JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 7, 2019

PUBLISHED BY ELSEVIER

Prognostic Implications of Left Atrial Enlargement in Degenerative Mitral Regurgitation

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ABSTRACT

BACKGROUND Left atrial enlargement is frequent in degenerative mitral regurgitation (DMR), but its link to outcomes remains unproven in routine clinical practice.

OBJECTIVES The purpose of this study was to assess whether left atrial volume index (LAVI) measured in routine clinical practice of multiple sonographers/cardiologists is associated independently with DMR survival.

METHODS A cohort of 5,769 (63 ± 16 years, 47% women) consecutive patients with degenerative mitral valve disease, in whom LAVI was prospectively measured, was enrolled and the long-term survival was analyzed.

RESULTS LAVI (43 ± 24 ml/m^2) was widely distributed (<40 ml/m^2 in 3,154 patients, 40 to 59 ml/m^2 in 1,606, and ≥60 ml/m^2 in 1,009). Overall survival throughout follow-up (10-year 66 ± 1%) was strongly associated with LAVI (79 ± 1% vs. 65 ± 2% and 54 ± 2% for LAVI <40, 40 to 59, and ≥60 ml/m^2, respectively; $p < 0.0001$) even after comprehensive adjustment, including for DMR severity (adjusted hazard ratio [HR]: 1.05 [95% confidence interval (CI): 1.03 to 1.08] per 10 ml/m^2; $p < 0.0001$). Mortality under medical management was profoundly affected by LAVI (adjusted HR: 1.07 [95% CI: 1.04 to 1.10] per 10 ml/mm^2 and 1.55 [95% CI: 1.31 to 1.84] for LAVI ≥60 ml/m^2 vs. <40 ml/m^2; both $p < 0.0001$) incrementally to adjusting variables ($p < 0.0001$) and in all subgroups, particularly sinus rhythm (adjusted HR: 1.25 [95% CI: 1.21 to 1.28]) or atrial fibrillation (adjusted HR: 1.10 [95% CI: 1.06 to 1.13] per 10 ml/m^2; both $p < 0.0001$). Thresholds of excess mortality in spline curve analysis were approximated at 40 ml/m^2 in all subgroups. Survival markedly improved after mitral surgery (time-dependent adjusted HR: 0.43 [95% CI: 0.36 to 0.53]; $p < 0.0001$) but remained modestly linked to LAVI (10-year survival 85 ± 3% vs. 86 ± 2% and 75 ± 3% for LAVI <40, 40 to 59, and ≥60 ml/m^2, respectively; $p < 0.0001$).

CONCLUSIONS The frequent left atrial enlargement of DMR as measured by LAVI in routine practice displays, overall and in all subsets, a powerful, incremental, and independent link to excess mortality, which is partially alleviated by mitral surgery. Hence, LAVI measurement should be part of routine DMR evaluation and the clinical decision-making process. (J Am Coll Cardiol 2019;74:858–70) © 2019 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most frequent valvular heart disease (1), and degenerative mitral regurgitation (DMR) is the predominant MR cause requiring surgical correction (2). When left unoperated, DMR is associated with serious outcome consequences (3), whereas in experts' hands, surgical treatment relying preferentially on mitral repair (4) restores life expectancy at minimal risk. The armamentarium of DMR treatment expanded recently with percutaneous repair, which can be performed in inoperable patients (5).

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Manuscript received March 8, 2019; revised manuscript received May 8, 2019, accepted June 3, 2019.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.06.032

To indicate mitral surgery, guidelines provide limited numbers of "individual triggers" such as Class I symptoms or signs of left ventricular (LV) dysfunction (6,7). However, indications based on these triggers are associated with increased post-operative mortality (8), while marked MR undertreatment is linked to excess mortality after diagnosis (9). These management challenges have provided crucial rationale for the ongoing active search for outcome markers that may be used as potential triggers for intervention.

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Left atrial (LA) enlargement has long been considered a pure MR consequence (10,11). However, recent pilot studies provided proof-of-concept that LA enlargement, measured by left atrium volume index (LAVI), may predict new arrhythmias (12) and mortality (12–14), possibly independently and incrementally to DMR severity. These pilot concepts were derived from selected series of heterogeneous MR causes, measuring M-mode diameters or LAVI exclusively by experts and only in sinus rhythm. Furthermore, outcome implications were observed only with marked LA enlargement, whereas moderate LA enlargement appeared to carry no untoward consequence. Hence, whether LAVI measured by multiple physicians/sonographers in routine practice carries independent prediction of outcome remains unproven. Consequently, LAVI measurement does not appear in U.S. guidelines (6) and is only involved in Class II indications in European guidelines (7).

To fill this gap of knowledge, an unselected cohort representing the entire consecutive experience with a single isolated diagnosis of degenerative mitral valve disease in a large routine clinical practice with prospective LAVI measurement regardless of rhythm would be required, also with comprehensive clinical and echocardiographic characterization and with long-term outcome defined. We gathered such a large cohort with DMR and examined the hypothesis that LAVI measured in routine clinical practice is an independent and incremental determinant of DMR outcome.

METHODS

Eligibility was screened in all consecutive inpatients and outpatients at Mayo Clinic, Rochester, Minnesota: 1) with diagnosis of degenerative mitral disease, defined as mitral valve prolapse (MVP) or flail leaflet by first Doppler echocardiography from 2003 to 2011; 2) age ≥18 years; 3) with LAVI measured prospectively at diagnosis in routine clinical practice; and 4) with comprehensive diagnostic evaluation of symptoms, clinical history, comorbidities, and rhythm status. We did not attempt to measure LAVI retrospectively, and patients without LAVI measurements were excluded. We excluded patients who denied research authorization (per Minnesota law) or presented any of the following: ≥ moderate aortic regurgitation or stenosis; ≥ moderate mitral stenosis; previous valvular surgery; congenital heart disease; or hypertrophic, restrictive, or constrictive cardiomyopathies (patent foramen ovale or tricuspid regurgitation not excluded). As low risk, written consent was waived by Mayo Institutional Review Board, which approved this study.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

DMR = degenerative mitral regurgitation

ERO = effective regurgitant orifice

LAVI = left atrial volume index

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MVP = mitral valve prolapse

RVol = regurgitant volume

ECHOCARDIOGRAPHIC EVALUATION. Echocardiography was performed by multiple trained sonographers (>100) and reviewed by cardiologists (>30) using diverse commercially available machines in routine clinical practice. Imaging uniform protocol included all views from standard windows and systematic measurement of left ventricular (LV) dimensions, left ventricular ejection fraction (LVEF) and cardiac index, LV filling, and systolic pulmonary pressures guided by American Society of Echocardiography recommendations. All diagnoses of valve diseases or associated conditions in the final report were selected from standard phrases among predefined diagnoses/descriptive-statement panels that were uniform for all physicians/sonographers. As per guidelines, DMR integrative severity grading used all information available (specific, supportive, and quantitative measures) to classify DMR in 4 grades: none/trivial, mild, moderate, and severe. DMR quantitation measuring effective regurgitant orifice (ERO) and regurgitant volume (RVol) was performed as often as possible. LAVI was measured using ASE-guided formulas, area-length or modified Simpson biplane, which in our laboratory were shown to provide similar results (12). All echocardiographic data (qualitative and quantitative) were extracted from the digital repository as originally/prospectively entered by clinical consultants/sonographers without modification.

