imaging characteristics showed worse left ventricular enlargement and ejection fraction, higher E/e', pulmonary pressure and more frequent moderate/severe FMR (all *P*<0.0001). Moreover, LACI was higher with higher FMR degrees (3.86 [2.94–5.29] without FMR, 5.38 [3.80–8.02] with mild FMR, 5.45 [1.49–8.07] with moderate/severe FMR; *P*<0.0001). Hence the proportion of patients with LACI ≥6 was higher with increasing FMR grade (Figure 1).

LACI-Associated Features

At univariate analysis (Table 2, left column), the clinical feature associated to increased LACI (≥6) are age, history of diabetes, arterial hypertension, and renal function (all *P*<0.0001). Among echocardiographic variables, left ventricular mass-index, ejection fraction, E/e', and the presence of moderate/severe FMR showed a strong association with increased LACI (all *P*<0.0001). At multivariable analysis (Table 2, right column), LACI ≥6 was

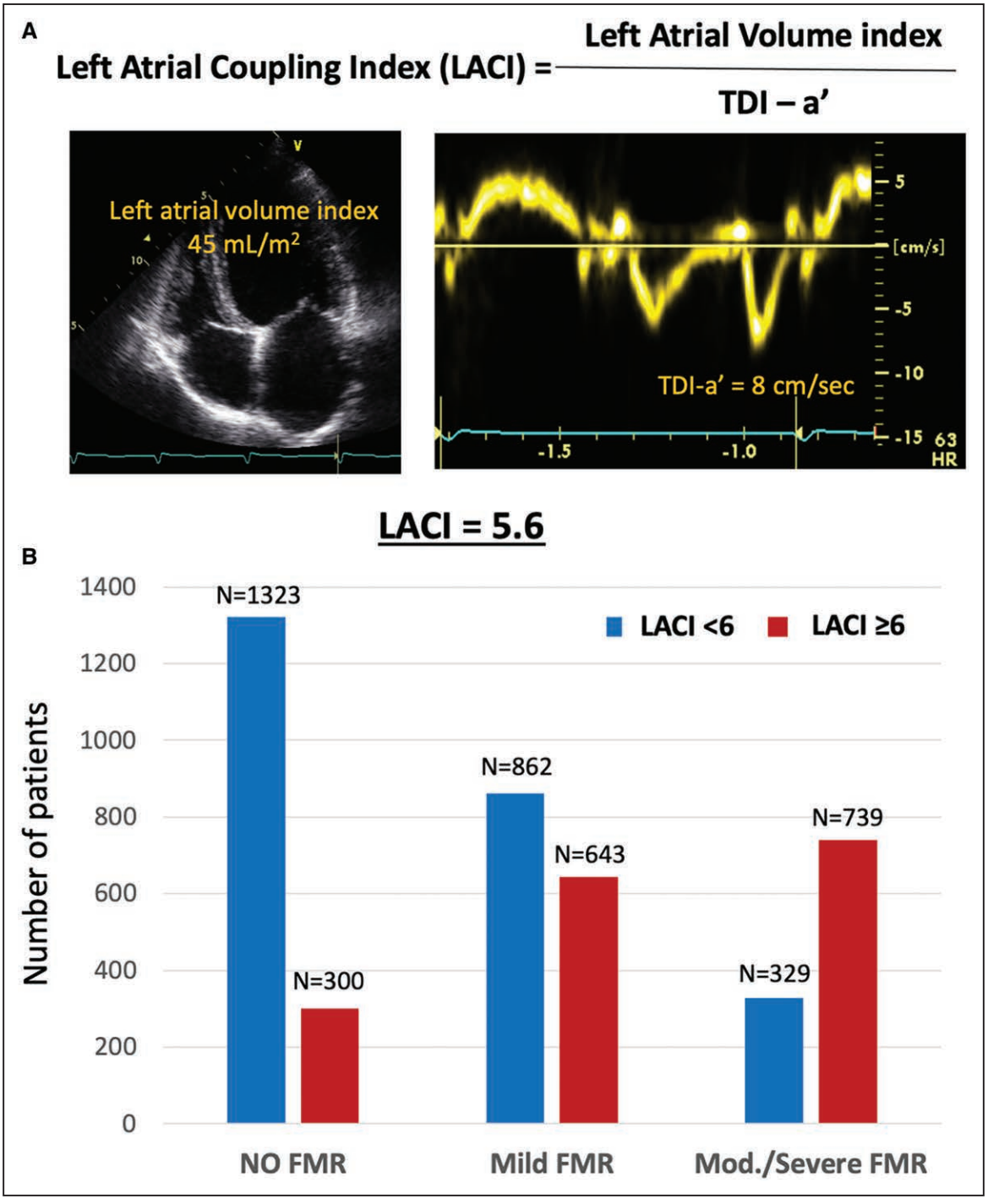

Figure 1. Left atrial coupling index (LACI) calculation and distribution.
Example of LACI calculation from a standard echocardiographic protocol (**A**); prevalence of increased LACI (≥6) across different functional mitral regurgitation (FMR) grades (**B**). TDI-a' indicates tissue-Doppler myocardial velocity at atrial contraction.

