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ORIGINAL RESEARCH

Incremental Prognosis by Left Atrial Functional Assessment: The Left Atrial Coupling Index in Patients With Floppy Mitral Valves

Benjamin Essayagh, MD; Giovanni Benfari, MD; Clémence Antoine, MD; Joseph Maalouf, MD; Sorin Pislaru, MD, PhD; Prabin Thapa, MSc; Hector I. Michelena, MD; Maurice Enriquez-Sarano, MD

BACKGROUND: Emerging data suggest important prognostic value to left atrial (LA) characteristics, but the independent impact of LA function on outcome remains unsubstantiated. Thus, we aimed to define the incremental prognostic value of LA coupling index (LACI), coupling volumetric and mechanical LA characteristics and calculated as the ratio of left atrial volume index to tissue Doppler imaging a′, in a large cohort of patients with isolated floppy mitral valve.

METHODS AND RESULTS: All consecutive 4792 patients (61±16 years, 48% women) with isolated floppy mitral valve in sinus rhythm diagnosed at Mayo Clinic from 2003 to 2011, comprehensively characterized and with prospectively measured left atrial volume index and tissue Doppler imaging a′ in routine practice, were enrolled, and their long-term survival analyzed. Overall, LACI was 5.8±3.7 and was <5 in 2422 versus ≥5 in 2370 patients. LACI was independently higher with older age, more mitral regurgitation (no 3.8±2.3, mild 5.1±3.0, moderate 6.5±3.8, and severe 7.8±4.3), and with diastolic (higher E/e′) and systolic (higher end-systolic dimension) left ventricular dysfunction (all $P \leq 0.0001$). At diagnosis, higher LACI was associated with more severe presentation (more dyspnea, more severe functional tricuspid regurgitation, and elevated pulmonary artery pressure, all $P \leq 0.0001$) independently of age, sex, comorbidity index, ventricular function, and mitral regurgitation severity. During 7.0±3.0 years follow-up, 1146 patients underwent mitral valve surgery (94% repair, 6% replacement), and 880 died, 780 under medical management. In spline curve analysis, LACI ≥5 was identified as the threshold for excess mortality, with much reduced 10-year survival under medical management (60±2% versus 85±1% for LACI <5, $P<0.0001$), even after comprehensive adjustment (adjusted hazard ratio, 1.30 [95% CI, 1.10–1.53] for LACI ≥5; $P=0.002$). Association of LACI ≥5 with higher mortality persisted, stratifying by mitral regurgitation severity of LA enlargement grade (all $P<0.001$) and after propensity-score matching ($P=0.02$). Multiple statistical methods confirmed the significant incremental predictive power of LACI over left atrial volume index (all $P<0.0001$).

CONCLUSIONS: LA functional assessment by LACI in routine practice is achievable in a large number of patients with floppy mitral valve using conventional Doppler echocardiographic measurements. Higher LACI is associated with worse clinical presentation, but irrespective of baseline characteristics, LACI is strongly, independently, and incrementally determinant of outcome, demonstrating the crucial importance of LA functional response to mitral valve disease.

Key Words: echocardiography ■ left atrial coupling index ■ left atrial function ■ mitral regurgitation ■ mitral valve surgery: survival

Floppy mitral valves (FMVs), with or without degenerative mitral regurgitation (DMR), are frequent,[1] with an estimated prevalence of 2.4%.[2] DMR severity is the most established determinant of FMV outcome[3] and can be corrected by mitral valve repair, which effectively restores life expectancy.[4] However,

Correspondence to: Maurice Enriquez-Sarano, MD, 100 3rd Ave S, Minneapolis, MN 55401. Email: sarano.maurice@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- In patients with floppy mitral valve without or with various degrees of degenerative mitral regurgitation, left atrial functional assessment by left atrial coupling index can be obtained in large numbers of patients in routine clinical practice.
- Left atrial coupling index identifies patients at risk of excess mortality, independently and incrementally to all baseline characteristics, a novelty of crucial clinical importance.

What Are the Clinical Implications?

- Left atrial coupling index source variables should be obtained during routine Doppler echocardiography and consistently calculated and reported.
- The strong association to long-term excess mortality for left atrial coupling index ≥5 incrementally to degenerative mitral regurgitation severity at diagnosis should be taken into account in clinical decision making for patients with floppy mitral valve irrespective of degenerative mitral regurgitation severity.
- The role of mitral valve repair in restoring/improving left atrial function should be carefully evaluated. Whether medical treatment effective in treating patients with left ventricular dysfunction has a role in preventing/treating left atrial dysfunction and potentially improving clinical outcomes should be evaluated in carefully designed clinical trials.

Nonstandard Abbreviations and Acronyms

DMR	degenerative mitral regurgitation
FMV	floppy mitral valve
LACI	left atrial coupling index
LAVI	left atrial volume index
TDI	tissue Doppler imaging

DMR remains markedly undertreated[5] with notable excess mortality,[6] despite emerging percutaneous techniques for patients previously deemed inoperable.[7] Discrepancy between effective but underused therapeutic options underscores the importance of detecting patients at high risk under medical management by sensitive methods. Clinical guidelines provide few class I surgical triggers to indicate mitral surgery,[8,9] heart failure symptoms, and left ventricular (LV) dysfunction that are relatively infrequent. This limited ability to identify high-risk patients has led to attempts at defining new outcome markers in pilot studies.[10] However, this effort remains challenging, because applicability of pilot series to routine clinical practice remains questionable. Hence, it is essential to analyze routine measurements in large clinical practices to evaluate those linked to clinical outcome incrementally to established markers to improve detection of patients who are at high risk.

In this endeavor, left atrial (LA) characteristics were emphasized recently with increasing strength. LA enlargement assessed by LA volume index (LAVI), shown initially to determine secondary arrhythmia occurrence in pilot studies,[11] has been linked in larger prospective cohorts to survival.[12] Recently, LAVI measured in routine practice showed strong linkage to excess mortality, incremental to DMR severity and irrespective of cardiac rhythm.[13] Rising interest in LA characteristics has led to inclusion of LA enlargement in European guidelines,[8] but also questioned whether LA function, crucial to cardiac output adequacy,[14] may provide refined incremental prognostic power. Seminal attempts at quantifying LA function appear to suggest potential value.[15,16] In that regard, the left atrial coupling index (LACI), coupling volumetric and mechanical LA characteristics, calculated as the ratio of LAVI to tissue Doppler a′ (a′-TDI) and easily measurable in routine practice, has shown promising results in other clinical contexts.[17] However, whether LACI provides truly independent and incremental prognostic information in FMV remains unsubstantiated.

To address these gaps in knowledge, a large and comprehensively characterized FMV cohort with both LAVI and a′-TDI prospectively measured in routine clinical practice with long-term follow-up is required. We gathered such a cohort and measured LACI for the first time in the context of FMV to evaluate its determinants, clinical consequences, and potential incremental value over conventional markers of outcome.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All consecutive patients were identified retrospectively with (1) FMV diagnosis at Mayo Clinic, Rochester, Minnesota, 2003 to 2011, with prolapse or flail leaflet with or without DMR by Doppler echocardiography; (2) age ≥18 years; (3) sinus rhythm; (4) prospective LAVI and a′-TDI measurement at the time of diagnosis in routine clinical practice; and (5) comprehensive diagnosis evaluation of symptoms, vital signs, clinical history, comorbidities, and rhythm at diagnosis. We did not attempt to measure LACI retrospectively, and patients without prospective LACI measurements were excluded. We excluded patients who denied research authorization (per Minnesota law) or with atrial fibrillation, moderate aortic regurgitation/stenosis, moderate

mitral stenosis, congenital heart disease (patent foramen ovale not excluded), cardiomyopathies dilated/hypertrophic/restrictive, previous valvular surgery, and significant pericardial disease. Because the study was low risk, written consent was waived by the Mayo Institutional Review Board, which approved this study.

Echocardiographic Evaluation

All Doppler echocardiographic data (qualitative and quantitative) were measured prospectively at diagnosis of FMV, stored in a dedicated digital repository, and collected electronically for this study without alteration. Echocardiographic examinations were performed by trained sonographers (>100) and reviewed by cardiologists (>30) in routine clinical practice with standardized interpretation frameworks. Uniform imaging protocol included all views from standard windows and systematic LV and hemodynamic measurements guided by the American Society of Echocardiography recommendations. As per the guidelines, DMR integrative severity grading was used for all patients, based on all information available (specific, supportive, and quantitative measures) to classify DMR in 4 grades: none/trivial, mild, moderate, and severe. DMR quantitation, performed as often as possible, measured effective regurgitant orifice and regurgitant volume. Diastolic filling assessed early (E) and late (A) inflow velocities, E/A ratio, E deceleration time, e′ (septal and lateral) and a′ using tissue Doppler, and E/e′ ratio. LACI is a volumetric to mechanical coupling index and was calculated as the ratio of reported LA volume indexed for body surface area (LAVI) to a′ by tissue Doppler at the medial mitral annulus. The unit of measurement is therefore $mL*m^{-2}*cm^{-1}*s$. Hence, all Doppler echocardiographic data, including LAVI, a′-TDI, and calculated LACI were produced in the routine practice of many practitioners without knowledge of clinical presentation, management, and outcome.