CLINICAL EVALUATION. Rhythm status was classified as atrial fibrillation (AF) with overt AF by electrocardiogram or with clinical notes demonstrating history of proven AF. Comorbidities were retrieved from the electronic medical record and summated by Charlson index. Clinical notes of patients' personal physicians that were analyzed by natural-language processing defined symptoms (dyspnea, chest pain, palpitations, and edema) at diagnosis.

FOLLOW-UP. The main outcome of interest was overall survival throughout follow-up in all patients. Secondary endpoints were survival under medical treatment in all patients with censoring at mitral surgery, and post-operative survival in operated patients. Occurrence and dates of deaths were retrieved using Accurint (LexisNexis, New York, New York), a proprietary resource gathering multiple national sources, including Social Security Death Index, and interrogated at the end of 2015. To ensure accurate mortality counts, patients alive based on Accurint were censored on December 31, 2014. Surgical procedures were retrieved using the Mayo Clinic surgical registry and by clinical notes for patients operated outside of Mayo Clinic. Type of mitral surgery (repair/replacement) was specified with potential associated procedures. As per routine clinical practice, therapeutic management was decided by patients' personal physicians.

STATISTICAL ANALYSIS. Continuous data is expressed as mean ± SD or median (interquartile range [IQR]) and compared using analysis of variance or Wilcoxon test. Qualitative data expressed as percentages were compared using chi-square tests. Survival was displayed using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable survival models were analyzed with main independent variable of interest defined by LAVI as continuous variable or categories (<40, 40 to <60, and ≥60 ml/m^2) defined in previous studies of mitral diseases (12,13). Proportional-hazards assumption was verified using Schoenfeld residuals ($p = 0.19$). Multivariable Cox-proportional-hazards models used 3 levels of adjustment: first, adjusted for baseline characteristics: age, sex, and comorbidity index (core model); second, adjusting additionally for mitral factors: LVEF, symptoms, and DMR grade (comprehensive model); and third, adjusting additionally individually for AF, pulmonary hypertension, E/e′, or tricuspid regurgitation. Hazard ratios (HRs) for LAVI were presented with 95% confidence intervals (CIs). Nested models were used to assess incremental model power with LAVI addition. We used the proportional hazards models to relate continuous LAVI to excess mortality, expressed as HR within the cohort and displayed as penalized polynomial spline plotted with 95% CI of point estimate using the "termplot" function in R version 3.4.2 (R Foundation, Vienna, Austria). Surgery's effect on outcome was analyzed as a time-dependent covariate during entire follow-up. All p values <0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. All patients diagnosed at Mayo Clinic from 2003 to 2011 with isolated degenerative mitral valve disease and LAVI measured in routine practice were included in the cohort, which encompassed 5,769 patients (2,684 women, age 63 ± 16 years). Baseline demographic/clinical characteristics (Table 1) are usual for a wide range of isolated DMR. Bileaflet MVP was found in 2,247 (39%) patients, posterior MVP in 2,510 (44%), and flail leaflet in 705 (12%). DMR severity by guideline-based integrative grading was severe in 28%, moderate in 22%, and mild in 30%, while 20% of patients had no or trivial MR, and median effective regurgitant orifice area was 19 mm^2 (IQR: 0 to 40 mm^2). Clinically, 36% had symptoms of dyspnea and 15% had AF. On average, LV dilatation was mild, LVEF was 63 ± 8%, and hemodynamically, cardiac index and pulmonary pressure were normal. Overall, LAVI was 43 ± 24 ml/m^2 (median 38 ml/m^2 [IQR: 29 to 52 ml/m^2]) and was <40 ml/m^2 in 3,154 patients (55%; median 29 ml/m^2 [IQR: 24 to 34 ml/m^2]), 40 to 59 ml/m^2 in 1,606 patients (28%; median 47 ml/m^2 [IQR: 43 to 53 ml/m^2]), and ≥60 ml/m^2 in 1,009 patients (17%; median 74 ml/m^2 [IQR: 65 to 89 ml/m^2]).

Table 1 (right part) shows baseline characteristics compared between LAVI subsets, almost all were statistically different due to the cohort's considerable size. Differences reaching clinically relevant magnitude were noted in the highest LAVI group: patients were older; were more often male; and had more frequent dyspnea, edema, and AF. A trend for more comorbidity with higher LAVI was associated with age. With higher LAVI, LV was also higher but with similar LVEF between groups. Hemodynamically, although differences in cardiac index were minimal, pulmonary pressure was higher with higher LAVI. DMR was more severe with higher LAVI by integrative grading, ERO, or RVol. Hence, higher LAVI was not isolated, but compounded many baseline characteristics differences. However, the wide distribution of all variables within subgroups suggested that LAVI is not completely correlated to any one variable and may yield independent and incremental value in its potential link to the outcome of DMR.

LONG-TERM OUTCOME AFTER DIAGNOSIS. Total follow-up was 6.8 ± 3.1 years, during which 1,405 patients (24%) underwent MV surgery (at 5 years, 8 ± 1% with LAVI <40 ml/m^2, 33 ± 1% with LAVI 40 to 59 ml/m^2, and 58 ± 2% with LAVI ≥60 ml/m^2; 92% repair, 8% replacement) and 1,304 (23%) died (1,142 under medical treatment and 162 after surgery).