significantly related to LV mass-index (OR, 1.26 [95% CI, 1.20–1.33], *P*<0.0001), ejection fraction (OR, 0.77 [95% CI, 0.69–0.84], *P*<0.0001), E/e' (OR, 1.14 [95% CI, 1.12–1.16], *P*<0.0001), moderate/severe FMR (OR, 2.79 [95% CI, 2.29–3.39], *P*<0.0001), and renal function (OR, 0.93 [95% CI, 0.92–0.96], *P*<0.0001).

Notably, patients' LACI value was not influenced by sex, age (Figure I in the Data Supplement), anthropometric measurement, blood pressure, and major cardiovascular risk factors were not associated with higher LACI.

LACI ≥6 was independently associated with signs of more advanced heart failure, such as New York Heart Association class III/IV, severe tricuspid regurgitation, and right ventricular dysfunction (Table 3). Testing LACI as a continuous variable did not affect the association with those clinical consequences.

Table 2. Determinants of Increased LACI

	OR for LACI ≥6		OR for LACI ≥6	
	Unadjusted	*P* value	Multivariable model	*P* value
Age (per 10 y)	1.26 (1.21–1.32)	<0.0001	…	0.9
Male sex	…	0.4		
Body mass index	…	0.1		
Systolic blood pressure	…	0.5		
Mass-index (per 20 g/m^2)	1.52 (1.46–1.59)	<0.0001	1.26 (1.20–1.33)	<0.0001
Ejection fraction (per 10%)	0.49 (0.45–0.53)	<0.0001	0.77 (0.69–0.84)	<0.0001
E/e'	1.16 (1.15–1.18)	<0.0001	1.14 (1.12–1.16)	<0.0001
Moderate/severe FMR	5.17 (4.45–6.01)	<0.0001	2.79 (2.29–3.39)	<0.0001
Diabetes	1.42 (1.23–1.63)	<0.0001	…	0.2
Systemic hypertension	1.26 (1.11–1.42)	<0.0001	…	0.1
COPD	…	0.6		
GFR, per 10 mL/min per m^2	0.89 (0.87–0.90)	<0.0001	0.93 (0.92–0.96)	<0.0001

COPD indicates chronic obstructive pulmonary disease; FMR, functional mitral regurgitation; GFR, glomerular filtration rate; LACI, left atrial volumetric/mechanical coupling index; and OR, odds ratio.

LACI Impact on Survival

During the 4.4 (3.0–5.9) years total follow-up, 286 (7%) patients underwent cardiac surgery (including 241 [84%] coronary artery bypass graft, 70 [24%] mitral surgery, 18 [6%] aortic valve surgery, and 32 [11%] other cardiac surgical procedures), 428 (10%) patients underwent defibrillator implantation, 14 (<1%) received a LV assist device, and 14 (<1%) underwent cardiac transplantation and were all censored at the time of those interventions. Thus, median follow-up under medical management was 4.0 (1.66–5.64) years; over this period, 1588 (38%) patients died.

One-year mortality under medical management doubled in patients with LACI above versus below 6 (10±1 versus 19±2%, respectively; *P*<0.0001). The odds for 1-year events associated to LAVI ≥6 were 1.88 (95% CI, 1.57–2.26), *P*<0.0001 unadjusted and 1.40 (95% CI, 1.09–1.74), *P*=0.009 adjusted for age, sex, ejection fraction, Charlson-comorbidity index, and FMR grades. Using LACI as continuous variable, the OR per 3-unit LACI increase was 1.14 (95% CI, 1.10–1.17), *P*<0.0001 unadjusted and OR, 1.11 (95% CI, 1.06–1.16), *P*<0.0001 after adjustment.

To assess the association between LACI as a continuous variable and the primary end point (mortality under medical management), a spline modeling of the risk ratio within the cohort was created (Figure 2). The curve is steep with steady increase of mortality risk from lower to higher LACI values in an almost linear fashion. Excess mortality within the study cohort (risk ratio >1) seems around the LACI value of 6, with a narrow CI, and it doubles for LACI value around 10, without plateau effect.