Clinical Evaluation

Patients' history, symptoms (dyspnea, edema, chest pain), medication, and comorbidities (summated as Charlson Comorbidity Index) were recorded at diagnosis by the patients' personal physicians in routine practice and retrieved from electronic medical records without alteration by natural language processing. Vital signs were measured at echocardiography.

Follow-Up Data

The primary end point was survival under medical management (driven by our hypothesis) in the overall cohort and matched subcohorts, censoring patients at last follow-up if they did not undergo surgery, or at mitral surgery if performed. Secondary end points were overall and postoperative survival. Surgical procedures were collected and dated using the Mayo Clinic surgical registry and clinical notes for patients operated on outside of the Mayo Clinic. Death occurrence and dates were recovered using Accurint, a proprietary resource gathering multiple national sources, including the Social Security Death Index, to define occurrence and date of death. To ensure accurate mortality counts, for patients reported alive by Accurint, follow-up was ended 6 months before Accurint interrogation.

Statistical Analysis

Continuous data were expressed as mean±SD, and distributions were assessed visually and with Shapiro-Wilk and Kolmogorov-Smirnov-Lillefors tests. *P* values for trends were obtained through Cochran-Armitage trend test or regression analysis, as appropriate.

Determinants of increased LACI were assessed by logistic regression and selected based on pathophysiologic links to atrial function: age, sex, systolic (left ventricular ejection fraction [LVEF], LV diameters) and diastolic (E/e′) measures of LV dysfunction, and DMR severity. Odd ratios (ORs) of increased LACI for these variables were reported unadjusted and in multivariable analysis. Potential consequences of increased LACI at diagnosis also used logistic regression. Survival rates (±SE) were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models assessed LACI association with long-term mortality (with LACI presented as categorical or continuous per 3-unit increments because close to LACI terciles). Three models were created for all end points: univariable model, core model (adjusted for age, sex, Charlson Comorbidity Index), and comprehensive model (adjusted additionally for LVEF, dyspnea, and DMR severity). Because of baseline differences between groups, LACI cases ≥5 were also matched to LACI controls <5 using a greedy nearest propensity-score matching algorithm. Success of propensity matching was assessed by comparing distributions in matched subsets (absolute standardized difference <10% indicated small imbalance), followed by Cox proportional hazard adjustment for persistent differences. Spline curve analysis evaluated relative risk of mortality associated with LACI as continuous variables and defined threshold of excess mortality. Incremental prognostic value of LACI was assessed by DMR grade and LAVI (with LAVI cutoffs based on previously defined prognostic thresholds and terciles),[13] by nested models, Cox proportional analysis, by receiver operating characteristic analysis for the categorical end point of 5-year mortality, and additionally by calculation of net reclassification index (see Data S1). JMP 14, SAS 9.4, and R software were used. Two-tailed $P<0.05$ was considered significant.

RESULTS

Baseline Characteristics

Among 5769 consecutive inpatients and outpatients diagnosed with isolated FMV and LAVI prospectively measured at diagnosis in routine clinical practice, 839 were excluded because of atrial fibrillation and 138 because of incomplete septal a′-TDI measurement. Thus, our final cohort comprised 4792 patients with FMV (2318 women, aged 61±16 years) with LAVI and a′-TDI comprehensively characterized at diagnosis. Baseline demographic/clinical characteristics (Table 1) are typical for a wide range of FMVs, with bileaflet prolapse in 1900 (40%), posterior prolapse in 2097 (44%), and flail leaflet in 534 (11%). By guideline-based integrative grading, DMR was severe in 26%, moderate in 21%, mild in 31% patients, whereas 23% patients had no/trivial DMR with effective regurgitant orifice of 23±24 mm^2. Clinically, 34% of patients had dyspnea, 17% chest pain, and Charlson Comorbidity Index was 1.2±2. On average, LV dilatation was mild, LVEF 63±7%, and hemodynamically, cardiac index and pulmonary pressure were within normal range. Overall, LACI was 5.8±3.7 (range, 0.8–36.2), <5 in 2422 patients and ≥5 in 2370 patients. Higher LACI resulted from a combination of larger LAVI (51±19 mL/m^2 versus 29±8 mL/m^2, P<0.0001) and lower a′-TDI (6±2 cm/s versus 9±2 cm/s, P<0.0001).

Table 1 compares high and low LACI subsets, with LACI threshold defined based on the survival analysis. Multiple baseline features were statistically different because of the cohort's considerable size, but fewer were also clinically significant, such as older age (68±13 years versus 55±16 years for LACI <5, P<0.0001), male prevalence, more frequent dyspnea (38% LACI ≥5 versus 28% LACI <5, P<0.0001), hypertension (45% LACI ≥5 versus 26% LACI <5, P<0.0001), and higher Charlson Comorbidity Index (1.0±1.0 LACI ≥5 versus 0.7±0.9 LACI <5, P<0.0001) By echocardiography, LACI ≥5 was associated with enlarged left ventricle, higher E/e′, pulmonary pressure, and more severe DMR, with a trend to receive more medical therapy (all P<0.0001; Table S1), whereas differences in cardiac index and LVEF were minimal. These wide distributions within each LACI subset suggest that LACI is not completely correlated to any unique variable and may portend independent consequences and associations to outcome.

LACI Determinants and Clinical Consequences

Univariably, LACI was significantly higher through different DMR grade (no, mild, moderate, severe DMR: 3.8±2.3, 5.1±3.0, 6.5±3.8, and 7.8±4.3, respectively; P<0.0001). Stratification in 3 LACI categories (<5, 5–9.9, ≥10) showed similarly linked DMR distributions (Table S2). Similarly, LACI was higher with LV end-systolic diameter ≥40 mm (8.5±5.4 versus 5.5±3.4, P<0.0001) and with E/e′ ≥14 (12.1±6.1 versus 10.6±5.0, P<0.0001). Table 2 shows in logistic analysis that independent determinants of LACI ≥5 were older age and higher LV end-systolic diameter, E/e′, and mitral regurgitation (MR) grade (all P<0.0001). Notably, higher LACI remained independently determined by MR presence (OR, 2.01 [95% CI, 1.24–1.76] versus no MR; P<0.0001) or severity (OR, 1.48 [95% CI, 1.18–1.85] for MR mild versus no/trivial P<0.001 and 2.65 [95% CI, 2.12–3.30] for MR moderate/severe versus no/trivial P<0.0001). Interestingly, LACI was not influenced by sex, body mass index, or blood pressure (P≥0.07), and smoking, systolic hypertension, diabetes, or coronary artery disease were not associated with LA functional impairment (all P≥0.2).

In term of clinical consequences at diagnosis, LACI (≥5 or continuous variable) was independently associated with more frequent dyspnea, severe functional tricuspid regurgitation, and elevated pulmonary artery pressure (Table 3), irrespective of age, sex, Charlson Comorbidity Index, ventricular function, and DMR severity (all P≤0.0003).

Long-Term Outcome After Diagnosis

Total follow-up was 7.0±3.0 years, during which 1146 underwent mitral valve surgery (94% repair, 6% replacement), and 880 died, mostly under medical management (n=780) and more seldomly after mitral valve surgery (n=100).

Survival under medical management was 87±1% at 5 years and 74±1% at 10 years. LACI (continuous) was strongly associated with long-term mortality (univariable HR, 1.43 [95% CI, 1.38–1.49], P<0.0001 per 3-unit increment) (Table 4). To assess LACI threshold for excess mortality, spline curve analysis of survival under medical management was conducted and demonstrated that excess mortality (within the cohort) occurred around LACI ≥5, and steeply increased without plateauing with more elevated LACI (Figure 1). Thus, LACI ≥5 was used as the data-defined threshold for excess mortality. Ten-year survival was 85±1% for LACI <5 and 60±2% for LACI ≥5 (P<0.0001) (Figure 2). Excess mortality under medical management was considerably higher with higher LACI (univariable hazard ratio [HR], 3.13 [95% CI, 2.70–3.64], for LACI ≥5 versus LACI <5; P<0.0001).

LACI predictive power for mortality, accounting for baseline characteristics differences, was demonstrated first by Cox proportional adjustment, with core model adjusted HRs attached to LACI of 1.16 (95% CI, 1.09–1.22) per 3-unit increment (P<0.0001) and with comprehensive model adjusted

