

# Impact of Left Atrial Volume on Clinical Outcome in Organic Mitral Regurgitation

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<b>Objectives</b>	The purpose of this paper was to assess the link between left atrial (LA) volume at diagnosis and outcome of patients with mitral regurgitation (MR).
<b>Background</b>	Left atrial enlargement is a consequence of organic MR, but its association with clinical outcome independently of MR severity is uncertain.
<b>Methods</b>	We prospectively enrolled 492 patients (age $63 \pm 15$ years, 60% men) in sinus rhythm with organic MR (regurgitant volume $68 \pm 42$ ml/beat) and performed at baseline triple echocardiographic quantitation (MR severity, LA volume, and left ventricular characteristics). Outcome with medical and surgical management was analyzed.
<b>Results</b>	Left atrial volume indexed to body surface area (LA index) was $55 \pm 26$ ml/m <sup>2</sup> ( $<40$ ml/m <sup>2</sup> in 158 patients, 40 to $59$ ml/m <sup>2</sup> in 160 patients, and $\geq 60$ ml/m <sup>2</sup> in 174 patients). Under medical management, 5-year survival was $80 \pm 2.9\%$ and cardiac events $28 \pm 3\%$ . Adjusting for established predictors of outcome, LA index was independently associated with survival after diagnosis (hazard ratio [HR]: 1.3 [95% confidence interval (CI): 1.1 to 1.5] per 10 ml/m <sup>2</sup> increment, $p = 0.001$ ). Patients with LA index $\geq 60$ ml/m <sup>2</sup> had lower 5-year survival than those with no or mild LA enlargement ( $p < 0.0001$ ) and than the rates of survival expected in the U.S. population ( $53 \pm 8.6\%$ vs. $76\%$ , $p = 0.017$ ). Compared with patients with LA index $<40$ ml/m <sup>2</sup> , those with LA index $\geq 60$ ml/m <sup>2</sup> had increased mortality (HR: 2.8 [95% CI: 1.2 to 6.5], $p = 0.016$ ) and cardiac events (HR: 5.2 [95% CI: 2.6 to 10.9], $p < 0.0001$ ) with medical management. Mitral surgery was associated with decreased mortality (HR: 0.46 [95% CI: 0.26 to 0.84], $p = 0.01$ ) and cardiac events (HR: 0.38 [95% CI: 0.23 to 0.62], $p = 0.0001$ ) and after surgery patients with LA index $\geq 60$ ml/m <sup>2</sup> versus $<60$ ml/m <sup>2</sup> did not incur excess mortality or cardiac events (both $p > 0.30$ ).
<b>Conclusions</b>	In organic MR, LA index at diagnosis predicts long-term outcome, incrementally to known predictors of outcome. This marker of risk is particularly important because mitral surgery in these patients markedly improves outcome and restores life expectancy. LA index should be measured in routine clinical practice for risk-stratification and for clinical decision making in patients with organic MR. (J Am Coll Cardiol 2010;56:570-8) © 2010 by the American College of Cardiology Foundation

Mitral regurgitation (MR) is frequent and its prevalence increases with age (1). Previous studies in organic MR (due to intrinsic valve lesions) have shown that patients with symptoms or decreased ejection fraction (EF)  $\leq 60\%$  incur high risk with medical management (2) and require mitral surgery (3,4) but sustain excess mortality post-operatively related to their severe presentation (5,6). Therefore, the

management of patients with MR remains debated (3,4). Whereas 1 study advocates a watchful-waiting strategy in asymptomatic severe MR (7), other studies, single- and multicenter, suggest that MR causes notable risks, improved by mitral surgery (8,9), particularly valve repair (9,10). In view of this controversy, identification of new criteria defining high-risk groups is warranted and has potential to refine management of patients with organic MR.

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Left atrial (LA) enlargement is a pathophysiologic response to volume overload in organic MR, which allows LA pressure homeostasis (11,12). Left atrial volume measure-

ment is now considered superior to LA diameter (13,14), and in the general population, larger LA volume has been associated with atrial fibrillation (15), stroke, congestive heart failure (16), and mortality (17). Left atrial enlargement was also suggested as predictive of outcome in ischemic or nonischemic cardiomyopathy (18,19). Conversely, in patients with atrial fibrillation (AF), LA volume prognostic utility is poor (13), which is probably related to independent AF effect on LA enlargement (14). In patients with organic MR, LA size is a marker for subsequent AF (14,20,21). However, actual impact of LA volume on outcome, particularly survival after diagnosis under medical and surgical management, and its usefulness in managing patients with organic MR, are poorly defined. To examine the hypothesis that LA volume predicts survival independently of MR severity, we prospectively enrolled patients with chronic organic MR in sinus rhythm and prospectively performed triple quantitation of LA volume, MR severity, and left ventricular (LV) characteristics to evaluate the predictive value of LA volume measured at diagnosis on outcome with medical or surgical management.

## Methods

**Study eligibility.** Between 1990 and 2000, we prospectively enrolled patients: 1) with at least mild organic MR (intrinsic mitral valve lesions); 2) in sinus rhythm at baseline; and 3) in whom triple quantitation of LA volume, LV volumes, and MR severity was available. Patients with papillary muscle rupture, functional MR, associated mitral valve stenosis of any degree, associated aortic or congenital heart disease, or previous valvular surgery were excluded. Patients with symptoms or decreased EF in the context of organic MR were not excluded. The study was approved by the Mayo Clinic Institutional Review Board.