Long-term survival is presented in Kaplan-Meier curves in Figure 3, stratifying the cohort by LACI ≥6 versus <6 (left) and by LACI quartiles (right). Five-year survival rate was considerably different 49±2% for the 1682 patients with LACI ≥6 and 72±1% for those with LACI<6. The survival curve of patients in the highest LACI quartile (ie, >8.1) showed early separation with progressive and considerable divergence versus lower quartiles. Of note, outcome of patients with LACI>8.1 was slightly worse versus LACI ≥6, in agreement with the steep increase of risk presented in the spline curve (Figure 2). The survival curves for the secondary end point (overall mortality) are reported in Figure II in the Data Supplement.

LACI was strongly associated with long-term mortality both tested as continuous or ≥ versus <6 (Table 4).

Table 3. Clinical Consequences of Increased LACI

	OR for LACI ≥6 vs <6		OR for LACI ≥6 vs <6	
	Unadjusted	*P* value	Adjusted for LV mass, LVEF, E/e', FMR, GFR	*P* value
Dyspnea	2.1 (1.85–2.38)	<0.0001	1.48 (1.26–1.76)	<0.0001
Systolic pulmonary pressure >50 mm Hg	5.1 (4.29–6.28)	<0.0001	2.12 (1.66–2.70)	<0.0001
Right ventricular dysfunction	3.69 (3.03–4.48)	<0.0001	1.96 (1.50–2.56)	<0.0001
Moderate-severe tricuspid regurgitation	4.26 (3.6–5.04)	<0.0001	2.55 (2.04–3.18)	<0.0001

FMR indicates functional mitral regurgitation; GFR, glomerular filtration rate; LACI, left atrial volumetric/mechanical coupling index; LV, left ventricular; LVEF, left ventricular ejection fraction; and OR, odds ratio.