Table 1. Baseline Characteristics Overall and Stratified by LACI <5 and ≥5

	Overall population	LACI <5	LACI ≥5	
	n=4792	n=2422	n=2370	*P* value
Clinical characteristics				
Age, y	61±16	54±16	68±13	<0.0001
Women, %	2381 (48)	1335 (55)	983 (41)	<0.0001
BMI, kg/m^2	25±5	24±5	26±4	<0.0001
Heart rate, bpm	67±12	68±12	66±12	<0.0001
Previous CABG, %	169 (4)	40 (2)	129 (5)	<0.0001
Hypertension, %	1687 (35)	612 (25)	1075 (45)	<0.0001
Charlson Comorbidity Index	1.2±2	0.7±0.9	1.0±1.0	<0.0001
Dyspnea, %	1613 (34)	686 (28)	927 (39)	<0.0001
Edema, %	467 (10)	164 (7)	303 (13)	<0.0001
Chest pain, %	849 (17)	447 (18)	402 (17)	0.2
LV and hemodynamic characteristics				
LVEDD, mm	51±7	49±5	53±7	<0.0001
Indexed LVEDD, mm/m^2	28±4	27±3	29±4	<0.0001
LVESD, mm	32±5	31±4	34±6	<0.0001
Indexed LVESD, mm/m^2	17±3	17±2	18±3	<0.0001
LVEF, %	63±7	63±6	63±8	0.07
CI, L/min per m^2	3.0±0.6	3.0±0.6	3.0±0.7	0.05
E wave, cm/s	8±3	8±2	9±3	<0.0001
E/A	1.3±0.6	1.3±0.6	1.2±0.7	<0.0001
E/e′ TDI	10.8±5.1	7.3±2.7	13.3±5.7	<0.0001
LAVI, mL/m^2	40±18	29±8	51±19	<0.0001
Medial a′-TDI, cm/s	8±3	9±2	6±2	<0.0001
LACI (LAVI/ a′-TDI)	5.8±3.7	3.3±1.0	8.4±3.7	<0.0001
Systolic PAP, mm Hg	33±12	29±8	37±14	<0.0001
Moderate–severe TR, n (%)	269 (6)	63 (3)	206 (9)	<0.0001
Mitral characteristics				
No/trivial MR, n (%)	1094 (23)	866 (36)	228 (10)	<0.0001
Mild MR, n (%)	1478 (31)	869 (36)	609 (26)	
Moderate MR, n (%)	996 (21)	400 (17)	596 (25)	
Severe MR, n (%)	1224 (26)	287 (12)	937 (40)	
ERO, mm^2	17 [0–38]	0 [0–21]	30 [15–47]	<0.0001
RVol, mL	31 [0–64]	0 [0–35]	50 [27–79]	<0.0001
Flail leaflet, n (%)	543 (11)	115 (5)	428 (18)	<0.0001
Posterior, n (%)	2097 (44)	944 (39)	1153 (49)	<0.0001
Bileaflet, n (%)	1900 (40)	956 (39)	944 (40)	0.8

Values are written as No. (%), median [IQR], or mean±SD as approriate.

BMI indicates body mass index; CABG, coronary artery bypass graft; CI, cardiac index; ERO, effective regurgitant orifice; LACI, left atrial coupling index; LAVI, left atrial volume index; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; PAP, pulmonary artery pressure; RVol, regurgitant volume; TDI, tissue Doppler imaging; and TR, tricuspid regurgitation.

HR of 1.30 (95% CI, 1.10–1.53) for LACI ≥5 versus LACI <5 (*P*=0.002) (Table 4). Adjusting additionally for LV end-systolic diameter did not alter our results (adjusted HR, 1.34 [95% CI, 1.12–1.59] for LACI ≥5 versus LACI <5, *P*=0.001 and 1.13 [95% CI, 1.07–1.20] per 3-unit increase; *P*<0.0001). Persistently strong and independent association with mortality was noted after adjusting additionally for diastolic dysfunction grade (adjusted HR, 1.44 [95% CI, 1.12–1.80]; *P*=0.02 for LACI ≥5 versus adjusted HR, 1.11 [95% CI, 1.02–1.18] for LACI <5; *P*=0.01 per 3-unit increase) or E/e′ (adjusted HR, 1.22 [95% CI, 1.03–1.45]; *P*=0.02 for LACI ≥5 versus adjusted HR, 1.08 [95% CI, 1.01–1.16]; *P*=0.03 for LACI <5, per 3-unit increase).

Table 2. Univariate and Multivariable Analysis of Increased LACI Determinants

	Univariate analysis		Multivariable analysis*	
	OR (95% CI) for LACI ≥5	*P* value	OR (95% CI) for LACI ≥5	*P* value
Age, for 10 y	1.98 (1.89–2.08)	<0.0001	1.89 (1.77–2.01)	<0.0001
LVESD	1.10 (1.08–1.11)	<0.0001	1.14 (1.13–1.16)	<0.0001
E/e′	1.43 (1.40–1.47)	<0.0001	1.33 (1.29–1.37)	<0.0001
MR vs no MR	4.63 (4.09–5.23)	<0.0001	2.01 (1.71–2.36)	<0.0001

LACI indicates left atrial coupling index; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; and OR, odds ratio.
*Adjusted for age, sex, LVESD, E/e′, and severe MR.

Importantly, propensity matching of LACI ≥5 and LACI <5 cohorts (n=732 each) resulted in excellent matched-groups balance, not only for age but also for sex, body mass index, hypertension, diabetes, dyslipidemia, dyspnea, Charlson Comorbidity Index, LV end-systolic diameter, LVEF, and MR severity (all *P*≥0.2) (Table S3). In these matched cohorts of similar age and equal left ventricle size at baseline, survival under medical management was 88±1% at 5 years and 92±1% and 85±2% in LACI <5 and LACI ≥5, respectively (*P*=0.02) (Figure S1). Cox proportional hazard analysis showed excess mortality associated with LACI ≥5 in these matched cohorts (HR, 1.37 [95% CI, 1.05–1.79], *P*=0.02 for LACI ≥5 versus LACI <5), similar to that of the entire cohort.

Stratification using 3 LACI levels also showed increasing excess mortality with higher LACI, with 10-year survival 85±1% for LACI <5, 64±2% for LACI 5 to 9.9, and 45±4% for LACI ≥10 (*P*<0.0001) (Figure S2) and a comprehensive model adjusted HR of 1.47 (95% CI, 1.17–1.85) for LACI ≥10 and adjusted HR of 1.26 (95% CI, 1.06–1.49) for LACI 5 to 9.9 (both versus LACI <5, *P*≤0.008).

Incremental Prognostic Value of LACI

LACI incremental predictive power for mortality, particularly over MR and LA volume, was demonstrated by several approaches; First, stratification by MR grade and LAVI: stratified by MR no/mild and MR moderate–severe (Figure 3A and 3B) and by LAVI ≥40 mL/m^2 and <40 mL/m^2 (Figure 3C and 3D) showed that survival under medical management was widely different with LACI ≥5 versus LACI <5. Furthermore, survival analysis, stratified by LACI and LAVI terciles showed higher mortality with higher LACI tercile in each of the LAVI strata (Figure S3). Second, nested models were used and confirmed that LACI provided incremental prognostic information over a′-TDI alone, LAVI alone, A wave of mitral inflow, or LAVI/A ratio, and over all conventional determinants of survival by showing robust increase in models power (χ^2) for predicting mortality with LACI addition (all *P*<0.0001). Third, receiver operating characteristic curve analysis for categorical 5-year mortality end point showed area under the curve for LACI of 0.66 (*P*<0.0001), for LAVI of 0.58 (*P*<0.0001), and when added to LAVI in a bivariate logistic model, LACI provided incremental power to the model (area under the curve, 0.68; *P*<0.0001). Finally, net reclassification improvement of LACI terciles versus LAVI guideline-based strata (<40, 40–59, and ≥60 mL/m^2) was considerable at 0.21±0.02 (*P*<0.0001). Hence, LACI provides considerable incremental predictive power for survival over all other determinants of survival.

To further confirm LACI association to survival, we examined overall survival throughout follow-up (89±1% at 5 years and 76±1% at 10 years) (Figure S4). Higher LACI was associated with higher long-term mortality with a univariable HR of 1.28 (95% CI, 1.25–1.32) per 3-unit increment and a HR of 2.62 (95% CI, 2.27–3.02) for LACI ≥5 (*P*<0.0001) (Table 4). Adjustment did not affect the powerful association of LACI to overall mortality, with adjusted HRs of 1.09 [95% CI, 1.03–1.14] per 3-unit increase (*P*<0.001) and 1.19 (95% CI, 1.02–1.39) for LACI ≥5 (*P*=0.03) (comprehensive model). Conversely, postoperative survival involved fewer events and was 94±1% at 5 years and 85±2% at 10 years

Table 3. Univariate and Multivariable Analysis of Clinical Consequences With Higher LACI

	Univariate analysis		Multivariable analysis*	
	OR (95% CI) for LACI ≥5 vs <5	*P* value	OR (95% CI) for LACI ≥5 vs <5	*P* value
Dyspnea	1.63 (1.44–1.83)	<0.0001	1.31 (1.13–1.51)	0.0003
≥Moderate FTR	3.56 (2.67–4.75)	<0.0001	1.79 (1.35–2.36)	<0.0001
sPAP ≥50 mm Hg	6.97 (5.12–9.48)	<0.0001	3.33 (2.38–4.65)	<0.0001

FTR indicates functional tricuspid regurgitation; LACI, left atrial coupling index; OR, odds ratio; and sPAP, systolic pulmonary artery pressure.
*Adjusted for age, sex, Charlson Comorbidity Index, left ventricular ejection fraction, and moderate-severe mitral regurgitation.

Table 4. Univariable and Multivariate HR of Mortality

	LACI increment	Mortality under medical treatment		Overall mortality		Postoperative mortality	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariable	Per 3 units	1.43 (1.38–1.49)	<0.0001	1.28 (1.25–1.32)	<0.0001	1.23 (1.13–1.31)	<0.0001
	≥5*	3.13 (2.70–3.64)	<0.0001	2.62 (2.27–3.02)	<0.0001	2.17 (1.27–3.71)	0.005
Adjusted on age, sex and Charlson Comorbidity Index, core model	Per 3 units	1.16 (1.09–1.22)	<0.0001	1.11 (1.06–1.17)	<0.0001	1.13 (1.00–1.24)	0.04
	≥5*	1.40 (1.19–1.65)	<0.0001	1.26 (1.08–1.46)	0.003	1.13 (0.65–1.95)	0.7
Further adjustment on LVEF, symptoms, and MR grade, comprehensive model	Per 3 units	1.12 (1.05–1.18)	0.0001	1.09 (1.03–1.14)	0.001	1.10 (0.97–1.22)	0.1
	≥5*	1.30 (1.10–1.53)	0.002	1.19 (1.02–1.39)	0.03	1.09 (0.63–1.89)	0.8

HR indicates hazard ratio; LACI, left atrial coupling index; LVEF, left ventricular ejection fraction; and MR, mitral regurgitation.
*vs LACI <5.