TABLE 1 Baseline Characteristics

	Overall Population (N = 5,769)	LAVI <40 ml/m² (n = 3,154)	LAVI 40 to <60 ml/m² (n = 1,606)	LAVI ≥60 ml/m² (n = 1,009)	p Value
Clinical characteristics					
Age, yrs	63 ± 16	59 ± 17	68 ± 14	70 ± 14	<0.0001
Female	47	55	38	33	<0.0001
BMI, kg/m²	25 ± 5	25 ± 5	26 ± 4	26 ± 5	<0.0001
Heart rate, beats/min	68 ± 14	68 ± 13	67 ± 14	71 ± 16	<0.0001
Atrial fibrillation	15	5	18	38	<0.0001
Previous CABG	4	3	6	7	<0.0001
Hypertension	38	33	45	42	<0.0001
Charlson index	1.3 ± 2	1.2 ± 2	1.5 ± 2	1.4 ± 2	<0.0001
Dyspnea	36	30	39	51	<0.0001
Edema	12	9	14	21	<0.0001
Palpitation	24	25	21	23	0.005
Chest pain	17	19	16	12	<0.0001
LV and hemodynamic characteristics					
LV-EDD, mm	51 ± 7	49 ± 5	53 ± 6	57 ± 8	<0.0001
Indexed LV-EDD, mm/m²	28 ± 4	27 ± 3	28 ± 3	30 ± 4	<0.0001
LV-ESD, mm	33 ± 6	31 ± 5	33 ± 6	36 ± 7	<0.0001
Indexed LV-ESD, mm/m²	18 ± 3	17 ± 3	18 ± 3	19 ± 4	<0.0001
LVEF, %	63 ± 8	63 ± 7	63 ± 8	62 ± 9	0.2
CI, l/min/m²	3.0 ± 0.7	3.0 ± 0.6	3.0 ± 0.7	2.9 ± 0.7	<0.0001
Systolic PAP, mm Hg	34 ± 13	30 ± 10	36 ± 14	43 ± 15	<0.0001
Moderate-severe TR	10	4	12	24	<0.0001
Mitral characteristics					
No/trivial MR	20	33	8	1	<0.0001
Mild MR	30	40	23	9	
Moderate MR	22	19	30	19	
Severe MR	28	8	39	71	
ERO, mm²	19 (0-40)	0 (0-18)	28 (16-43)	44 (28-59)	<0.0001
RVol, ml	34 (0-65)	0 (0-32)	47 (28-72)	72 (49-95)	<0.0001
Flail leaflet	12	3	16	34	<0.0001
Bileaflet	39	39	39	38	0.68
Posterior	44	39	47	52	<0.0001

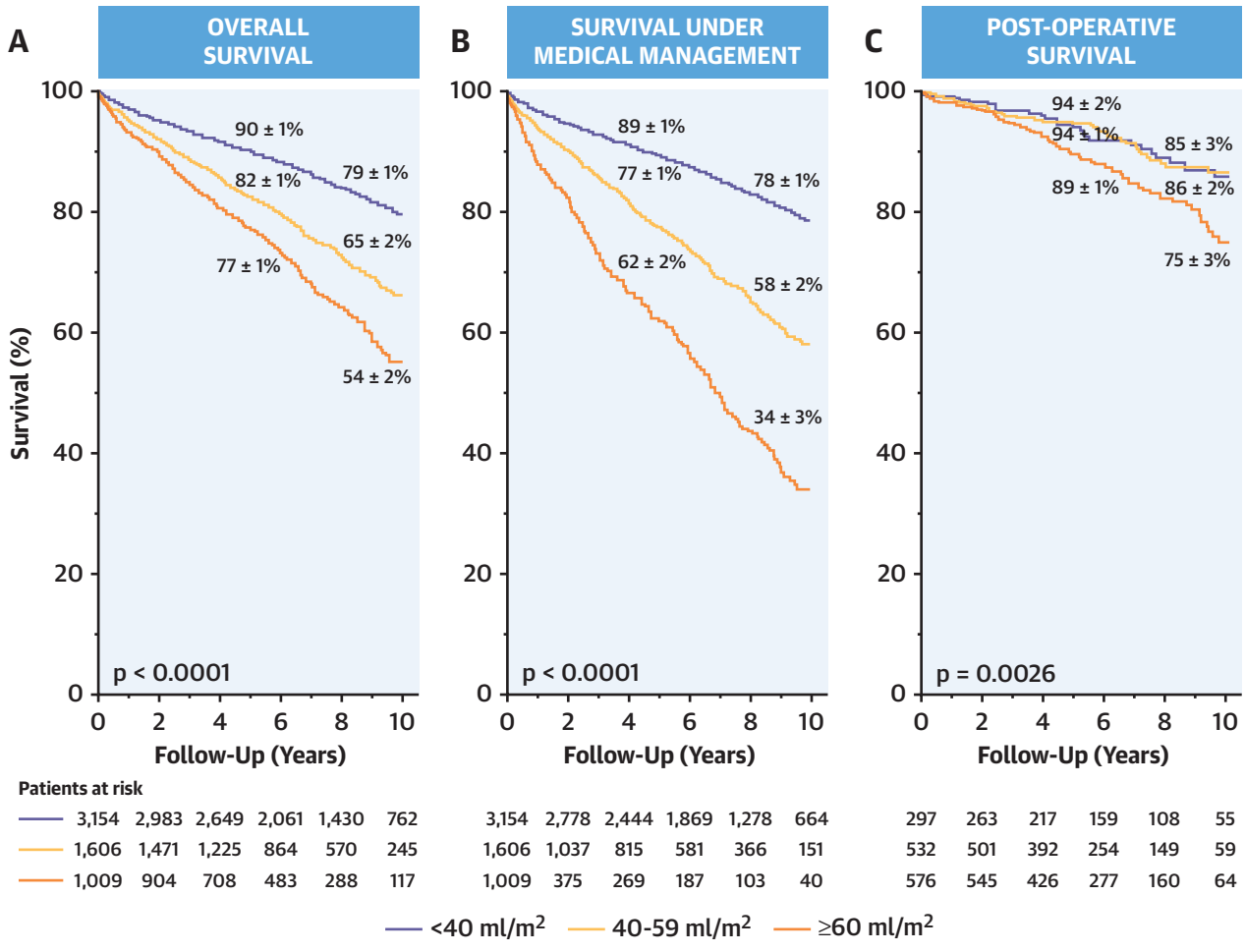
Values are mean ± SD, %, or median (interquartile range).

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; LAVI = left atrial volume index; LV = left ventricle/ventricular; MR = mitral regurgitation; PAP = pulmonary artery pressure; RVol = regurgitant volume; TR = tricuspid regurgitation.

OVERALL SURVIVAL. Survival throughout follow-up was 94 ± 1% at 1 year, 83 ± 1% at 5 years, and 66 ± 1% at 10 years. The 10-year overall survival stratified by LAVI categories was considerably different: 79 ± 1% for LAVI <40 ml/m², 65 ± 2% for LAVI 40 to 59 ml/m², and 54 ± 2% for LAVI ≥60 ml/m²; p < 0.0001 (Figure 1A). Higher LAVI (continuous) was associated with higher long-term mortality with univariable HR: 1.12 (95% CI: 1.10 to 1.14) per 10 ml/m² (Table 2). Univariable HRs of mortality associated with LA enlargement were 2.50 (95% CI: 2.19 to 2.88; p < 0.0001) for LAVI ≥60 ml/m² versus LAVI <40 ml/m² and 1.81 (95% CI: 1.59 to 2.05; p < 0.0001) for LAVI 40 to 59 ml/m² versus LAVI <40 ml/m². It was 1.39 (95% CI: 1.21 to 1.60; p < 0.0001) for LAVI ≥60 ml/m² versus 40 to 59 ml/m².