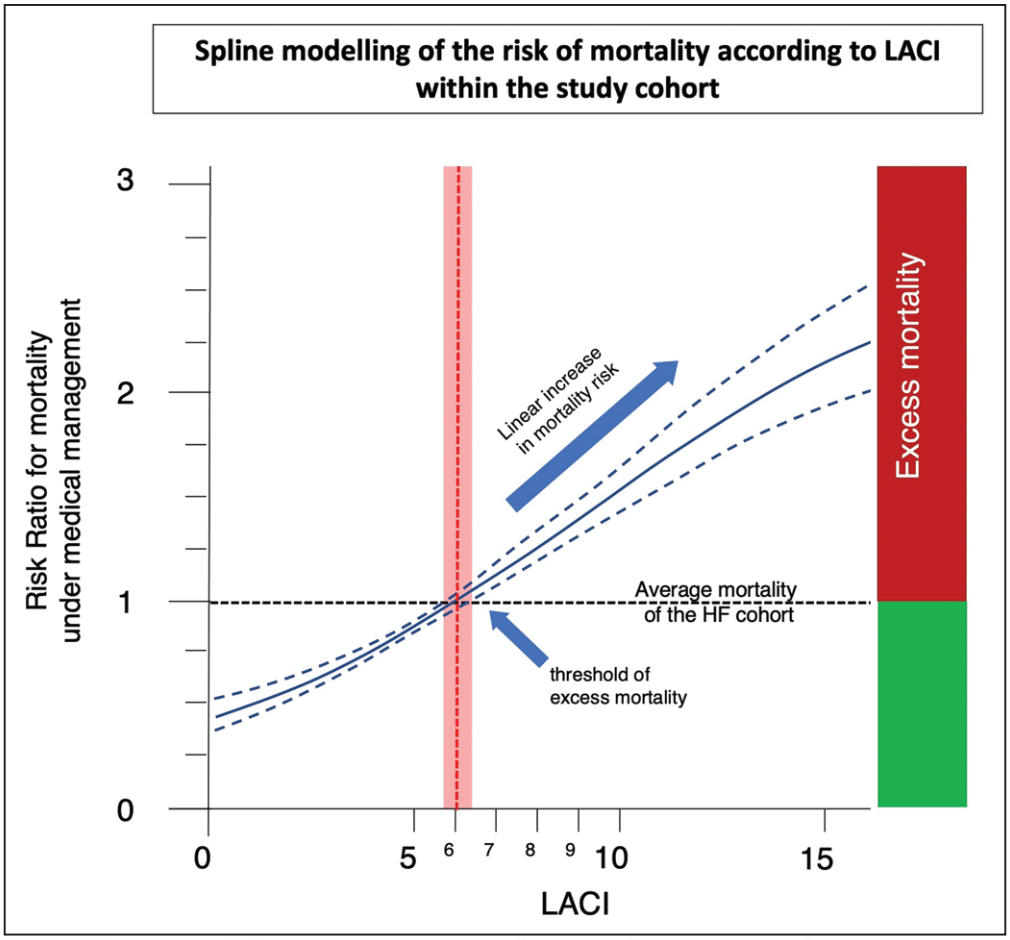

Figure 2. Spline modeling of the risk of mortality under medical management within the study cohort across left atrial coupling index (LACI) values. The level of 1 indicates the average mortality of the study cohort. The LACI value of 6 is the threshold where excess mortality begins; the risk steeply increases for higher LACI values, without plateau effect. HF indicates heart failure.

In detail, adjusted hazard ratio for LACI ≥6 was 1.41 (1.23–1.61), *P*<0.0001 in the comprehensively adjusted model. LACI remained significantly associated with mortality if LA volume index, systolic pulmonary pressure level, chronic resynchronization therapy, or New York Heart Association class were added to the comprehensive model. Consistently, if Meta-Analysis Global Group in Chronic score was used instead of Charlson-index, LACI maintained its significant association with survival (hazard ratio, 1.32 [1.16–1.51], *P*<0.0001 for LACI ≥6 and hazard ratio 1.07 [1.06–1.10], *P*<0.0001 for LACI 3-unit increase).

LACI showed incremental prognostic value versus Meta-Analysis Global Group in Chronic score, E/e', and LA volume index in 3 bivariate survival model (all *P* value for increment <0.0001). Of note, LACI did not completely eliminate the role of LA volume, which maintained his demonstrated positive association to mortality.

Results were comparable when the secondary end point (overall mortality) was analyzed (Table II in the Data Supplement) with adjusted hazard ratio 1.40 (1.23–1.59), *P*<0.0001 for LACI ≥6 and hazard ratio 1.08 (1.06–1.11), *P*<0.0001 for LACI 3-unit increase.

The exploration of alternative end points, created by censoring only at the time of left ventricular assist device and transplant, or using left ventricular assist device and transplant as events did not change the relationship between LACI and survival (all *P*<0.0001).

LACI Link to FMR and HFrEF Subsets

The prevalence of LACI ≥6 was remarkably different across FMR grades (18% in no-FMR, 38% in mild FMR, 44% in moderate or severe FMR), as shown in the Figure 1. Kaplan-Meier curves for LACI ≥ versus <6 are presented stratified by FMR grades and lower survival with LACI ≥6 was clear and persistent at any grade of regurgitation (Figure 4) without eliminating the higher mortality associated with higher grades of FMR. Accordingly, after comprehensive adjustment, the adjusted hazard ratio was 1.45 (1.13–1.86), *P*=0.004 in the 1623 patients with HFrEF without FMR, 1.42 (1.16–1.77), *P*=0.0008, in the 1505 patients with mild FMR, and 1.38 (1.01–1.66), *P*=0.04 in the 1068 with moderate/severe FMR. Interestingly, no interaction between mitral regurgitation and LACI was detectable (*P*=0.3).