(Figure S4). Although univariately LACI was associated with postoperative survival, in multivariable analysis, LACI mortality link after mitral surgery remained directionally worse but lost statistical significance (Table 4). However, overall survival accounting for mitral surgery as a time-dependent covariate in multivariable analysis remained independently linked to LACI, irrespective of treatment ($P<0.0001$), but was also markedly improved by surgery adjusting for LACI (time-dependent adjusted HR, 0.40 [95% CI, 0.28–0.65]; $P<0.0001$).

DISCUSSION

The present study addresses for the first time LA functional assessment by standard Doppler echocardiography in a large FMV cohort. Of core importance was inclusion of consecutive patients diagnosed with isolated FMV involving all DMR grades, comprehensively characterized, with LAVI and a′-TDI measured prospectively at diagnosis in routine practice. Taking advantage of these unique assets, we found that in patients with FMV, LA functional impairment, expressed through higher LACI, was frequent but not isolated and independently associated with more severe DMR, older age, and worse LV systolic and diastolic function. At diagnosis, higher LACI is independently associated with more severe clinical presentation, more dyspnea, more pulmonary hypertension, and more tricuspid regurgitation. The most important result is that higher LACI is strongly and independently associated with excess mortality, which was considerable under medical management, adjusting for any potential confounders and irrespective of DMR severity and LA size (Figure 4). Spline curve analysis over the entire LACI range determined the excess mortality threshold of LACI ≥5 and sharp increase with each LACI increment. The prognostic importance of LACI is underscored by its incremental power over conventional determinants but also over LAVI with large net reclassification index >20%. Hence, LA functional response to the mitral disease, measured by LACI, is a strong, independent, and incremental determinant of outcome widely applicable in routine clinical practice.

LA Functional Assessment

The left atrium has long been considered a passive receptacle of mitral or LV alterations. However, recent data demonstrated a nonlinear response of LA enlargement to the mitral disease, sometimes even independent of MR severity.[18] This response variability led to the concept that LA alterations may have independent impact on outcome.[11,12] In turn, this concept led to partial inclusion of severe LA enlargement in valvular diseases guidelines.[8] Most recent data further demonstrated the strength of this association in the specific

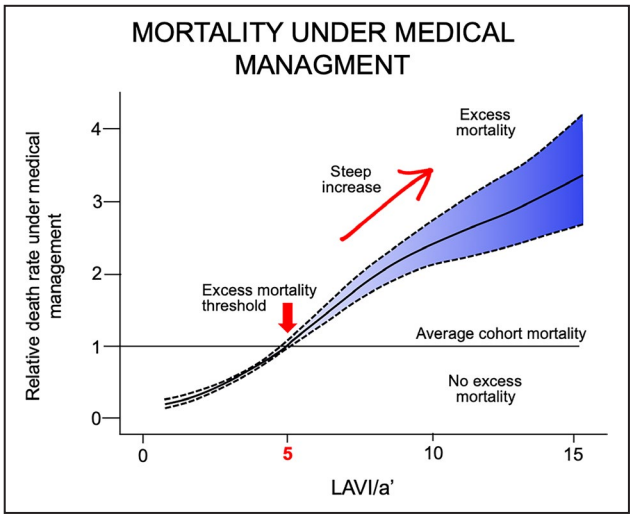

Figure 1. Spline curve of mortality risk according to LACI. The graph represents mortality under medical management. The line of hazard ratio=1 represents average cohort mortality with excess mortality for values >1 with LACI values on the *x* axis. With LACI ≥5, excess mortality appears under medical management, rapidly and steeply increasing with LACI increment. LACI indicates left atrial coupling index; and LAVI, left atrial volume index.

context of routine clinical practice and independently of cardiac rhythm.[13] The strength of association between LA volume and outcome, by emphasizing LA importance, warranted refinement of LA characterization beyond LA enlargement. LA enlargement is a purely morphometric measurement and does not provide LA functional assessment, which may carry incremental information.[18]

However, LA function is particularly difficult to characterize because it involves 3 phases. The booster pump phase (only active contraction) follows the passive conduit phase during ventricular diastole, whereas the reservoir phase in systole (closed mitral valve) receives inflow from pulmonary veins and mitral regurgitant volume.[20] Although left atrial physiology has been scarcely studied versus ventricular physiology, animal studies have demonstrated that in vivo, preload and chamber function are coupled.[21] Hence, it is essential in evaluating LA function to couple a measure of atrial stretch (LAVI) to a measure of mechanical LA activity (a′-TDI, less affected by LV diastolic function than A wave).

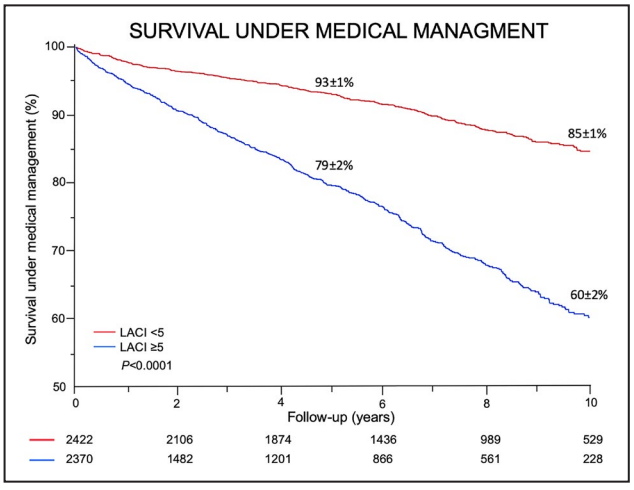

Figure 2. Survival stratified by LACI. Survival stratified by LACI <5 and ≥5 under medical management throughout follow-up. Note the large mortality difference between LACI subgroups. Figures indicate estimated survival±SE. LACI indicates left atrial coupling index.

These complex interactions tie in well with our findings that higher LACI is linked to older age, more severe DMR, LV enlargement, and LV diastolic dysfunction. Potential consequences of reduced atrial function are congruent with our finding of more severe symptoms, pulmonary hypertension, and tricuspid regurgitation in patients with higher LACI. Ultimately, LA fibrosis as underlying physiological mechanism for LA functional impairment, suggested by canine models,[22] appears operative in studies using magnetic resonance cardiac imaging[23] and intraoperative atrial biopsies.[24] Although these concepts are of great interest, the currently missing/uncertain link remains that between LA functional status and outcome.

In that regard, LA function may be a risk marker in various clinical context.[25] Seminal studies suggested that LA reservoir function may be a harbinger of first atrial fibrillation,[26] whereas reduced LA compliance may limit exercise capacity[27] and quality of life.[15] LA alterations in patients with MR was mainly evaluated using LA dimensions. Our cohort is the first to demonstrate on a large scale using routine measurements that LA functional assessment provides incremental prognostic information, not only over standard prognostic markers in DMR but over the LAVI itself and over any measure of LA mechanical activity. This incremental power was indisputable, confirmed stratified by MR grade and LAVI, by nested models, by net reclassification improvement of LACI versus LAVI, by Cox proportional hazards analysis, and additionally by receiver operating characteristic curve analysis. Similar impact in functional MR, a radically different condition versus FMV in regard to MR mechanism, LV function, and outcome,[16,17] emphasized also the clinical significance of LACI, which provides incremental prognostic information in mitral conditions of different causes/contexts. These new concepts suggest that more bench research is needed to better understand the underlying mechanism of LA dysfunction.