Adjustment did not affect the powerful association of LAVI with mortality (Table 2). Multivariable proportional hazard core model adjusted for age, sex, and comorbidity index showed adjusted HR: 1.06 (95% CI: 1.04 to 1.08; p < 0.0001) per 10 ml/m². The addition of LAVI to the core model provided incremental power (p < 0.0001). After additional adjustment for mitral characteristics (DMR grade, symptoms, EF, comprehensive model), LAVI remained highly associated with excess mortality (adjusted HR: 1.05 [95% CI: 1.03 to 1.08] per 10 ml/m²; p < 0.0001). Using alternatively quantitative MR measures in comprehensive models showed similar adjusted HRs: 1.06 (95% CI: 1.03 to 1.09; p = 0.0002) per 10 ml/m² for ERO adjustment and 1.06 (95% CI: 1.03 to 1.09; p < 0.0001) per

FIGURE 1 Survival Stratified by LA Enlargement



Survival of DMR stratified by LAVI <40, 40 to 59, and ≥60 ml/m^2 throughout follow-up **(A)**, under medical management **(B),** and post-operatively **(C)**. Note the large mortality difference between LAVI groups. Excess mortality, considerable under medical management, is markedly attenuated after mitral surgery. Figures indicate estimated survival ± SE. DMR = degenerative mitral regurgitation; LAVI = left atrial volume index (in ml/m^2).

10 ml/m^2 for RVol adjustment. LAVI remained independently associated with excess mortality even after additional adjustment for AF (HR: 1.03 [95% CI: 1.01 to 1.06]; p = 0.016), pulmonary hypertension (HR: 1.03 [95% CI: 1.00 to 1.05]; p = 0.022), and tricuspid regurgitation (HR: 1.04 [95% CI: 1.01 to 1.07]; p = 0.0016 per 10 ml/m^2). LAVI remained significant after adjusting for surgery as a time-dependent variable (adjusted HR: 1.07 [95% CI: 1.04 to 1.09] per 10 ml/m^2; p < 0.0001). In all models, LAVI addition increased models' power (all p < 0.0001).

Spline curves displayed excess mortality as HR >1 (Figure 2A) and showed no excess mortality with low LAVI <40ml/m^2, whereas excess mortality steeply increased with LAVI >40 ml/m^2 before tending to flatten out with higher LAVI.

SURVIVAL UNDER MEDICAL MANAGEMENT. Survival under medical management was 79 ± 1% at 5 years and 62 ± 1% at 10 years. Ten-year survival was 78 ± 1% for LAVI <40 ml/m^2, 58 ± 2% for LAVI 40 to 59 ml/m^2, and 34 ± 3% for LAVI ≥60 ml/m^2; p < 0.0001 (Figure 1B). LAVI (continuous) was strongly associated with long-term mortality (univariable HR: 1.22 [95% CI: 1.20 to 1.24]; p < 0.0001 per 10 ml/m^2) (Table 2). Excess mortality was considerably higher with higher LAVI with univariable HRs: 4.36 (95% CI: 3.75 to 5.08; p < 0.0001) for LAVI ≥60 ml/m^2 versus LAVI <40 ml/m^2, 2.27 (95% CI: 1.99 to 2.60; p < 0.0001) for LAVI 40 to 59 ml/m^2 versus <40 ml/m^2,

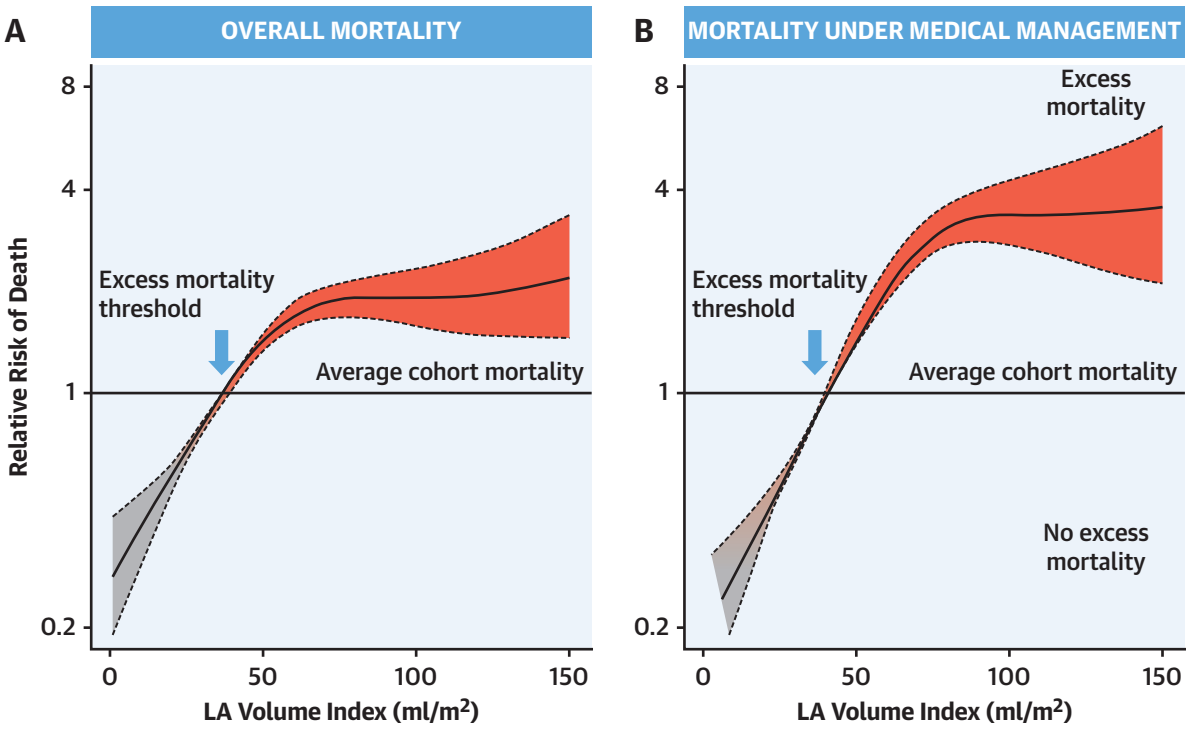
TABLE 2 Univariable and Multivariate HRs of Mortality

		Overall Mortality		Mortality Under Medical Treatment		Post-Operative Mortality	
	LAVI Increment	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Univariable	per 10 ml/m^2	1.12 (1.10-1.14)	<0.0001	1.22 (1.20-1.24)	<0.0001	1.08 (1.04-1.13)	0.0002
	≥60 ml/m^2*	2.51 (2.19-2.88)	<0.0001	4.36 (3.75-5.08)	<0.0001	1.65 (1.08-2.51)	0.02
	40-59 ml/m^2*	1.81 (1.59-2.05)	<0.0001	2.27 (1.99-2.60)	<0.0001	0.94 (0.59-1.50)	0.8
Adjusted on age, sex, and Charlson index (core model)	per 10 ml/m^2	1.06 (1.04-1.08)	<0.0001	1.10 (1.08-1.13)	<0.0001	1.05 (1.00-1.10)	0.03
	≥60 ml/m^2*	1.46 (1.27-1.68)	<0.0001	1.87 (1.59-2.19)	<0.0001	1.33 (0.87-2.04)	0.19
	40-59 ml/m^2*	1.09 (0.96-1.25)	0.18	1.20 (1.05-1.38)	0.009	1.04 (0.65-1.67)	0.86
Further adjustment on LVEF, symptoms and MR grade (comprehensive model)	per 10 ml/m^2	1.05 (1.03-1.08)	<0.0001	1.07 (1.04-1.10)	<0.0001	1.05 (1.00-1.11)	0.05
	≥60 ml/m^2*	1.37 (1.17-1.60)	0.0001	1.55 (1.31-1.84)	0.0001	1.26 (0.80-1.98)	0.3
	40-59 ml/m^2*	1.08 (0.94-1.23)	0.28	1.12 (0.98-1.29)	0.1	1.06 (0.66-1.71)	0.8