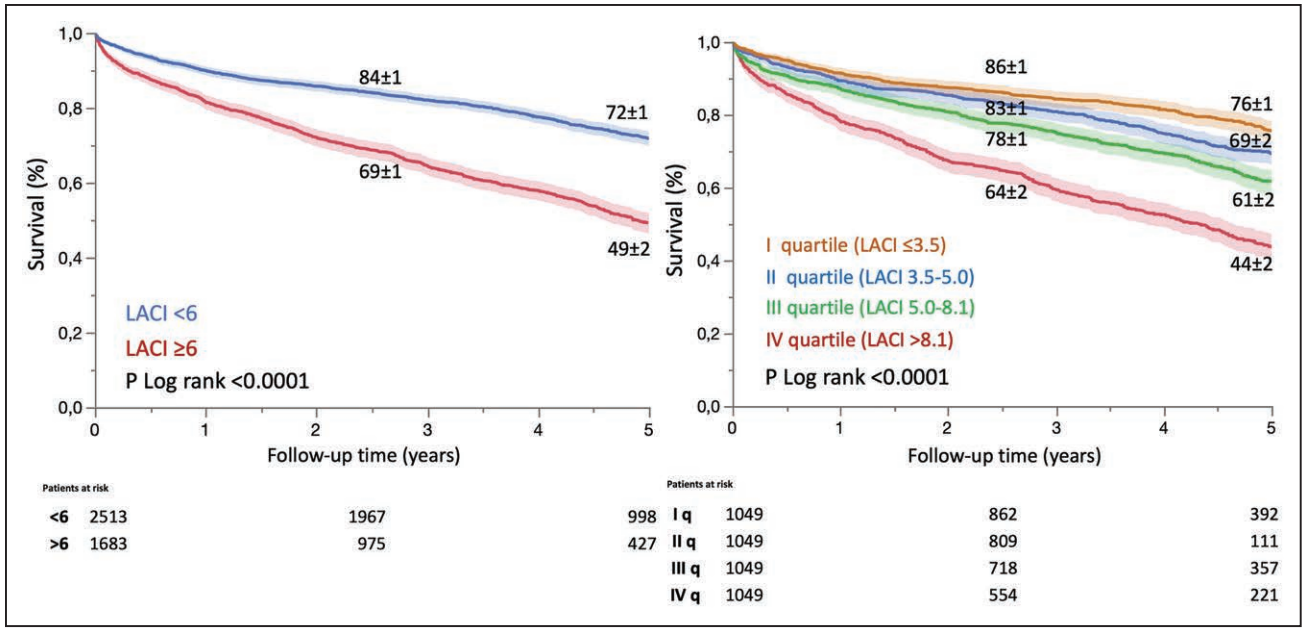

Figure 3. **Kaplan-Meier curves illustrating the survival under medical management for left atrial coupling index (LACI) < vs ≥6 (left) and for LACI quartiles (right).**

Hazards for subgroup analysis based on clinical and echocardiographic HFrEF features are presented in Figure 5; increased LACI was invariably associated to worse outcome: particularly in female patients, across different FMR grades, in the presence or absence of elevated systolic pulmonary pressure, and regardless of diastolic dysfunction measures. The relationship between LACI and survival persisted in the subgroup of patients with LVEF 40% to 49% (after comprehensive adjustment, hazard ratio for LACI 3-unit increase was 1.11 [1.07–1.15], *P*<0.000 and for LACI ≥6 was 1.40 [1.16–1.70], *P*=0.0006) and with LVEF <40% (after comprehensive adjustment, hazard ratio for LACI 3-unit increase was 1.08 [1.05–1.11], *P*<0.0001 and for LACI ≥6 was 1.43 [1.09–1.88], *P*=0.0001). In regard to GFR, no significant interaction with LACI prognostic value (*P*=0.5) was noted, and LACI ≥6 remained highly predictive of mortality in the subgroup of 335 (8%) patients with low GFR (<30 mL/min per m^2): hazard ratio, 1.57 (1.09–2.28), *P*=0.02 after comprehensive adjustment.

FMR quantitative assessment by proximal velocity surface area method was available for 74% (792/1068) of patients with moderate or severe FMR. Median effective regurgitant orifice was 0.19 (0.14–0.27) cm^2 and regurgitant volume 33 (25–45) mL. Quantitative FMR measures correlated only modestly with LACI (R=0.29, *P*<0.0001 for effective regurgitant orifice and R=0.17, *P*<0.0001 for regurgitant volume). Replacing FMR grade by effective regurgitant orifice or regurgitant volume in the comprehensive survival model including age, sex, LVEF, LV mass, E/e', comor-

Table 4. **Cox Proportional Hazard Model for Survival Under Medical Management**

	HR (95% CI) Unadjusted	*P* value	HR (95% CI) Adjusted for age, sex, ejection fraction, Charlson-index	*P* value	HR (95% CI) Adjusted for age, sex, ejection fraction, Charlson-index, E/e', left ventricular mass, FMR grade, GFR	*P* value
LACI ≥6	2.15 (1.94–2.37)	<0.0001	1.57 (1.42–1.74)	<0.0001	1.41 (1.23–1.61)	<0.0001
LACI per 3-unit increase	1.11 (1.10–1.14)	<0.0001	1.11 (1.10–1.14)	<0.0001	1.10 (1.07–1.12)	<0.0001
No FMR (N=1623)						
LACI ≥6	2.04 (1.67–2.48)	<0.0001	1.11 (1.05–1.17)	<0.0001	1.45 (1.13–1.86)	0.004
Mild FMR (N=1505)						
LACI ≥6	1.92 (1.63–2.26)	<0.0001	1.51 (1.28–1.80)	<0.0001	1.42 (1.16–1.77)	0.0008
Moderate or severe FMR (N=1068)						
LACI ≥6	1.72 (1.40–2.11)	<0.0001	1.44 (1.67–1.78)	<0.0001	1.38 (1.01–1.66)	0.04

FMR indicates functional mitral regurgitation; GFR, glomerular filtration rate; HR, hazard ratio; and LACI, left atrial volumetric/mechanical coupling index.