Another important finding is that LA functional impairment by LACI, which has received modest attention, may precede LA dilatation. In contrast, LA functional assessment by volume cyclical change may be affected by technical difficulties[28] and hindered by LA overload with LA dysfunction masked by MR,[29] and

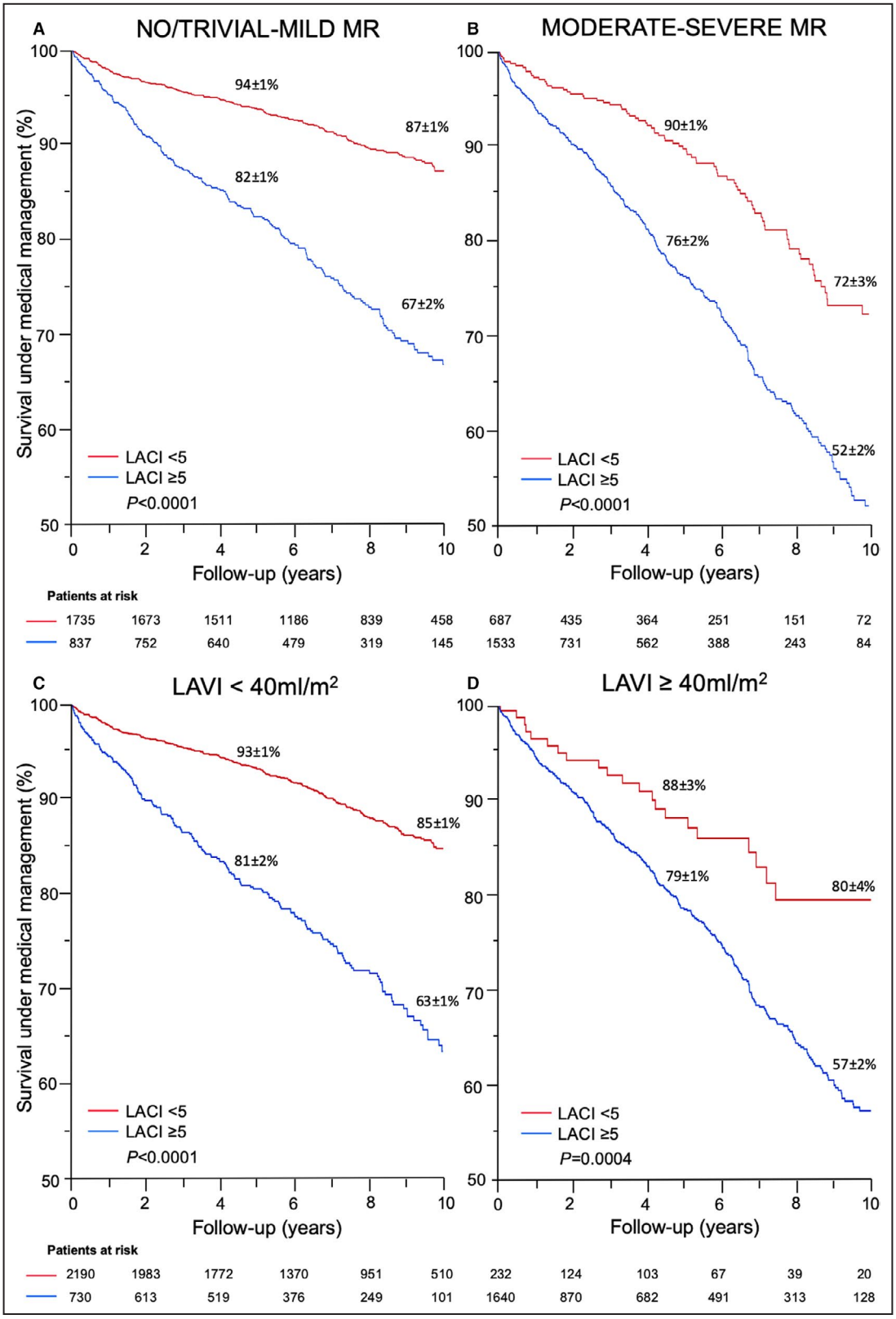

Figure 3. Impact on survival of LACI in MR and LAVI subgroups.
Survival under medical management by LACI groups, stratified by no/mild MR (**A**) and moderate–severe MR (**B**), and with LAVI <40 mL/m^2 (**C**) and ≥40 mL/m^2 (**D**). In both subgroups, patients with LACI ≥5 (blue curve) incur much higher mortality than those with LACI <5 (red curve). LACI indicates left atrial coupling index; LAVI, left atrial volume index; and MR, mitral regurgitation.

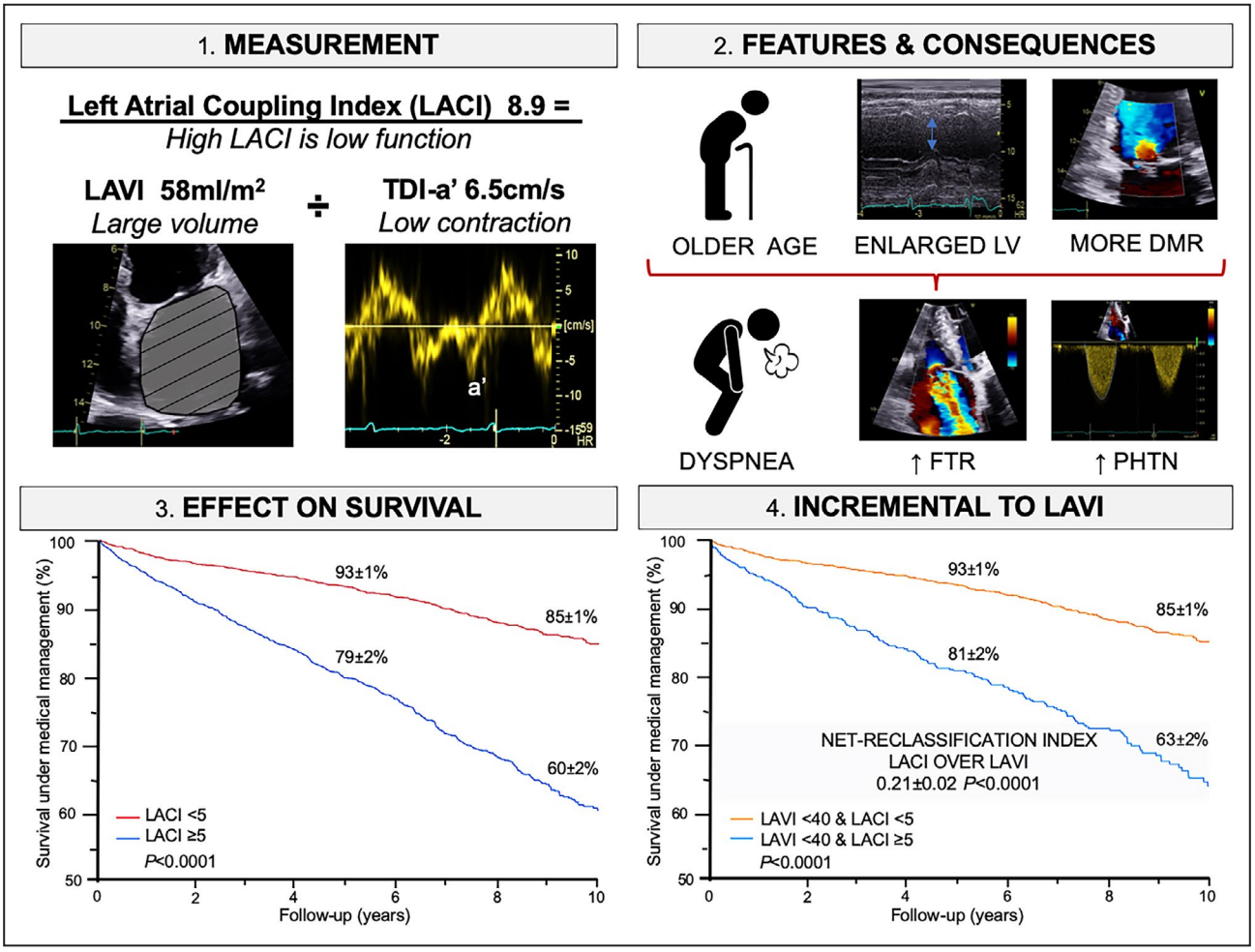

Figure 4. LACI in floppy mitral valves.
(Top left) Measurement of LACI using LAVI over tissue Doppler imaging septal a′. (Top right) LACI-associated features and clinical consequences. (Bottom left) Survival stratified by LACI <5 and ≥5 throughout follow-up. Note the large mortality difference between LACI groups. (Bottom right) LACI incremental prognostic measurement over LAVI, with nested model and survival stratified by LACI <5 and ≥5 in patients with LAVI <40 mL/m². Note the excess mortality with LACI ≥5 vs <5 and no left atrial enlargement. DMR indicates degenerative mitral regurgitation; FTR, functional tricuspid regurgitation; LACI, left atrial coupling index; LAVI, left atrial volume index; LV, left ventricle; PHTN, pulmonary hypertension; and TDI, tissue Doppler imaging.

only detectable at advanced stages.[30,31] These pitfalls yielded interest in LA intrinsic functional assessment. Speckle tracking is to be encouraged for this purpose despite technical complexities,[15] and uncertain implementation in routine practice,[32] but will require future comparative analysis of prognostic value, particularly to LACI. At present, LACI, which our cohort demonstrates as providing LA functional assessment in a large number of patients, is immediately available in routine practice and provides considerable incremental prognostic power, warranting deployment in patients with FMV and DMR.

FMV and DMR Management

In the effort to integrate LA functional assessment in DMR clinical management with the aim of reducing DMR pervasive undertreatment,[5] identifying new and powerful markers of outcome, easily quantifiable and applicable to routine practice, is paramount. Guidelines follow different courses, either suggesting prompt evaluation for early repair[9] or accumulation of risk factors to enhance decision making.[8] However, in view of the aging population with DMR[1,5] that may imply higher surgical risk,[33] both approaches may be justified in different segments of the DMR population. Thus, it is essential to define multiple prognosis markers in regard to long-term outcome. Several objective measures have proven their worth in addition to the classic symptomatic status and LV function, such as DMR quantified severity,[34] occurrence of pulmonary hypertension,[35] activation of natriuretic peptides,[10] and more preliminarily, exercise capacity reduction.[36] Among atrial complications of mitral diseases, atrial fibrillation occurrence is a potent marker of outcome[37]

but late stage, implying persistent postoperative risk.[38] LA volume assessment is more sensitive with less untoward implications during postoperative outcomes.[12,13] Furthermore, promising seminal studies of LA functional assessment[39] suggested incremental links to outcome, a concept that has been supported,[15,24,31,40] in various clinical contexts,[16,17] but without the large cohorts of FMV with all DMR grades to ascertain conclusively the incremental prognostic power. Thus, we combined LAVI and a′-TDI (both routinely measured, validated, and reproductible) in calculating LACI and analyzed its incremental prognostic power in the present large cohort of patients with FMV without and with DMR of any degree. In that regard, it is important to note that FMV elevated risk during follow-up does not just affect patients with severe DMR,[34] because determinants of mortality in FMV are incompletely understood,[6] and recent data suggest that subsets with less than severe MR may be at notable risk.[41] This approach demonstrates that LACI proves not only independent of known markers of outcome but also has crucial incremental prognostic value,[42] with considerable net reclassification improvement of 21% versus LAVI. Although overall mortality is lower in patients with less DMR, there is notable risk not captured by a single MR assessment and revealed by LACI analysis, as demonstrated for the first time by our study.