**Doppler-echocardiographic measurements.** Comprehensive Doppler and 2-dimensional echocardiography provided data prospectively recorded and used as measured at diagnosis without alteration. Patients underwent triple quantitation of LV characteristics (volumes and mass), LA volume, and MR. Left ventricular volumes (biplane modified Simpson rule) and EF were measured from apical views. Left atrial volume was calculated using the apical biplane area-length method (14,22) and indexed to body surface area (LA index). Left atrium is enlarged with LA index  $\geq 40$  ml/m<sup>2</sup>, a threshold previously defined in a normal population (14). Accordingly, patients were stratified in 3 subgroups, as LA index within normal range ( $<40$  ml/m<sup>2</sup>, n = 158), mildly enlarged LA index (40 to 59 ml/m<sup>2</sup>, n = 160), and severely enlarged LA index ( $\geq 60$  ml/m<sup>2</sup>, n = 174).

Mitral regurgitation was quantified by at least 2 of 3 validated methods, averaged to calculate regurgitant volume (RVol) and effective regurgitant orifice area (ERO). Methods used were the proximal-isovelocity-surface-area method (23) in 391 patients, quantitative Doppler method (using mitral and aortic stroke volumes) in 485 and quantitative

2-dimensional method (using LV volumes and aortic stroke volume) in all patients (22). Because ERO was not measurable in 32 patients, RVol, which has similar prognostic value as ERO (8) and was consistently measurable in all patients, was used as measure of MR severity (mild MR:  $<30$  ml/beat, moderate MR: 30 to 59 ml/beat, and severe MR:  $\geq 60$  ml/beat) (24). Mitral flow profile recorded, from apical views at leaflets' tips, diastolic E and A velocities, E-wave deceleration time, and E/A ratio. Tricuspid regurgitant velocity (continuous-wave Doppler) allowed calculation of pulmonary artery systolic pressure.

**Clinical assessment and follow-up.** Baseline clinical characteristics were recorded at diagnosis. Symptomatic patients were those with frank dyspnea with exercise or at rest. Coronary disease diagnosis was based on a history of myocardial infarction or on angiography during the episode of care. Integrated Charlson comorbidity score was calculated. Clinical outcome was monitored by return visits, mailed questionnaires, review of medical records, and by telephone calls to patients, referring cardiologists, and primary care physicians. The patient's personal physician using all information available conducted, independently of investigators, clinical management and decided follow-up and surgical timing, guided by available recommendations. Cause of death was classified as cardiovascular or noncardiovascular according to death certificates, next-of-kin interview, and hospital and autopsy records. Congestive heart failure was diagnosed during follow-up using a combination of major and minor criteria recommended by the Framingham Heart Study (25). Electrocardiogram confirmation of AF was required.

**Statistical analysis.** Continuous variables are summarized as mean  $\pm$  SD and compared between groups using 1-way analysis of variance or Student *t* tests. Post hoc comparisons used Bonferroni tests. Non-normally distributed variables (Charlson index) comparisons used nonparametric Kruskal-Wallis test. Categorical data were compared using chi-square tests. End points with conservative management were overall survival and combined cardiac events end point (cardiac death/AF/congestive heart failure), with follow-up censored at mitral surgery if performed. Surgery's effect on outcome was analyzed as time-dependent covariate using the entire follow-up, and survival curves were constructed accordingly. Event rates, estimated using Kaplan-Meier method, were compared using log-rank test. Observed mortality was compared to that expected in the U.S. population using log-rank test. Univariate and multivariate Cox proportional hazards analyzed LA index prediction of mortality and cardiac events with calculation of hazard ratios (HRs). Multivariate

## Abbreviations and Acronyms

<b>AF</b>	= atrial fibrillation
<b>EF</b>	= ejection fraction
<b>ERO</b>	= effective regurgitant orifice
<b>LA</b>	= left atrium/atrial
<b>LA index</b>	= left atrial volume indexed to body surface area
<b>LV</b>	= left ventricle
<b>MR</b>	= mitral regurgitation
<b>RVol</b>	= regurgitant volume

analyses adjusted for known predictive variables (age, sex, symptoms, EF, regurgitant volume). A value of  $p < 0.05$  was considered statistically significant.

## Results

**Baseline characteristics.** Baseline characteristics (Table 1) demonstrate usual predominance of degenerative MR (prolapse in 81%, rheumatic in 5%, and miscellaneous in remainder of patients), in older men with rare symptoms at presentation. Mitral regurgitation grade was mild in 110 (22%), moderate in 110 (22%), and severe in 272 (56%) patients by quantitative criteria (24). Regurgitant volume averaged  $68 \pm 42$  ml, ERO  $42 \pm 29$  mm<sup>2</sup>, LV diameter index  $31 \pm 4$  mm/m<sup>2</sup> (end diastole) and  $19 \pm 4$  mm/m<sup>2</sup> (end systole), LA volume  $103 \pm 49$  ml, and LA index  $55 \pm 26$  ml/m<sup>2</sup>. Left atrial index was  $67 \pm 26$  ml/m<sup>2</sup> in severe MR compared with  $47 \pm 16$  ml/m<sup>2</sup> ( $p < 0.0001$ ) in moderate MR. Medical therapy included angiotensin-converting enzyme inhibitors in 225 (46%) patients, angiotensin-receptor blocker in 110 (22%) patients, calcium-channel blocker in 135 (27%) patients, diuretic in 188 (38%) patients, and beta-blocker in 177 (36%) patients.