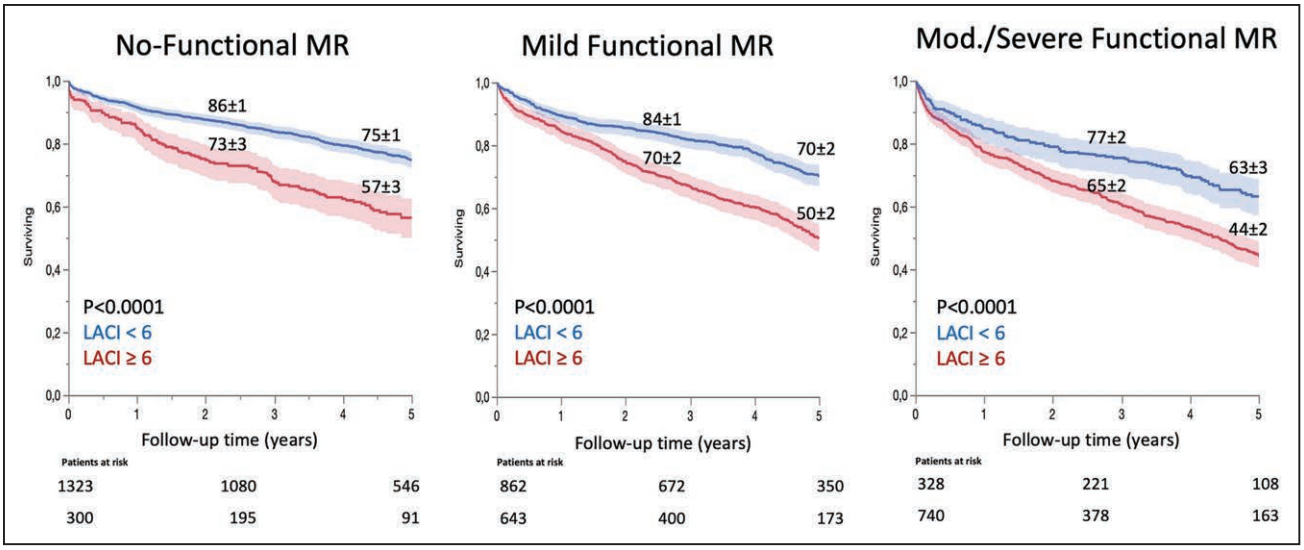

Figure 4. Kaplan-Meier curves for survival under medical management for left atrial coupling index (LACI) < vs ≥6 in patients with no-functional mitral regurgitation (FMR), mild-FMR, or moderate/severe FMR.
Increased LACI identifies patients at high risk of mortality within any FMR grade.

bidities, and GFR did not affect the impact of LACI (hazard ratios per 3-unit increase in LACI were 1.10 [1.06–1.13], *P*<0.0001 adjusting for effective regurgitant orifice and 1.10 [1.06–1.14], *P*<0.0001 adjusting for regurgitant volume).

DISCUSSION

The present study is the first large cohort of patients with HFrEF investigating the clinical determinants and outcome implication of the LACI. It shows that LACI is measurable in routine practice in large number of patients within the set of standard measurements by Doppler-Echocardiography. Higher LACI correspond to weaker atrial mechanical activity for larger volume index and is strongly associated with higher grades of FMR, with higher E/e' but not exclusively and with several markers of increased volume/pressure overload in HFrEF. In terms of outcome, LACI is strongly and independently associated with mortality. Most importantly, higher LACI, particularly ≥6, is associated with higher excess mortality, incrementally to all baseline characteristics, particularly FMR severity, irrespective of how it is graded. Furthermore, higher LACI remains associated with higher mortality in all subsets of patients, including in all grades of FMR. Hence, the present data emphasize that the LA is not just a passive reflector of mitral and ventricular alterations but an integrator of these alterations and overloads that has important consequences throughout the follow-up in HFrEF. Thus, the atrial coupling index measured as LACI should be part of routine LA evaluation in clinical practice, of prognostic assessment and clinical decision-making in patients diagnosed with HFrEF.