Although therapeutic triggers and thresholds mentioned in guidelines for DMR have only been based on outcome studies with no clinical trials available,[8,9] clinical implications of our LACI findings should be prudent and focus on defining paths to clear therapeutic options. Our data show that LA functional alterations have considerable prognostic implications, incremental to LV functional alterations, often interpreted in light of DMR severity. In patients with severe DMR complicating FMV, we believe our data are quite encouraging in considering prompt mitral repair based on LACI ≥5. The considerable outcome improvement after repair is associated with a narrowing of survival differences between high and low LACI, suggesting that suppression of volume overload may have favorable outcome implications with high preoperative LACI. Whether simultaneous LA volume reduction surgery may provide benefits,[43] and may affect postoperative impaired functional capacity,[24] remains an open question. In patients with no/mild DMR, in whom mitral repair is not considered, the unresolved question is whether medical treatment similar to that for LV dysfunction[44] may yield improved LA contractile function and possibly outcome. To resolve these questions, randomized clinical trials are warranted. In the remaining subset of patients with moderate DMR, in which mitral surgery is not a current consideration, it is legitimate to question whether mitral repair may improve outcome in those with LACI ≥5. In parallel, patients who may present with a higher operative risk may require higher LACI thresholds (≥10). These pertinent open questions that affect patients with FMV at any DMR grade emphasize the importance of our design, whereby we included the whole DMR range, not only to maximize power to reveal the LACI-DMR link, but most importantly, to demonstrate LACI association with presentation[40] and outcome independent and at any DMR grade. The novel finding that LA functional assessment is not only possible and simple, but that it is also powerfully and incrementally associated with clinical outcome, not only raises clinical therapeutic questions but also underscores considerable gaps of knowledge in terms of biological mechanisms and paths linking atrial dysfunction and worse clinical outcomes. Most importantly, it emphasizes the need to quantify LA functional assessment beyond morphometric LAVI and to generalize LACI measurement in routine clinical practice.

Study's Strengths and Limitations

Although patients were identified retrospectively, all were consecutively included and all characteristics, echocardiographic or clinical, were prospectively collected at baseline in routine practice without knowledge of clinical outcomes and retrieved electronically without modification, emphasizing applicability of present results to all-comers with FMV. Also, patients were not entered into protocolized care, and clinical decisions were made with their personal physicians using all information available, an approach reflective and relevant to routine clinical practice. There is growing interest in LA characteristics, and morphological assessment by LAVI is validated as linked to outcome in routine practice,[13] but LA functional assessment by LACI, as shown in the present study, provides incremental information, which may extend to other methods of LA functional assessment in the future. In that regard, LA deformation imaging, though possible[15] and practically feasible,[39] will require demonstration of its incremental link to outcome during prolonged follow-up in sizable series, emphasizing the immediate importance of measuring LACI. LACI can only be calculated in sinus rhythm, but atrial fibrillation is already synonymous with high risk,[37] reducing the importance of outcome markers in this context. a′-TDI was measured medially based on high reproducibility and strong association with hemodynamic measurements,[16,39,45] whereas lateral measurement is prone to variability and is poorly associated with outcome. As a matter of verification, we also gathered lateral a′-TDI; the hypothetical lateral LACI demonstrated weaker association to outcome (χ^2 for lateral versus medial a′-TDI LACI in Cox proportional analysis 67 versus 312) ($P<0.0001$). Although indexing LAVI to LV end-diastolic volume index, has been proposed,[46] estimated end-diastolic volume index in the present study has no prognostic power

adjusted to ejection fraction (P=0.90) or LAVI (P=0.60), and in nested models, the calculated LAVI/end-diastolic volume index has lower prognostic power than LAVI alone and LACI in particular (both P<0.0001). Additional discussion on strengths and limitations of the study is available in Data S2.

CONCLUSIONS

In the present large and unique cohort of isolated FMV with a wide range of DMR, LACI was prospectively measured in routine practice while linked to age, DMR severity, and LV function, which underscores the wide variability of LA functional response to mitral valve disease. LACI conveys in the FMV population a powerful, independent, and critically incremental link to excess mortality after diagnosis, which is a novelty of our study. Hence, LACI should be routinely measured in patients with FMV and its value integrated into clinical decision making. Biological mechanisms, therapies, and links to untoward clinical events of LA functional alterations should be actively researched.

ARTICLE INFORMATION

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Affiliations

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (B.E., G.B., C.A., J.M., S.P., P.T., H.I.M., M.E.-S.); Department of Cardiovascular Medicine, Simone Veil Hospital, Cannes, France (B.E.); Department of Cardiovascular Medicine, University of Verona, Verona, Italy (G.B.); and Minneapolis Heart Institute, Minneapolis, MN (M.E.-S.).

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Supplemental Material

Data S1–S2
Tables S1–S3
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Statistical Methodology: The Net Reclassification Improvement

The Net Reclassification Improvement (NRI) is a statistical tool proposed to assess improvement in model performance offered by a new method of classification compared to a reference one (*Stat Med.* 2008 Jan 30;27(2):157-72; discussion 207-12). The NRI indicates how much more frequently appropriate reclassification occurs than inappropriate reclassification with the use of a new model of classification. The NRI is based on reclassification tables constructed separately for participants with and without the interest event, and quantifies the correct movement in categories, upwards for events and downwards for non-events.(*Stat Med.* 2011 Jan 15;30(1):11-21.).

We defined an upward movement (up) as a change into higher category based on the new algorithm and downward movement (down) as a change in the opposite direction. The NRI is then defined as: NRI=P(up|event)−P(down|event)+P(down|non-event)−P(up|non-event). The null hypothesis for NRI = 0 is tested using Z statistic following McNemar asymptotic test for correlated proportions.

Accordingly, NRI for LACI over LAVI used a categorical approach dividing LACI into 3 terciles groups (≤ 3.8, 3.8-6.3, > 6.3; all *n=1597*) and LAVI in 3 subgroups (<40ml/m^2, 40-60ml/m^2, ≥60ml/m^2, *n=2920, 1275 and 597* respectively) so that it is not based on a single LAVI cut point that would not capture the risk of the highest LAVI. Net-reclassification-improvement of LACI vs. LAVI was considerable at 0.21±0.02, P<0.0001.

Data S2. Supplemental Discussion: Strengths and limitations of the study

Guideline-recommended surgical triggers and thresholds are mostly based on clinical cohorts but in the future, prospective cohorts of large size should be planned. Including full spectrum of DMR severity, a strength of our study, was paramount in demonstrating LACI prognostic power at each DMR grade for improved risk-assessment for all patients with FMV.

Due to legal restrictions to access to death certificates combined with vagaries of coding death causes, we could not evaluate "cardiac mortality" as endpoint but rather focused on the most robust endpoint of overall mortality. Excess cardiac-mortality without excess total-mortality is inconceivable, making the issue of "cardiac mortality" moot. Furthermore, potential contribution of comorbidities to mortality were taken into account through adjustment for comorbidity-index.

While LA function may affect outcome in numerous contexts of ventricular or valvular diseases, our present focus on the outcome of FMV may be questioned. In that regard, it is important to note that addressing all clinical contexts in a mixed bag is not appropriate due to the specific outcomes and determinants in each disease. The potential prognostic power of LACI remains to be supported by future studies within each well-defined clinical context with sufficient power and long-term follow-up. In our opinion, FMV is a critical target for assessing LACI power for multiple reasons: 1-the LA overload potentially caused by DMR; 2-the prognostic importance of LA characteristics at any degree of FMR; 3-the recently demonstrated profound undertreatment of patients with DMR; 4-The excess mortality observed in patients with less than severe DMR; 5-the successful therapeutic options in patients with DMR, with surgical or transcatheter repair; 6-the lack of LA characteristics mention in the 2020 US valvular guidelines. However, we deeply support future well designed studies addressing LACI incremental power in various other types of cardiac diseases.