*Versus LAVI group <40 ml/m^2.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

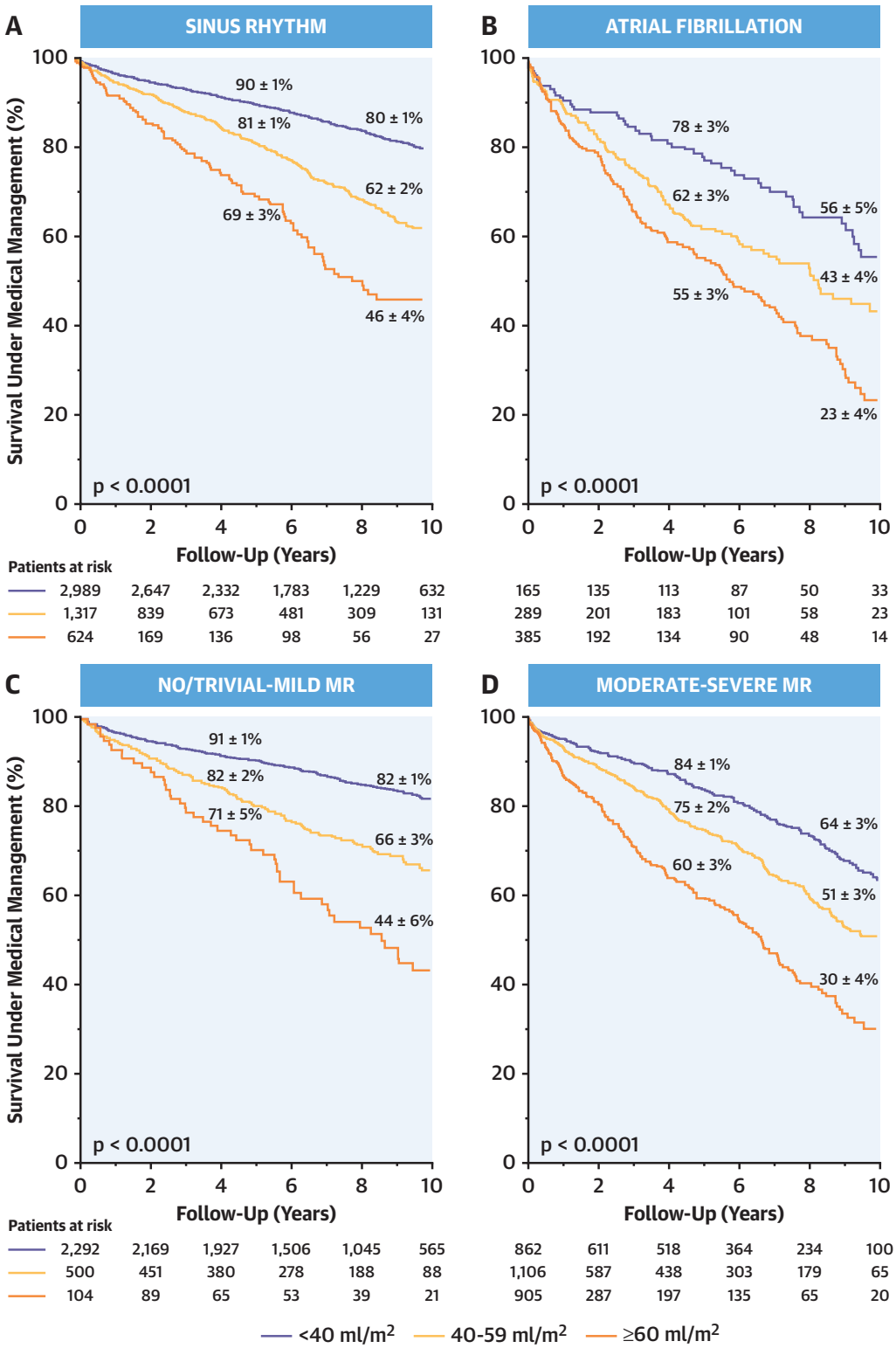
and 1.92 (95% CI: 1.64 to 2.24; p < 0.0001) for LAVI ≥60 ml/m^2 versus 40 to 59 ml/m^2. Stratification by AF or sinus rhythm showed a similar trend for increase in mortality with LAVI enlargement (Figures 3A and 3B). Core-model adjusted HRs for mortality attached to LAVI (per 10 ml/mm^2 LAVI increment) were 1.14 (95% CI: 1.09 to 1.18; p < 0.0001) with sinus rhythm and 1.05 (95% CI: 1.01 to 1.09; p = 0.012) with atrial fibrillation. Stratification by MR grade showed persistent association between enlarged LAVI and outcome (Figures 3C and 3D). Core-model adjusted HRs for mortality attached to LAVI