Baseline characteristics stratified by LA index  $<40$ , 40 to 59, and  $\geq 60$  ml/m<sup>2</sup> are shown Table 1. With higher LA index, patients were older, were more often men and symp-

tomatic, had more severe MR mostly related to prolapse, and had larger LV remodeling and hypertrophy. Despite LA enlargement, higher LA index was associated with higher pulmonary artery systolic pressure and early filling due to MR. Of note, patients with larger LA had no excess coronary disease, comorbidity (Charlson index mean and 25% to 75% quartiles: 0.75 [0 to 1], 0.82 [0 to 1], 0.78 [0 to 1] for LA index  $<40$ , 40 to 59, and  $\geq 60$ ,  $p = 0.68$ ) or hypertension.

**LA index and survival.** During follow-up, 54 patients died under conservative management (5-year survival:  $80 \pm 2.9\%$ ) and 35 of cardiovascular cause (5-year cardiovascular mortality:  $14 \pm 2.6\%$ ). In univariate analysis (Table 2), LA enlargement strongly predicted mortality under conservative management (HR: 1.3 [95% confidence interval (CI): 1.2 to 1.5] per 10 ml/m<sup>2</sup> LA index increment,  $p < 0.0001$ ), specifically with LA index  $\geq 60$  ml/m<sup>2</sup> but not significantly with LA index 40 to 59 ml/m<sup>2</sup>. Patients with LA index  $\geq 60$  ml/m<sup>2</sup> incurred lower 5-year survival ( $53 \pm 8.6\%$ ) compared with LA index 40 to 59 ml/m<sup>2</sup> ( $84 \pm 4.8\%$ ) and  $<40$  ml/m<sup>2</sup> ( $90 \pm 3\%$ ,  $p < 0.0001$ ) (Fig. 1). Difference in survival between LA index 40 to 59 and  $<40$  ml/m<sup>2</sup> did not reach significance ( $p = 0.26$ ).

Comparison to expected survival in the population showed no difference with LA index  $<40$  ml/m<sup>2</sup> (expected 88%,  $p = 0.81$ ) or 40 to 59 ml/m<sup>2</sup> (expected 86%,  $p =$

**Table 1** Baseline Clinical and Echocardiographic Characteristics of the Entire Patient Population and Stratified by Categories of LA Index

	All Patients (n = 492)	LA Index, ml/m <sup>2</sup>			p Value
		$<40$ (n = 158)	40 to 59 (n = 160)	$\geq 60$ (n = 174)	
Age, yrs	$62 \pm 15$	$60 \pm 15$	$62 \pm 15$	$65 \pm 14^*$	0.003
Men, n (%)	296 (60)	75 (48)	97 (61)*	124 (71)††	$<0.0001$
Symptoms, n (%)	44 (8.9)	1 (0.6)	12 (7.5)*	31 (18)††	$<0.0001$
BSA, m <sup>2</sup>	$1.86 \pm 0.21$	$1.83 \pm 0.21$	$1.87 \pm 0.21$	$1.88 \pm 0.21$	0.08
Systolic BP, mm Hg	$135 \pm 19$	$136 \pm 21$	$134 \pm 18$	$133 \pm 18$	0.37
Diastolic BP, mm Hg	$79 \pm 10$	$78 \pm 10$	$77 \pm 9$	$76 \pm 10$	0.23
Hypertension, n (%)	189 (38)	68 (43)	62 (39)	59 (34)	0.44
Coronary artery disease, n (%)	45 (9.1)	14 (8.9)	12 (7.5)	19 (10)	0.80
Valve prolapse, n (%)	398 (81)	98 (62)	137 (86)†	163 (94)††	$<0.0001$
RVol, ml/beat	$68 \pm 42$	$37 \pm 27$	$65 \pm 32†$	$100 \pm 42†§$	$<0.0001$
ERO, mm <sup>2</sup>	$42 \pm 29$	$22 \pm 16$	$38 \pm 22†$	$63 \pm 30†§$	$<0.0001$
LVD, mm	$56 \pm 8$	$51 \pm 6$	$56 \pm 6†$	$61 \pm 8†§$	$<0.0001$
LVS, mm	$34 \pm 7$	$31 \pm 5$	$35 \pm 6†$	$37 \pm 7††$	$<0.0001$
LV mass, g/m <sup>2</sup>	$113 \pm 27$	$95 \pm 24$	$114 \pm 23†$	$128 \pm 24†§$	$<0.0001$
LV EDVI, ml/m <sup>2</sup>	$109 \pm 28$	$88 \pm 19$	$107 \pm 23†$	$130 \pm 25†§$	$<0.0001$
LV ESVI, ml/m <sup>2</sup>	$34 \pm 14$	$28 \pm 10$	$32 \pm 13^*$	$39 \pm 15†§$	$<0.0001$
EF, %	$69 \pm 8$	$68 \pm 8$	$71 \pm 8^*$	$70 \pm 8$	0.03
Mitral E-wave, cm/s	$99 \pm 31$	$85 \pm 24$	$96 \pm 31^*$	$115 \pm 30†§$	$<0.0001$
Mitral E/A	$1.5 \pm 0.8$	$1.3 \pm 0.5$	$1.5 \pm 0.9$	$1.8 \pm 0.8††$	$<0.0001$
Mitral DT, ms	$209 \pm 45$	$211 \pm 41$	$210 \pm 46$	$206 \pm 47$	0.59
LA index, ml/m <sup>2</sup>	$55 \pm 26$	$30 \pm 6$	$49 \pm 6$	$83 \pm 21$	—
PASP, mm Hg	$39 \pm 13$	$34 \pm 6$	$35 \pm 8$	$45 \pm 16††$	$<0.0001$