Table S1: Medical Treatment in the study population, overall and by LACI <5 and ≥5

	Overall (n=4792)	LACI <5 (n=2422)	LACI ≥5 (n=2370)	*P* value
ARB	539 (11)	183 (8)	356 (15)	<0.0001
ACE-I	1224 (26)	373 (15)	851 (36)	<0.0001
Anti HTN	2962 (62)	1142 (47)	1820 (77)	<0.0001
Spironolactone	161 (3)	53 (2)	108 (5)	<0.0001
Statins	1454 (30)	518 (21)	936 (39)	<0.0001
Aspirin	2673 (56)	1094 (45)	1579 (67)	<0.0001
Digoxin	190 (4)	38 (2)	152 (6)	<0.0001
Anti-Arrhythmic	439 (9)	96 (4)	343 (14)	<0.0001
Ca-Inhibitor	651 (14)	221 (9)	430 (18)	<0.0001
Beta Blockers	1998 (42)	716 (30)	1282 (54)	<0.0001
Diuretics	1409 (29)	435 (18)	974 (41)	<0.0001

Table S2: Baseline characteristics overall and stratified by LACI categories

	Overall population (n= 4792)	LACI <5 (n=2422)	LACI 5-<9.9 (n=1831)	LACI ≥10 (n=539)	*P* value
Clinical Characteristics					
Age, yrs	61±16	54±16	67±13	73±11	<0.0001
Female, %	2381 (48)	1335 (55)	769 (42)	214 (40)	<0.0001
BMI, kg/m^2	25±5	24±5	26±4	26±4	<0.0001
Heart rate, bpm	67±12	68±12	66±14	66±12	<0.0001
Previous CABG, %	169 (4)	40 (2)	83 (5)	46 (9)	<0.0001
Hypertension, %	1687 (35)	612 (25)	794 (43)	281 (52)	<0.0001
Charlson Index	1.2±2	0.7±0.9	1.0±1.2	1.2±1.2	<0.0001
Dyspnea, %	1613 (34)	686 (28)	664 (36)	263 (49)	<0.0001
Edema, %	467 (10)	164 (7)	221 (12)	82 (15)	<0.0001
Chest Pain, %	849 (17)	447 (18)	315 (17)	87 (16)	0.3
LV & Hemodynamic Characteristics					
LV-EDD, mm	51±7	49±6	53±7	55±7	<0.0001
Indexed LV-EDD, mm/m^2	28±4	27±3	28±4	30±4	<0.0001
LV-ESD, mm	32±5	31±4	33±6	36±7	<0.0001
Indexed LV-ESD, mm/m^2	17±3	17±2	18±3	19±4	<0.0001
LV-EF, %	63±7	63±6	63±7	61±10	<0.0001
CI, L/min/m^2	3.0±0.6	3.0±0.6	3.0±0.6	3.0±0.7	0.08
E wave, cm/s	8±3	8±2	9±3	9±4	<0.0001
E/A	1.3±0.6	1.3±0.6	1.2±0.6	1.4±0.8	<0.0001
E/e’	11±5	8±3	12±5	17±7	<0.0001
LAVI, ml/m^2	40±18	29±8	46±14	67±25	<0.0001
Medial a’-TDI, cm/s	8±3	9±2	7±2	5±2	<0.0001
LACI (LAVI/a’-TDI)	5.8±3.7	3.3±1.0	6.9 ±1.3	13.5±4.4	<0.0001
Systolic PAP, mm Hg	33±12	29±8	35±13	41±16	<0.0001
Moderate-severe TR, n (%)	269 (6)	63 (3)	145 (8)	61 (11)	<0.0001
Mitral Characteristics					
No/ trivial MR, n (%)	1094 (23)	866 (36)	197 (11)	31 (6)	<0.0001
Mild MR, n (%)	1478 (31)	869 (36)	515 (28)	94 (17)	
Moderate MR, n (%)	996 (21)	400 (17)	458 (25)	138 (26)	
Severe MR, n (%)	1224 (26)	287 (12)	661 (36)	276 (51)	
ERO, mm^2	23±24	12±19	31±24	38±24	<0.0001
RVol, ml	38±38	20±29	51±37	64±37	<0.0001
Flail leaflet, n (%)	543 (11)	115 (5)	294 (16)	134 (25)	<0.0001
Posterior, n (%)	2097 (44)	944 (39)	883 (48)	270 (50)	<0.0001
Bileaflet, n (%)	1900 (40)	956 (39)	744 (41)	200 (37)	0.3

BMI: body-mass-index; CABG: Coronary-artery-bypass-graft; CI: Cardiac index; EDD: End-diastolic diameter; EF: Ejection-fraction; ERO: Effective-Regurgitant-Orifice; ESD: End-systolic diameter; LV: Left Ventricle; MR: Mitral Regurgitation; PAP: Pulmonary-artery-pressure; RVol: Regurgitant Volume

Table S3: Baseline characteristics of study population by LACI >5 vs <5 groups of matched age, comorbidities and FMV outcome determinants.

	LACI <5 N=732	LACI ≥5 N=732	*P* value
Clinical Characteristics			
Age, yrs	63±12	63±13	0.9
Female, %	344 (47)	350 (48)	0.8
BMI, kg/m^2	25±5	25±4	0.6
Heart rate, bpm	66±12	67±12	0.2
Hypertension, %	256 (35)	270 (37)	0.4
Diabetes, %	41 (6)	37 (5)	0.6
Dyslipidemia, %	291 (40)	267 (36)	0.2
Dyspnea, %	242 (33)	257 (35)	0.4
Charlson Index	0.83±1.1	0.82±1.0	1
Echocardiographic variables			
Bileaflet, %	290 (40)	321 (44)	0.1
Posterior, %	324 (44)	314 (43)	0.9
Flail leaflet, %	76 (10)	84 (11)	0.5
LV-EDD, mm	51±6	51±6	0.2
Indexed LV-EDD, mm/m^2	27±3	28±4	0.1
LV-ESD, mm	32±5	32±5	0.7
Indexed LV-ESD, mm/m^2	17±3	17±3	0.5
LV-EF, %	64±6	64±7	0.3
LACI	3.7±0.9	7.3±2.7	<0.0001
Mitral regurgitation, %			1
No/ trivial MR	130 (18)	132 (18)	
Mild MR	266 (36)	258 (35)	
Moderate MR	159 (22)	162 (22)	
Severe MR	177 (24)	180 (25)	
ERO, mm^2	23±23	25±24	0.4
RVol, ml	38±35	40±37	0.4

BMI: body-mass-index; EDD: End-diastolic diameter; EF: Ejection-fraction; ERO: Effective-Regurgitant-Orifice; ESD: End-systolic diameter; LV: Left Ventricle; MR: Mitral Regurgitation; RVol: Regurgitant Volume.

Figure S1:Survival of matched cohort stratified by LACI subgroups.

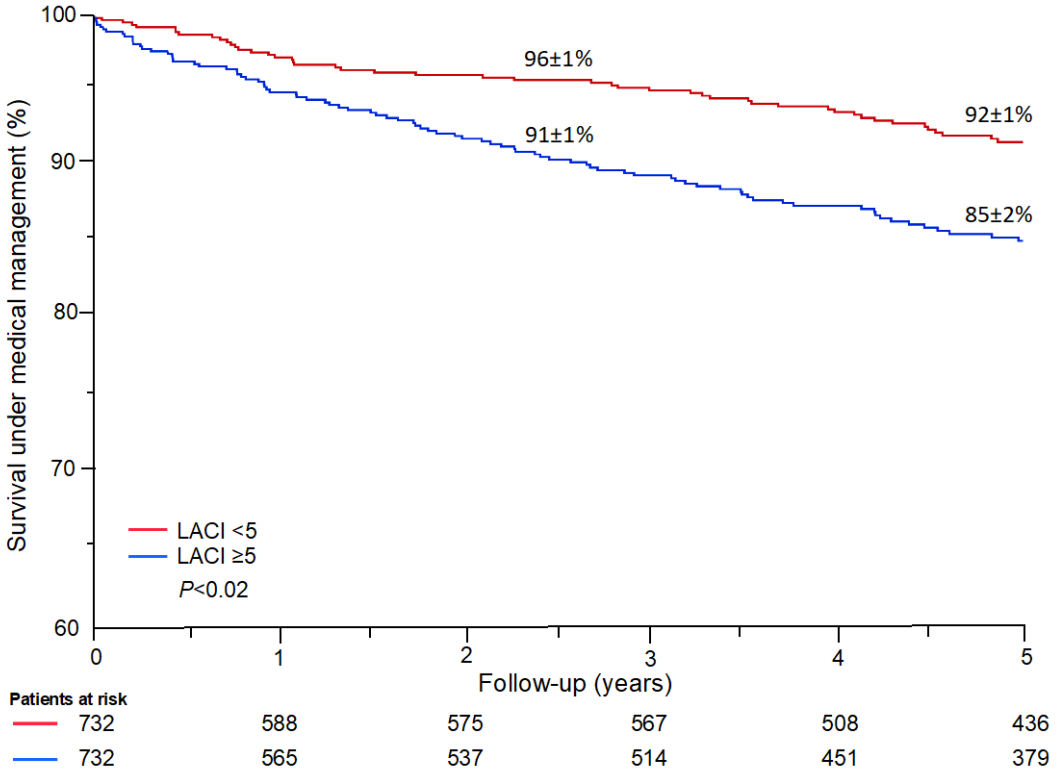
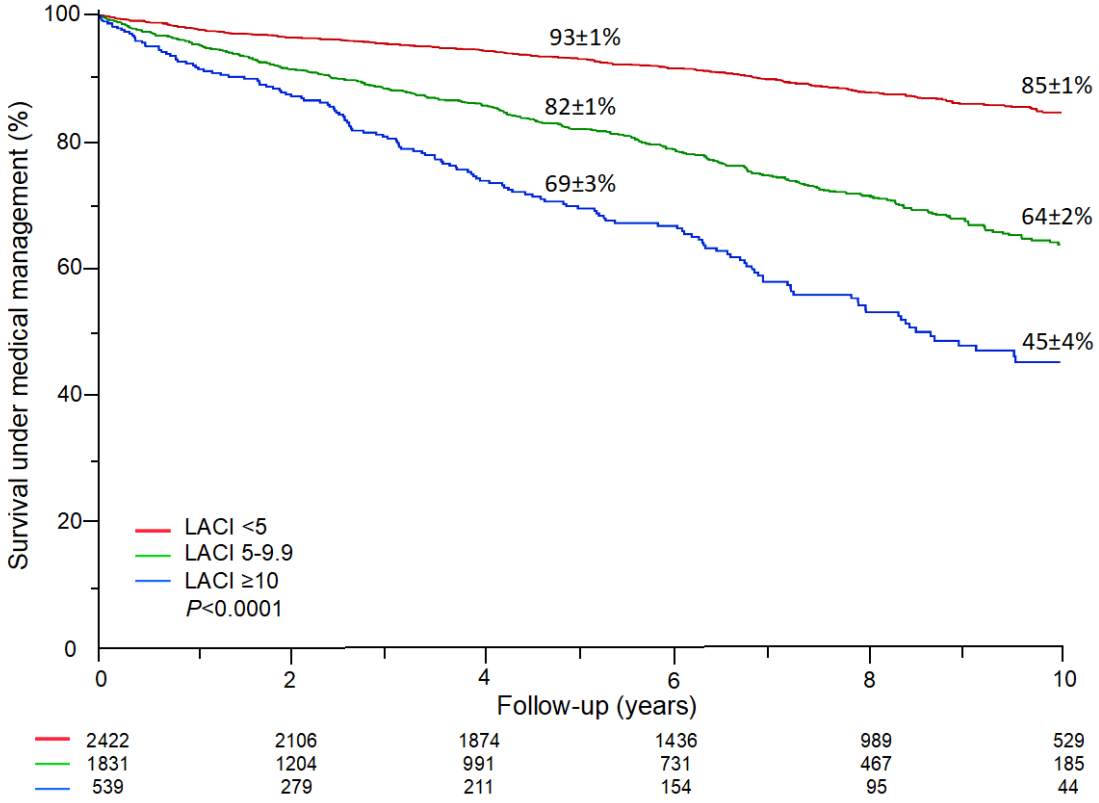