FIGURE 2 Spline Curves of Mortality Risk According to LAVI



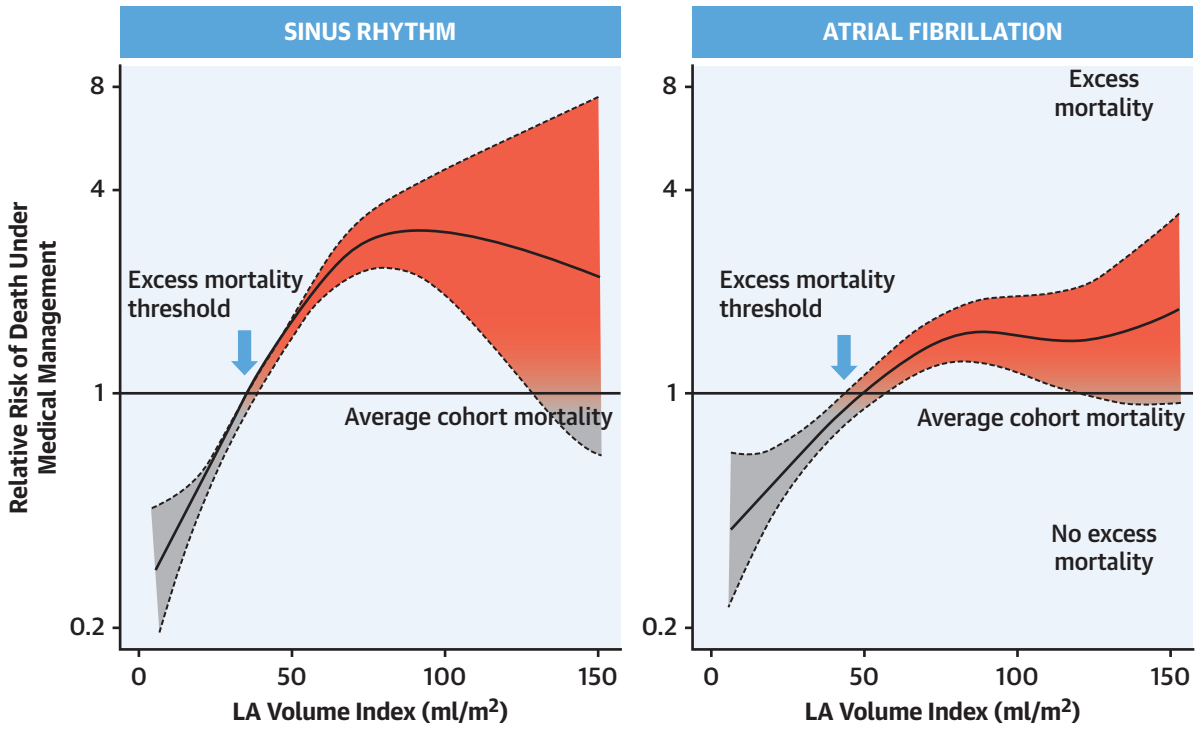
(A) Mortality throughout follow-up and **(B)** mortality under medical management. The line of hazard ratio = 1 represents the average cohort mortality with excess mortality for values >1 with left atrial volume index (LAVI) values on the x-axis. With LAVI approximately ≥40 ml/m^2, excess mortality appears under medical management, rapidly increasing with LAVI. Risk-plateauing trend for markedly high LAVI values is higher under medical management.

FIGURE 3 Impact on Survival of LA Enlargement in Subgroups



Survival under medical management by LAVI categories, stratified by sinus rhythm **(A)** or atrial fibrillation **(B)**, with no/mild DMR **(C)**, and moderate/severe DMR **(D)**. In all groups, patients with LAVI ≥60 ml/m^2 **(orange)** incur much higher mortality than those with LAVI 40 to 59 ml/m^2 **(yellow)** and LAVI <40 ml/m^2 **(purple)**. Abbreviations as in Figure 1.

FIGURE 4 Scale of Mortality Risk According to Baseline Cardiac Rhythm



Spline curves of excess mortality under medical management according to LAVI, in sinus rhythm **(left)** and atrial fibrillation **(right)**, with presentation similar to Figure 2. Note similar intercepts with line of risk = 1 in both subgroups.

(per 10 ml/mm^2) were 1.11 (95% CI: 1.07 to 1.15; $p < 0.0001$) with no to mild MR and 1.03 (95% CI: 1.00 to 1.06; $p < 0.0001$) with moderate to severe MR. Stratification by guideline-based triggers for surgery could not analyze the small group of isolated Class II triggers (n = 254) but showed LAVI adjusted HRs per 10 ml/mm^2 of 1.05 (95% CI: 1.03 to 1.07; $p < 0.0001$) with Class I triggers and 1.06 (95% CI: 1.01 to 1.13; $p = 0.04$) with no baseline surgical trigger.

LAVI's powerful association with mortality under medical management was demonstrated by comparison to expected survival (Online Figure 1) and persisted in multivariable core and comprehensive models (Table 2, center) and after additional adjustment for AF (adjusted HR: 1.05 [95% CI: 1.02 to 1.08]; $p = 0.002$ per 10 ml/m^2), pulmonary hypertension (adjusted HR: 1.04 [95% CI: 1.02 to 1.07]; $p = 0.0018$), and moderate/severe tricuspid regurgitation (adjusted HR: 1.06 [95% CI: 1.03 to 1.09]; $p < 0.0001$). For each adjustment, LAVI added incremental power to the model (all $p < 0.003$).

Excess mortality under medical management (clinically most important outcome unaffected by improved post-surgical survival) occurred around LAVI 40 ml/m^2 in spline curve analysis (Figure 2B), steeply increased between 40 and 60 ml/m^2, and tended to stabilize with markedly elevated LAVI, despite slight continued increasing risk. Thresholds for excess mortality appear slightly higher with AF, but with clear and marked excess mortality in both subgroups with LAVI ≥60 ml/m^2 (Figure 4).

SURVIVAL AFTER MITRAL SURGERY. Post-operative survival was 91 ± 1% at 5 years and 79 ± 1% at 10 years. Ten-year post-operative survival by LAVI categories was 85 ± 3% for LAVI <40 ml/m^2, 86 ± 2% for LAVI 40 to 59 ml/m^2, and 75 ± 3% for LAVI ≥60 ml/m^2; $p = 0.0026$ (Figure 1C). Enlarged LA was univariably associated with long-term mortality (HR: 1.08 [95% CI: 1.04 to 1.13]; $p = 0.0002$ per 10 ml/m^2) (Table 2), particularly for severe LA enlargement (HR: 1.65 [95% CI: 1.10 to 2.55]; $p = 0.02$ for LAVI ≥60 ml/m^2 vs. <40 ml/m^2 and 1.75 [95% CI: 1.23 to 2.52]; $p < 0.0017$ vs. LAVI 40 to 59 ml/m^2). By multivariate analysis, the link between LAVI and mortality was significant but not large (Table 2, right) and was mostly for severe LA enlargement (Figure 1C).

Multivariable Cox proportional hazards analysis with mitral surgery as time-dependent covariate, considering LAVI as continuous or categorical variable, demonstrated that surgery was associated with improved survival in the core model (adjusted HR: 0.53 [95% CI: 0.44 to 0.63]; $p < 0.0001$) and comprehensive model (adjusted HR: 0.43 [95% CI: 0.36 to 0.53]; $p < 0.0001$). See the Online Appendix for complementary analysis.

DISCUSSION

The present study, which gathered for the first time in the context of isolated DMR a considerable cohort of >5,000 patients, with unified diagnosis, extensive characterization of potential confounders/comorbidities, and long-term follow-up, provides unique power to assess the independent link between LA enlargement and long-term mortality (**Central Illustration**). Consecutive eligible patients were all enrolled regardless of DMR severity to minimize bias. Most uniquely, recommended LAVI was measured prospectively by multiple sonographers/cardiologists in routine clinical practice, so that the present results are widely applicable to routine clinical practice.