\* $p < 0.05$  versus LA index  $<40$  ml/m<sup>2</sup>; † $p < 0.0001$  versus LA index  $<40$  ml/m<sup>2</sup>; ‡ $p < 0.05$  versus LA index 40 to 59 ml/m<sup>2</sup>; § $p < 0.0001$  versus LA index 40 to 59 ml/m<sup>2</sup>.

BP = blood pressure; BSA = body surface area; DT = deceleration time; EF = ejection fraction; ERO = effective regurgitant orifice; ESVI = left ventricular end-systolic volumes indexed (normalized to body surface area); LA index = left atrial volume indexed to body surface area; LVD = left ventricular end-diastolic diameter; LV EDVI = left ventricular end-diastolic volumes indexed (normalized to body surface area); LVS = left ventricular end-systolic diameter; PASP = pulmonary artery systolic pressure; RVol = regurgitant volume.

Table 2	Risk of Death and Cardiac Events Among Patients With Chronic Organic MR in Sinus Rhythm Under Medical Management				
	Death		Cardiac Event		
	HR (95% CI)	p Value	HR (95% CI)	p Value	
Unadjusted					
Per 10 ml/m <sup>2</sup> increment in LA index	1.3 (1.2–1.5)	<0.0001	1.4 (1.3–1.5)	<0.0001	
LA index 40 to 59 ml/m <sup>2</sup> *	1.5 (0.97–3.0)	0.29	2.1 (1.1–3.8)	0.026	
LA index ≥ 60 ml/m <sup>2</sup> *	4.2 (2.2–8.1)	<0.0001	6.7 (3.9–11.8)	<0.0001	
Adjusted†					
Per 10 ml/m <sup>2</sup> increment in LA index	1.3 (1.1–1.5)	0.001	1.3 (1.1–1.5)	<0.0001	
LA index 40 to 59 ml/m <sup>2</sup> *	1.4 (0.7–3.0)	0.34	2.8 (1.5–5.5)	0.001	
LA index ≥60 ml/m <sup>2</sup> *	2.8 (1.2–6.5)	0.016	5.2 (2.6–10.9)	<0.0001	

Cardiac events are defined as death from cardiovascular causes, heart failure, and atrial fibrillation. \*The reference group was made-up of the patients with a LA index <40 ml/m<sup>2</sup>. †HRs adjusted for age, sex, symptoms, ejection fraction, and regurgitant volume.  
CI = confidence interval; HR = hazard ratio; LA index = left atrial volume indexed to body surface area; MR = mitral regurgitation.

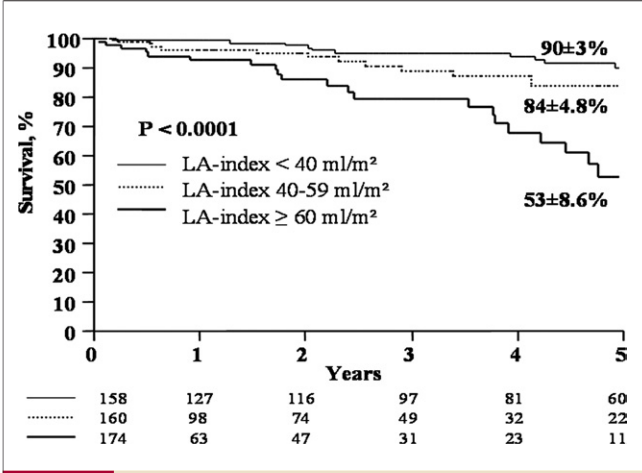
0.90). However, survival was significantly lower than expected in patients with LA index ≥60 ml/m<sup>2</sup> (expected 76%, p = 0.017).

In multivariate analysis, adjusting for age, sex, symptoms, EF, and regurgitant volume, LA index independently predicted survival (HR: 1.3 [95% CI: 1.1 to 1.5] per 10 ml/m<sup>2</sup> increment and 2.8 [95% CI: 1.2 to 6.5] for LA index ≥60 ml/m<sup>2</sup>) (Table 2). After further adjustment for Charlson comorbidity index, LA index predictive value remained unchanged (HR: 2.9 [95% CI: 1.3 to 6.7], p = 0.009).

**LA index and cardiac events.** During follow-up with medical management, 32 patients experienced new onset of AF (5-year: 10.9 ± 2.1%) and 49 patients experienced heart failure (5-year: 16.9 ± 2.6%). Thus, 86 patients experienced a cardiac event (5-year: 28 ± 3%) during follow-up under conservative management.