Figure S2: Survival stratified by LACI categories



Survival under medical management stratified by LACI<5, 5-9.9 and ≥10. Note the large mortality difference between LACI subgroups. Figures indicate estimated survival±SE. LACI: left-atrial-coupling-index

Figure S3: Cox analysis of LACI cohort terciles by LAVI terciles.

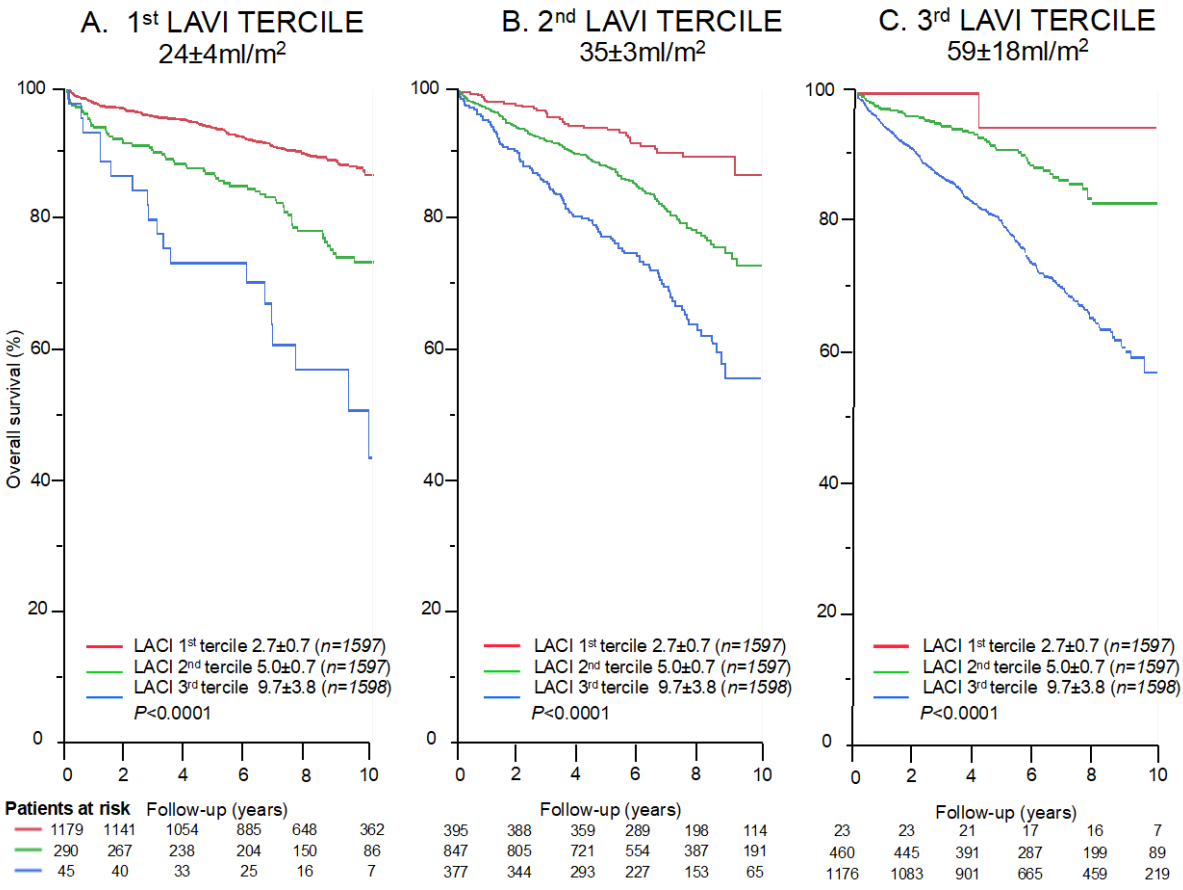
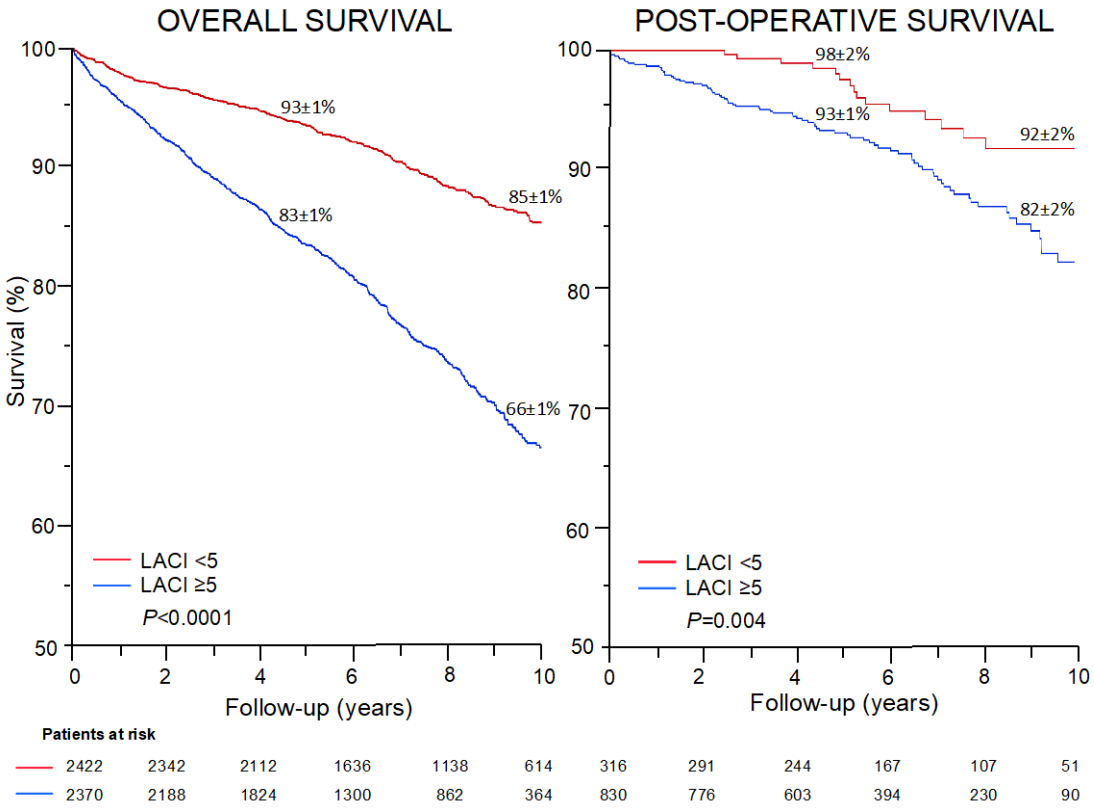


Figure S4: Survival stratified by LACI<5 and ≥5 overall and post-mitral surgery



Note the large excess-mortality with LACI≥5 vs <5 overall, partially alleviated post-mitral surgery. Figures indicate estimated survival±SE. LACI: left-atrial-coupling-index