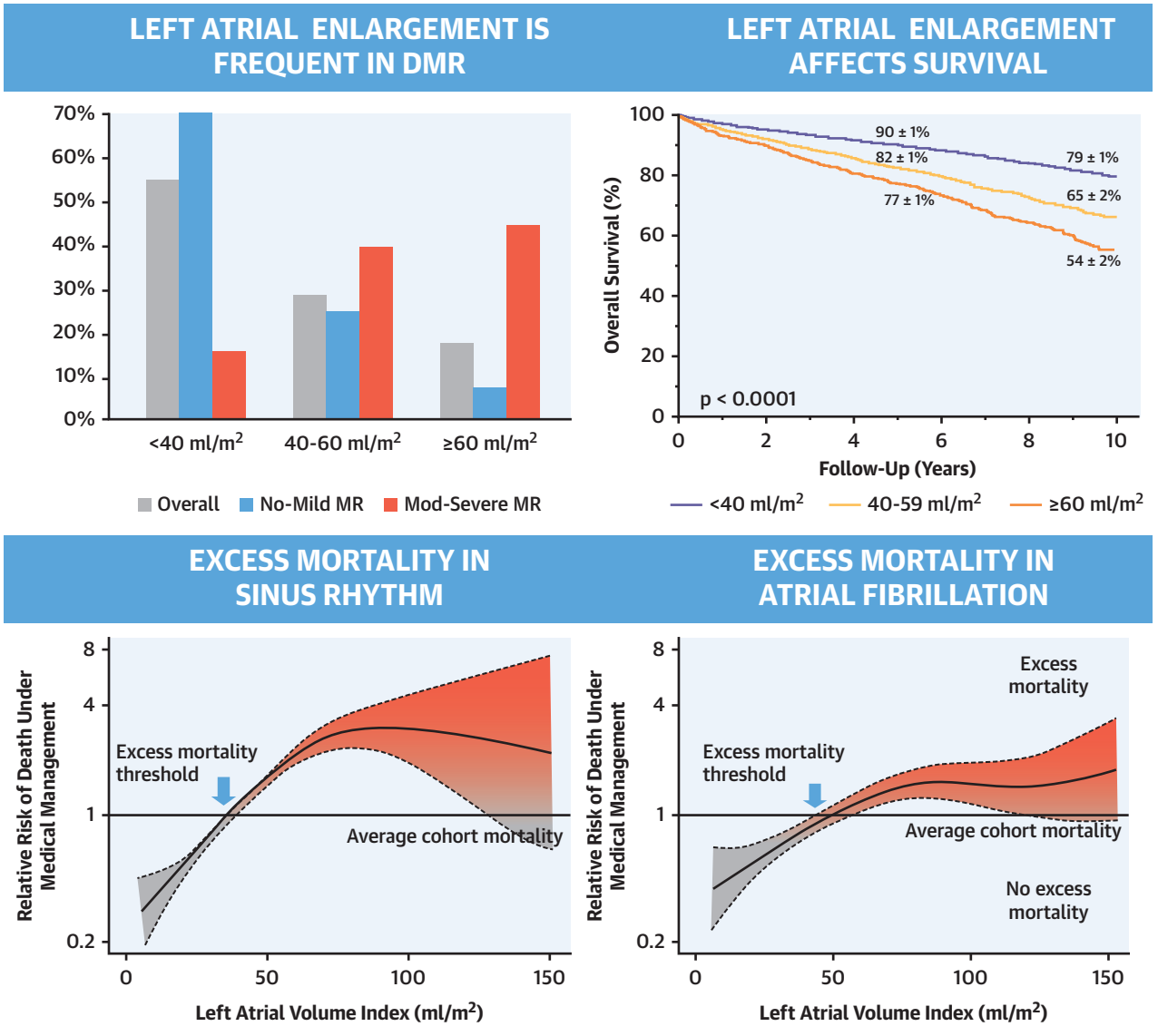
We found that LA enlargement is common at DMR diagnosis and is generally not isolated, observed more often in older patients with more severe MR. However, wide-ranging LA enlargement is observed within each DMR grade, rhythm, or age, demonstrating that LA response to DMR is highly variable between patients. Our main outcome result of major statistical robustness is that higher LAVI is associated with higher mortality throughout follow-up, independently and incrementally to baseline characteristics, including age, comorbidity, MR severity, symptoms, and LVEF. Under medical treatment, considerable mortality is observed independently with LAVI ≥60 ml/m^2 but even with LAVI 40 to 59 ml/m^2 and in all subgroups, including by rhythm and MR severity. Novel spline curve analysis shows excess mortality appearing around 40 ml/m^2 and becoming considerable with LAVI ≥60 ml/m^2. After mitral surgery, excess mortality is mostly alleviated, but our study demonstrates for the first time that it remains detectable for patients with LAVI ≥60 ml/m^2. Therefore, LA enlargement measured by echocardiographic LAVI in routine practice has considerable, independent, and incremental prediction power for survival after DMR diagnosis. The similar HRs per LAVI increment pre- and postoperatively should not deter from indicating surgery based on marked LA enlargement, as surgery considerably reduces the high absolute mortality under medical management associated with LA enlargement to much lower levels (10-year 66% to 25%). Although previous pilot studies involving exclusive experts' measurements hinted at such an impact (12,13), the present new evidence obtained in a large routine practice ascertains the link between LAVI and mortality in DMR within the context of routine practice, and warrants the use of routine LAVI measurements integrated into clinical decision-making for DMR.

LA ENLARGEMENT IN DMR. LA in DMR is the receptacle of RVol and has long been considered a passive bystander, reflecting volume overload (12,15) and progressively expanding in response to MR progression (16). This secondary LA dilatation in-turn results in increased LA compliance (11), which has long been known to maintain lower atrial and pulmonary pressures (10,11), yielding the long asymptomatic phase of severe MR. However, LA response to RVol is not uniform, involving considerable individual variability in our cohort and in previous studies irrespective of cardiac rhythm (12,13). This considerable variability has been supported by episodic reports of giant LA dilatation in mitral valve diseases (17), by animal observations in native canine myxomatous disease (18), and in experimentally induced severe MR (19).

The mechanisms modulating the LA enlargement response to MR are not well understood. Experimental (19,20) and clinical (21,22) studies potentially linked variable LA fibrosis extent to LA enlargement. Variability in neuro-hormonal activation with alterations involving K-channels (23), in patterns of atrial protein expression (18), or cytokine/fibroblast interaction (24) may all contribute to variable LA response to RVol. Genetic variants, such as mutations in the NNPA (25) or MYHA7 (26) gene, may affect LA proteins expression and response to volumetric stimulus. Putative mechanisms warrant clarification, as evidence is mounting that LA enlargement is not a passive bystander but is strongly and independently linked to excess mortality not just in DMR, but also in hypertension (27), in cardiomyopathy (28), with stress testing (29), or in a general population without MR (30). Irrespective of excessive LA enlargement mechanisms, the marked variability of LA response to DMR linked to subsequent survival has considerable implications for DMR management.

DMR OUTCOME AND MANAGEMENT. DMR is the most frequent organic MR and is the most frequent indication for mitral surgery in Western countries (2). Surgical valve repair, feasible in most DMR patients, restores life expectancy with very low operative mortality and MR recurrence rates (31). To indicate mitral surgery, guidelines define few individual

CENTRAL ILLUSTRATION **Left Atrial Enlargement in Degenerative Mitral Regurgitation**



Essayagh, B. et al. J Am Coll Cardiol. 2019;74(7):858–70.