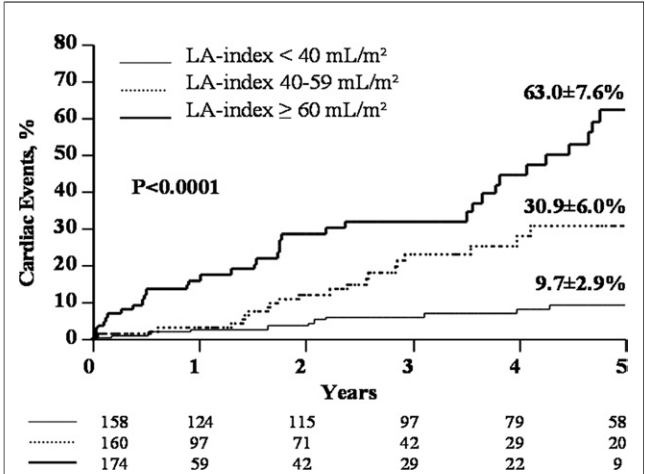
In univariate analysis (Table 2), LA enlargement strongly predicted cardiac events under conservative management. Patients with LA index ≥60 ml/m<sup>2</sup> had frequent cardiac events (5-year: 63 ± 8%) versus 40 to 59 ml/m<sup>2</sup> (31 ± 6%) and <40 ml/m<sup>2</sup> (9.7 ± 3%, p < 0.0001) (Fig. 2). Patients with LA index 40 to 59 ml/m<sup>2</sup> had cardiac events more frequent than with LA index <40 ml/m<sup>2</sup> (p = 0.002) but lower than with LA index ≥60 ml/m<sup>2</sup> (p < 0.0001).

In multivariate analysis, adjusting for age, sex, symptoms, EF, and regurgitant volume, LA index independently predicted cardiac events under conservative management (Table 2). The LA index link to cardiac events remained unchanged after further adjustment for Charlson comorbidity index (HR: 5.4 [95% CI: 2.7 to 11.0] for LA index ≥60 ml/m<sup>2</sup>), coronary artery disease, LV mass, or pulmonary pressure (all p < 0.0001).



**Figure 1** Survival After Diagnosis According to LA Volume

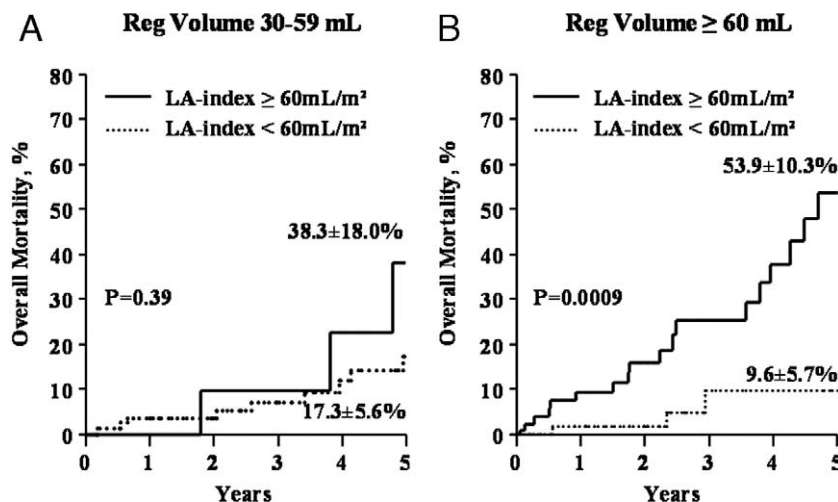
Survival after diagnosis under medical management in patients with organic mitral regurgitation in sinus rhythm at baseline according to stratification by left atrial volume indexed to body surface area (left atrial index <40, 40 to 59, or ≥60 ml/m<sup>2</sup>). Note that patients with left atrial index ≥60 ml/m<sup>2</sup> incur lower survival than patients with smaller left atrium and also incur excess mortality compared with that expected in the normal population (5-year observed survival: 53% vs. 76% expected, p = 0.017). LA index = left atrial volume indexed to body surface area.



**Figure 2** Cardiac Events After Diagnosis According to LA Volume

Rates of cardiac events (cardiac death, atrial fibrillation, or congestive heart failure) after diagnosis under medical management in patients with organic mitral regurgitation in sinus rhythm at baseline according to stratification by left atrial volume indexed to body surface area (left atrial index <40, 40 to 59, or ≥60 ml/m<sup>2</sup>). Note that all event rates are significantly different from each other (all p < 0.01). Abbreviation as in Figure 1.





**Figure 3** Mortality Associated With LA Enlargement, Stratified by Regurgitant Volume

Overall mortality under medical management according to left atrial index ( $<60$  or  $\geq 60$  mL/m<sup>2</sup>) in patients with moderate (A) or severe (B) mitral regurgitation at baseline. Note that mortality is particularly in patients with both severe mitral regurgitation and severe left atrial enlargement. Abbreviation as in Figure 1.

**Subgroup analysis.** Outcome analysis was stratified by RVol and LA index. Among 110 patients with RVol 30 to 59 mL, 18 had LA index  $\geq 60$  and 92 LA index  $< 60$  mL/m<sup>2</sup>, and among 272 patients with RVol  $\geq 60$  mL/beat, 151 had LA index  $\geq 60$  and 121 LA index  $< 60$  mL/m<sup>2</sup>.