Integrating LA Morphology and Mechanics

LA functions in a 3-phase (reservoir, conduit, and booster pump) cycle, which interplays dynamically with the LV.[17] In the early, preclinical stages of heart failure a compensatory increase in active LA contribution to LV filling (LA booster pump function) contributes to maintenance of cardiovascular hemodynamics, cardiac output, and neurohumoral balance.[18] In patients with HFrEF, LA contribution to diastolic performance further decreases along with the reduced LV compliance and LA volume may increase, because of elevated LV filling pressure. Determinants of LA enlargement are multiple in HFrEF.[2] Thus, adding information on atrial pump function has been suggested as possibly improving detection of atrial alterations.[19] Attempts at characterizing atrial contractile function is difficult, relying on measures technically difficult to obtain,[5] or of difficult interpretation.[8] These pilot studies attest to the renewed interest in LA function; however, they are often limited by the small cohort size or short follow-up. In the present study, we focused on easily measurable variables, feasible in routine practice, and of physiological significance (LAVI and TDI-a'). These were combined into the LACI and generate its suggested clinical potential.[13] Of remarkable importance for clinical practice, LACI can be obtained from standard echocardiographic protocol, without need for additional acquisition or postprocessing software.

The predictive value of this approach was proposed in other clinical settings (ischemic heart disease and stroke)[10,20] or in relatively small cohorts with wide LVEF range.[8,13] Our study, of unique cohort size and long-term follow-up, provides multiple, novel contributions about relationship with outcome, determinants, and clinical implication of LACI in HFrEF. First, we took advantage