(Top Left) Distribution of left atrial volume index (LAVI) <40, 40 to 59, and ≥60 ml/m^2 in overall cohort **(gray bars)**, with no/mild degenerative mitral regurgitation (DMR) **(blue bars)** and with moderate/severe DMR **(red bars)**. Note high frequency of left atrial (LA) enlargement in response to DMR. **(Top right)** Overall survival stratified by LAVI underscores excess mortality with LA enlargement. **(Bottom)** Spline curves display excess mortality (hazard ratio >1) with higher LAVI in sinus rhythm **(lower left)** and atrial fibrillation **(lower right)**, considerable for LAVI ≥60 ml/m^2.

triggers codifying surgical management similarly in the United States and European Union (6,7). Despite these favorable conditions, recent evidence suggests that a minority of patients with MR ultimately undergo lifesaving interventions (9). Undertreatment, pervasive across continents (9,32), may be due to difficulties in interpreting subjective symptoms and their cause in elderly patients and to rarity of Class I objective triggers for surgery (LVEF <60%, end-systolic diameter ≥40 mm) (33). This conundrum is the major rationale for investigating other potential objective markers of DMR outcome, preceding consideration for inclusion among guideline-recognized triggers for mitral surgery. Increasing

availability of percutaneous approaches (5) reinforces the need for developing extended prognostic markers, which could be combined into widely applicable risk scores (34). Markers being considered, such as exercise testing (35) or B-type natriuretic peptide measurement (36), are variably linked to outcome. We believe that LAVI measurement is a prominent candidate for such a role in DMR. Pilot studies suggested that LA enlargement (12,13), even measured by M-mode (14), contributes to outcome prediction. With recent emphasis on characterizing LA enlargement by LAVI (37), pilot studies suggesting that LAVI measured by few experts may affect outcome (12,13) raise the question of whether these results can be extended to routine clinical practice with LAVI measured by many sonographers/cardiologists. The present study, conducted in a unified MR cause (vs. heterogeneous causes in pilot studies), shows that LAVI measured prospectively by multiple practitioners, despite pressures of routine practice, is independently and incrementally determinant of DMR survival.

The pathophysiological link between LA enlargement and excess mortality is independent of AF but is not fully defined. Irrespective of causal considerations, this link between LAVI and outcome is undeniable. Furthermore, as mitral surgery sizably downgrades mortality risks attached to LA enlargement, LA-associated excess mortality is strongly linked to DMR. DMR is the central cause of mortality and LA enlargement is the consequence; however, mortality is profoundly modulated by individual response to MR, which is not directly treated by surgery but leads to a mitral surgery decision that improves prognosis similarly to existing surgical indications based on MR consequences, such as LV size/function and pulmonary hypertension. Thus, we believe LAVI measurement should be used consistently in patients with DMR. LAVI ≥60 ml/m^2 marks considerable risk, particularly under medical management, but LAVI 40 to 59 ml/m^2 also represents a zone of rapidly increasing risk of excess mortality (a new observation of our study). Because some risk persists after mitral surgery with LAVI ≥60 ml/m^2, consideration may be given to mitral surgery with high-moderate LA enlargement (50 to 59 ml/m^2). High LAVI may also be useful to consider in special circumstances: patients in whom a Class II trigger, particularly AF (38), has been detected but with uncertainty regarding its link to DMR, or patients with ERO inching toward the 40-mm^2 threshold who are now known to incur notable risk (39). In such cases, the excess risk that high LAVI portends may further incentivize reconsidering management, requiring careful clinical interpretation. Such mandatory careful interpretation is not solely necessary for LAVI results integration into management/intervention decisions, as all established surgical triggers require ascertaining their link to DMR rather than to comorbidity. Irrespectively, the present study establishes for the first time that LAVI measured in routine practice provides considerable value for risk prediction in DMR that warrants its consistent use in clinical practice.

STUDY STRENGTHS AND LIMITATIONS. Although we retrospectively identified patients with isolated DMR, LAVI measurements and all characteristics, echocardiographic and clinical data, were prospectively collected at baseline, stored immediately post-measurement, and retrieved electronically without modification. Patients were not entered into protocolized care, and all decisions were made with personal physicians using all information available, including LAVI, which makes our results relevant to routine clinical practice. LA enlargement does not appear in isolation, and potential confounders were addressed by extensive adjustment in survival analysis, made possible by considerable cohort power. In view of access restriction to death certificates to define cardiac deaths and of vagaries of coding hospitalization cause for reimbursement to define cardiac hospitalization, we analyzed the most robust endpoint of overall mortality. Inclusion of AF may be criticized, but its status as a Class II trigger implies clinical interpretation of its significance (6,7), which will be helped by our finding that marked LA enlargement marks poor outcome even with AF. Regarding potential inclusion in guideline criteria, importantly, our study is not a clinical trial defining formal indications for intervention, but rather a cohort outcome study. Such an approach, used for all Class I and II triggers for MR surgery in current guidelines (6,7), is appropriate as prospective trials are unlikely to ever be conducted. Thresholds were different from normalcy-based thresholds for general populations (37), as we used MR-specific legitimate thresholds previously documented as associated with outcome (12,13). MR-specific LAVI thresholds display stronger outcome links (Online Table 1), probably due to frequent LA dilatation with MR. Hence, similarly to LV characterization in MR (6,7), LA characterization using MR-specific thresholds appears most logical; relates to precedents (12,13), European guidelines (7), and spline analysis; and is

effective in all subgroups (Online Table 2). With LAVI's considerable importance in routine DMR assessment, future studies should assess post-operative LA reverse-remodeling.

CONCLUSIONS

The present study demonstrates in a large, consecutive, isolated DMR cohort with prospectively measured LAVI in routine clinical practice that LA enlargement is frequent, displays marked individual variability, and has a powerful, incremental, and independent link to excess mortality after diagnosis, irrespective of rhythm, age, or MR severity at diagnosis. The link between LA enlargement and mortality, particularly strong under medical management and for LAVI ≥60 ml/m^2, is greatly alleviated by mitral surgery, demonstrating its direct link to DMR. Hence, LA enlargement measured by LAVI should be part of comprehensive DMR evaluation and clinical decision-making in routine clinical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with DMR, an enlarged LAVI identifies individuals at increased risk of mortality, independent of the severity of MR or presence of atrial fibrillation.

TRANSLATIONAL OUTLOOK: Further studies are needed to understand the pathophysiological mechanisms linking LA enlargement to prognosis in patients with DMR, including hemodynamic forces, myocardial degeneration, genetics, and other factors.

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KEY WORDS echocardiography, left atrium, mitral regurgitation, mitral valve surgery, survival

APPENDIX For a supplemental figure and tables, please see the online version of this paper.