Higher mortality under conservative management associated with LA index  $\geq 60$  mL/m<sup>2</sup> was considerable in patients with RVol  $\geq 60$  mL/beat (5-year:  $54 \pm 10\%$  vs.  $10 \pm 6\%$ ,  $p = 0.0009$ ) but did not reach significance with RVol 30 to 59 mL/beat (5-year:  $38 \pm 18\%$  vs.  $17 \pm 6\%$ ,  $p = 0.39$ ) (Fig. 3). In patients with RVol  $\geq 60$  mL/beat, observed long-term mortality was higher than expected with LA index  $\geq 60$  mL/m<sup>2</sup> (expected 27%,  $p = 0.041$ ) but was not different with LA index  $< 60$  mL/m<sup>2</sup> (expected 16%,  $p = 0.11$ ). Similarly, with RVol 30 to 59, observed long-term mortality was higher than expected with LA index  $\geq 60$  mL/m<sup>2</sup> (expected 19%,  $p = 0.0023$ ) but was not different with LA index  $< 60$  mL/m<sup>2</sup> (expected 14%,  $p = 0.72$ ).

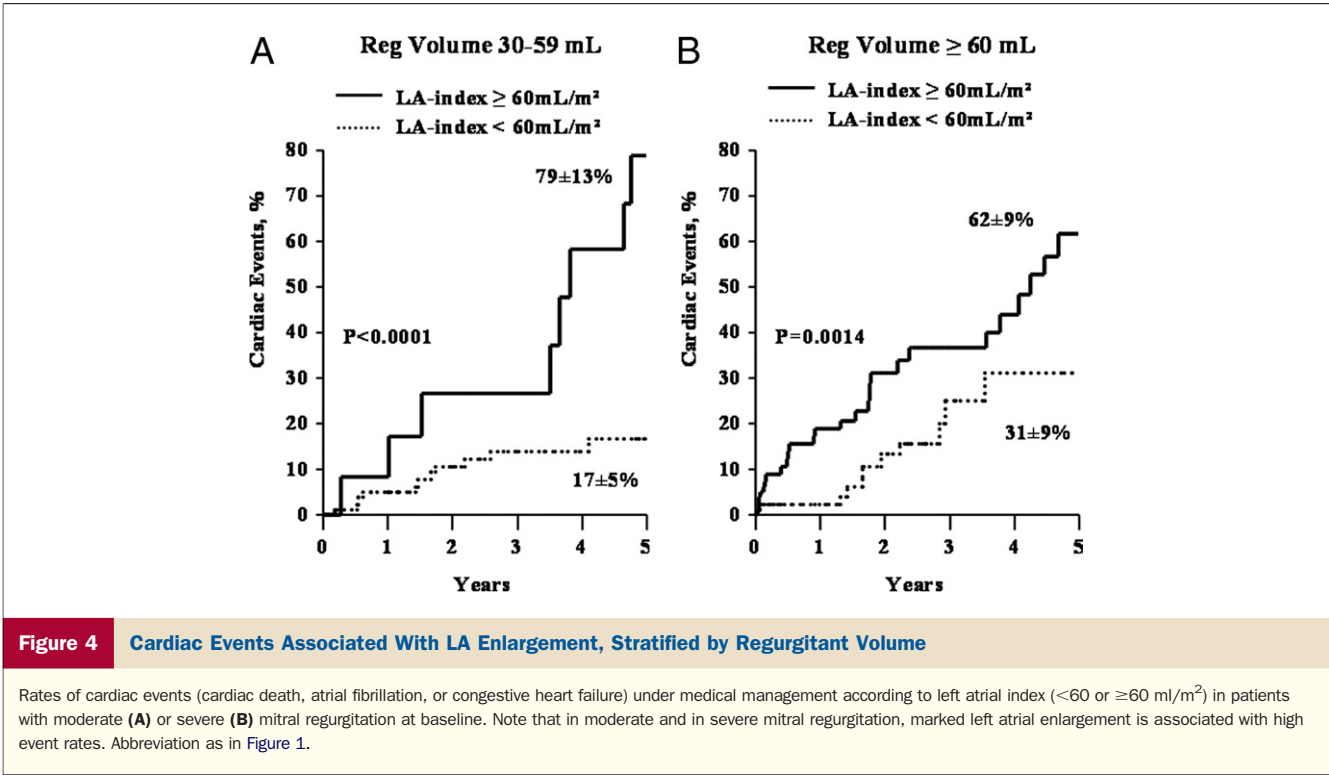
Cardiac events were more frequent with LA index  $\geq 60$  mL/m<sup>2</sup> whether they had RVol  $\geq 60$  mL/beat (5-year:  $62 \pm 9\%$  vs.  $31 \pm 9\%$ ,  $p = 0.0014$ ) or 30 to 59 mL/beat (5-year:  $79 \pm 13\%$  vs.  $17 \pm 5\%$ ,  $p < 0.0001$ ) (Fig. 4).