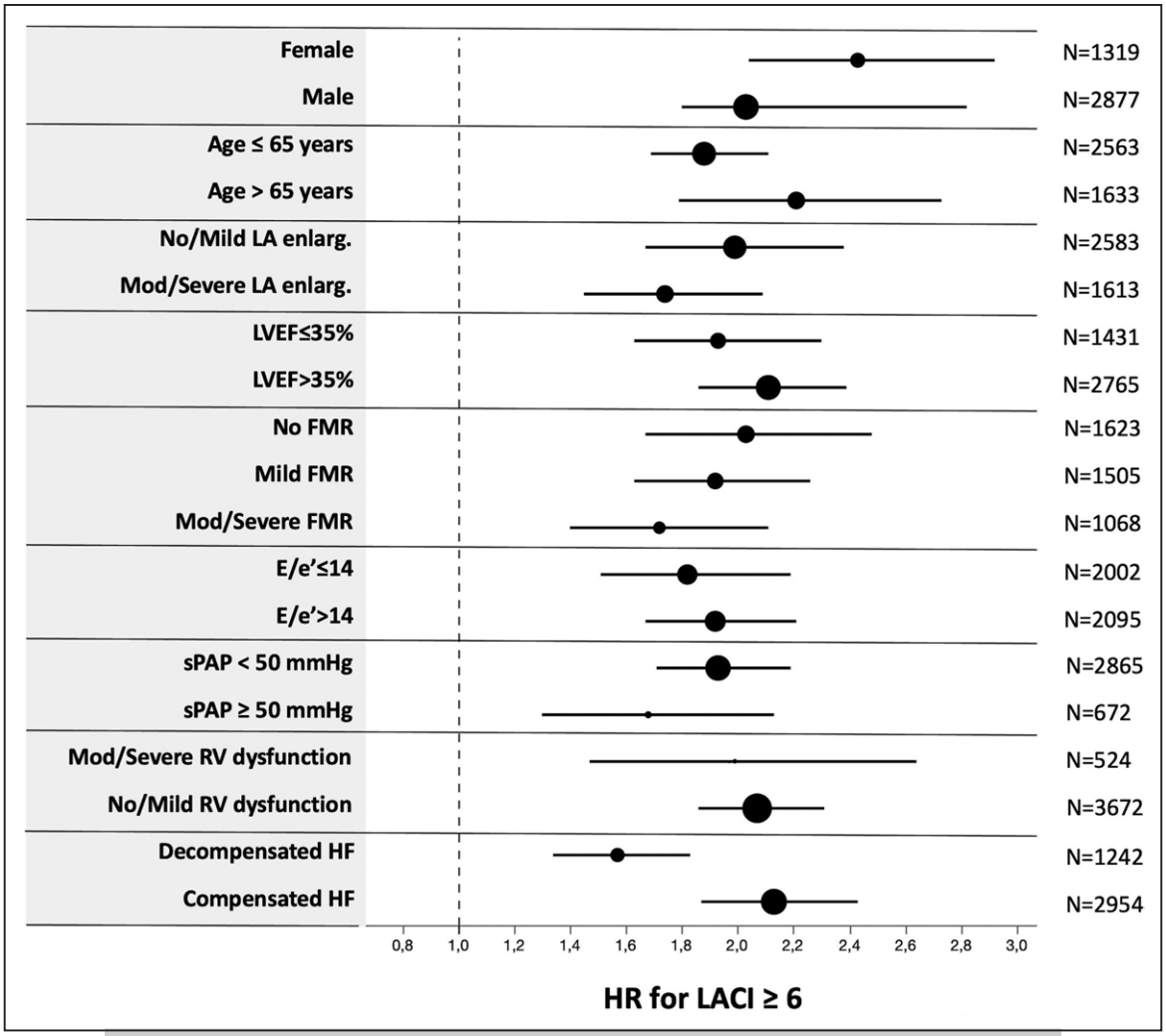

Figure 5. Forest plot displaying the hazard ratio (HR) for mortality under medical management associated to left atrial coupling index (LACI) ≥6 stratified for the most important clinical and echocardiographic features of patients with heart failure (HF).
The size of the circles represents the proportion of patients in each subgroup. FMR indicates functional mitral regurgitation; LA, left atrium; LVEF, left ventricular ejection fraction; RV, right ventricular; and sPAP, systolic pulmonary artery pressure.

of this large cohort to reveal that the association of LACI with mortality under medical management is almost linear, steep, without any plateau effect. Second, while LACI determinants, LV mass, LVEF, E/e', and FMR are determinants of outcome by their own account, LACI provides incremental prognostic power to all these variables. Neither sex nor age influenced LACI value, in contrast to other measures of diastolic function.[1,2] Third, significant markers of clinical status severity, that is, dyspnea, pulmonary arterial hypertension, tricuspid regurgitation, and right ventricular dysfunction, are strongly linked to elevated LACI, underscoring its relevance to hemodynamic deterioration in patients with LV dysfunction.[21]

Interaction Between Prognostic Value of LACI and FMR

FMR is a conundrum about its pathogenesis, evaluation, and consequences on outcome.[22] A recent meta-analysis showed that, independently from the way it was detected and graded, FMR portends higher rates of all-cause mortality (in ischemic or nonischemic etiologies) and cardiac morbid events.[23] Noteworthy, even patients with mild FMR may carry worse prognosis, although this is matter of debate,[24] but the fact that LA is the receptacle of the regurgitant volume raises particular attention on potential interactions FMR-LACI.

Relatively few studies have focused on LA mechanics in patients with FMR, although FMR severity was included in predictive models.[4,5] Recently, a small study of interplay between LA function (as total LA emptying fraction) and FMR[7] found survival lower in patients with FMR and LA dysfunction. Physiologically, our study shows that LACI is worse with increasing FMR grades. Outcome-wise, our study with comprehensive characterization of all comorbidities allows detecting intrinsic independent outcome-impact of both LA characteristics and FMR, as shown in part in

the lower rows of Table 4. Furthermore, we used a measure of LA volumetric/mechanical coupling from routinely measured variables, LAVI and TDI-a'. Thus, our findings may have immediate implications on clinical practice, due to feasibility and simplicity of LACI. In addition, we could separately explore interaction between LA function and FMR grades, with large numbers of moderate/severe FMR, generally underrepresented. This power allowed adjustment for all confounders and examination of all subsets. Whether LACI modulatory effect on FMR outcome played a role in recent discordant results of FMR treatment trials[25–27] is uncertain due to insufficient data in these trials but warrants further studies.

Strengths and Limitations

Our cohort was retrospectively identified but all measurements were performed prospectively and retrieved unaltered. Thus, our results are highly applicable to routine clinical practice.

LACI is only applicable to patients in sinus rhythm, similarly to all methods assessing LA mechanical function. Whether other LA indices are applicable to all patients irrespective of rhythm will require further studies. We calculated LACI using medial TDI-a' based on its high reproducibility and strong association with hemodynamic measurements.[28] However, we also collected available lateral TDI-a' and for completeness used this value to calculate a lateral-LACI, which displayed much weaker association to outcome (at bivariate analysis, the $\chi 2$ for lateral and medial TDI-a' were 8.4 versus 127.1, $P<0.0001$). We further tested the ratio of LAVI to pulsed-Doppler A wave, but this index showed much weaker outcome prediction than LACI.

Although the collection of death causes cannot be achieved for legal reasons, overall survival represents a robust end point; furthermore, the extensive adjustment for all comorbidities allows us to reasonably account for their contribution to mortality.

Conclusions

The present large cohort of patients with HFrEF investigating the LACI shows that higher LACI is strongly associated with higher FMR grades but also integrates markers of increased volume/pressure overload in HFrEF. Most importantly, higher LACI, particularly ≥6 is, independently of these determinants, associated with higher excess mortality, incrementally to all baseline characteristics, particularly FMR severity. Hence, the present data emphasize LA characteristics importance suggesting that atrial coupling index measured as LACI should be part of routine LA evaluation in clinical practice for prognostic assessment and clinical decision-making in patients diagnosed with HFrEF.

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