Patients with severe MR (RVol  $\geq 60$  mL/beat) and symptoms or EF  $< 60\%$  ( $n = 52$ ) were followed medically for  $0.5 \pm 1.16$  years and surgery was delayed because patients were initially felt to be well under medical treatment. Excluding these patients, and analyzing only patients without class I surgical indication by guidelines, results were unchanged. Indeed, LA index predicted mortality (HR: 1.25 [95% CI: 1.07 to 1.44] per 10 mL/m<sup>2</sup>,  $p < 0.01$  or 2.9 [95% CI: 1.24 to 6.5] for LA index  $\geq 60$  mL/m<sup>2</sup>,  $p = 0.015$ ) and cardiac events (HR: 1.29 [95% CI: 1.15 to 1.44] per 10 mL/m<sup>2</sup>,  $p < 0.0001$  or 5.4 [95% CI: 2.6 to 11.4] for LA index  $\geq 60$  mL/m<sup>2</sup>,

$p < 0.0001$  and 2.8 [95% CI: 1.5 to 5.4] for LA index 40 to 59 mL/m<sup>2</sup>,  $p < 0.001$ ).

**Mitral valve surgery and outcome.** Mitral surgery was ultimately performed in 265 patients, involving valve repair in 240 patients (90.6%) and valve replacement in 25 patients (mechanical:  $n = 18$ , bioprosthesis:  $n = 7$ ). Forty patients (15.1%) underwent concomitant coronary bypass surgery and 7 had a Maze procedure. As expected, patients who underwent surgery after diagnosis versus those who remained medically managed, had larger RVol ( $89 \pm 37$  mL vs.  $43 \pm 32$  mL,  $p < 0.001$ ) and LA index ( $63 \pm 25$  mL/m<sup>2</sup> vs.  $46 \pm 23$  mL/m<sup>2</sup>,  $p < 0.001$ ). During total follow-up (including pre- and post-operative period), 80 patients died (survival:  $85 \pm 1.8\%$  5 years after diagnosis), and 26 patients died after mitral surgery (survival:  $91 \pm 2.0\%$  5 years after surgery). New onset AF occurred in 26 patients and heart failure in 15 patients. There was no difference in post-operative outcome after stratification by pre-operative LA index  $\geq 60$  or  $< 60$  mL/m<sup>2</sup> (5-year post-operative mortality:  $9.1 \pm 2.0\%$  vs.  $8.7 \pm 2.8\%$ ,  $p = 0.98$ ; and cardiovascular events:  $20 \pm 3.9\%$  vs.  $16.8 \pm 3.9\%$ ,  $p = 0.34$ ).

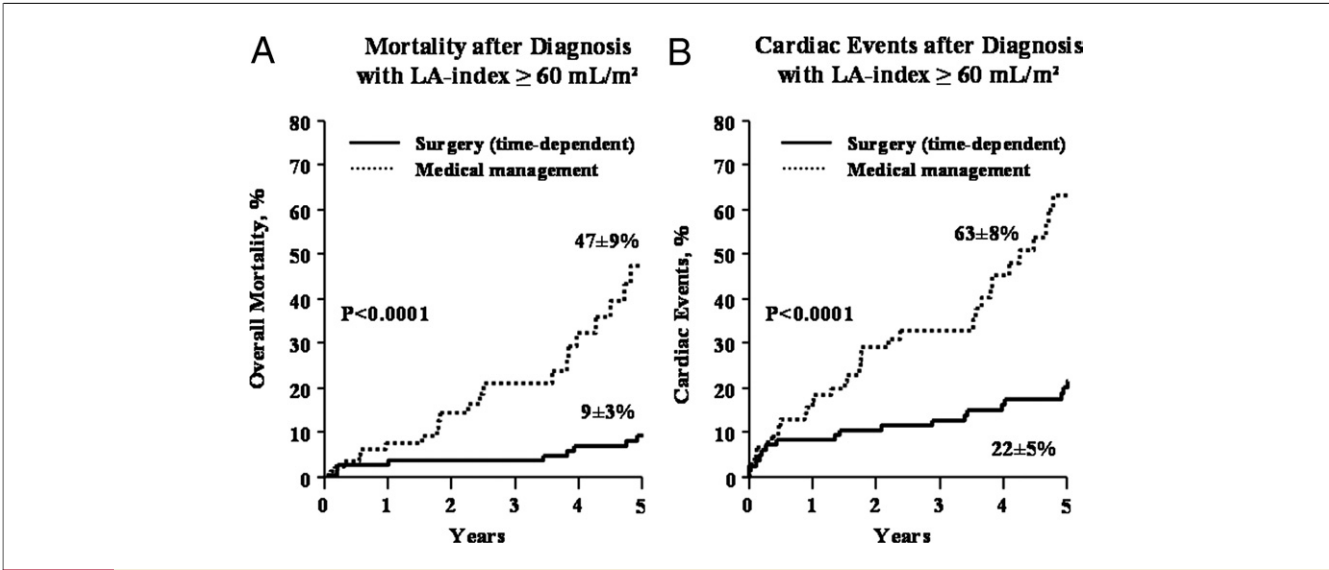
Cox proportional hazards analysis with mitral surgery as time-dependent covariate demonstrated that surgery was associated with improved survival univariately (HR: 0.46 [95% CI: 0.29 to 0.75];  $p = 0.0016$ ). Accounting for the younger age and more frequent male sex of operated patients, in multivariate analysis adjusted for age, sex, symptoms, regurgitant volume, EF, and LA index, mitral surgery remained associated with improved survival (HR: 0.46 [95% CI: 0.26 to 0.84];  $p = 0.01$ ). Likewise, surgery was associated with decreased cardiac events univariately (HR: 0.56 [95% CI: 0.37 to 0.83];  $p = 0.0045$ ) and after



adjustment (0.38 [95% CI: 0.23 to 0.62];  $p = 0.0001$ ). In patients with LA index  $\geq 60 \text{ mL/m}^2$ , mitral surgery (as time-dependent variable) was particularly beneficial compared with medical management, with decreased mortality ( $9 \pm 3\%$  vs.  $47 \pm 9\%$ ; HR: 0.19 [95% CI: 0.09 to 0.38];  $p = 0.001$ ) (Fig. 5A) and cardiac events ( $22 \pm 5\%$  vs.  $63 \pm 8\%$ ; HR: 0.22 [95% CI: 0.12 to 0.39];  $p = 0.001$ ) (Fig. 5B).

Discussion

The present prospective study focused on the influence of LA enlargement on prognosis in patients with organic MR in sinus rhythm at diagnosis. In this large cohort of patients with organic MR, we observed that baseline LA index strongly and independently predicts survival in patients with



**Figure 5 Outcome in Patients With Markedly Enlarged LA Compared Between Surgical and Medical Management**

Overall mortality (A) and cardiac events (B) over the entire follow-up compared between surgical management performed during follow-up (surgery is a time-dependent variable) and medical management in patients with LA index  $\geq 60 \text{ mL/m}^2$  at baseline. Note that for both mortality and cardiac events, there is a marked outcome benefit to the surgical approach in these patients with markedly dilated LA. Abbreviation as in Figure 1.

organic MR, adjusting for known predictors of survival. Marked LA enlargement (LA index  $\geq 60$  ml/m<sup>2</sup>) is associated with excess mortality in patients with organic MR compared with expected mortality in the population. Left atrial index is also a powerful predictor of cardiac events (cardiac death, congestive heart failure, AF) under medical management with moderate or severe MR. Mitral surgery is associated with improvement of outcome, particularly in patients with LA index  $\geq 60$  ml/m<sup>2</sup>. Importantly, although marked LA enlargement is a marker of high risk under medical management, it is not associated with untoward effects after mitral surgery, so that it allows restoration of life expectancy after surgical correction of MR. Therefore, assessment of LA enlargement by measuring LA index should be performed routinely in patients with organic MR and used in considering surgical treatment.

**Influence of MR on LA remodeling.** Left atrial enlargement is frequent in chronic organic MR (2,14,20), is progressive (12,26), and is understood as compensatory response to volume overload (11,12,14), resulting in increased atrial compliance and contributing to persistently normal atrial and pulmonary pressures (11,12). Hence, progressive LA enlargement due to organic MR is considered as a mechanism delaying occurrence of symptoms and heart failure.

In the present study, patients with higher LA enlargement had higher RVol and LV volumes, confirming its general link to the volume overload due to MR, which elicits LA (2,14,20,27) and LV remodeling (28,29) in organic MR. However, there is considerable individual variability in LA enlargement, which is potentially linked to LV diastolic impairment (30) and end-diastolic pressure elevation (29) that affect LA pressure and further remodeling (31). Whereas normal LA is compliant with low pressure, it stretches and stiffens with chronic stress (32). Organic MR induces LA remodeling with atrial interstitial fibrosis experimentally (33) and in humans seen at a late stage (34) impairing LA elastic properties and compliance with elevated LA pressure (11,29,35,36). Indeed, in organic MR, higher LA enlargement is associated with paradoxically higher pulmonary pressure (14) and with marked hormonal (B-natriuretic peptide) activation (37) and reduced functional capacity (38). Hence, marked LA enlargement is not just a benign compensatory mechanism but likely reflects severe consequences of volume overload in organic MR with important implications for outcome.

**LA enlargement and outcome in organic MR.** The size of LA is considered a predictor of AF occurrence (15), which is logical but is potentially tainted by the fact that LA enlargement may be the consequence of previous undetected paroxysmal AF (14). However, it is more consequential that LA enlargement predicts poor outcomes in various clinical (18,19) or epidemiological (16,17,39) circumstances. In organic MR, LA enlargement predicts future AF (14,20,21) and limited observations suggest that it is associated with subsequent occurrence of heart failure (2). The present

study confirms and most importantly extends these observations by demonstrating for the first time the strong value of LA index measured at diagnosis, in predicting death or cardiac events under conservative management, independently of known outcome predictors in patients with organic MR in sinus rhythm at diagnosis.

Patients with LA index  $\geq 60$  ml/m<sup>2</sup> incur excess mortality under medical management compared with the U.S. population and compared with patients with MR and lower LA enlargement, even after adjustment and stratification by RVol. Furthermore, LA index  $\geq 60$  ml/m<sup>2</sup> also strongly and independently predicts cardiac events with medical management, even after adjustment and stratification by RVol. Less severe LA enlargement (LA index 40 to 59 ml/m<sup>2</sup>) had less notable consequences on survival after diagnosis. Severe LA enlargement, complicating severe or even moderate regurgitation, is thus a harbinger of poor outcome in patients with organic MR, even in those without symptoms and with preserved LVEF. Therefore, LA volume should be part of comprehensive echocardiographic examination and should be used in considering surgical treatment in patients with severe organic MR.

**Effect of surgery on prognosis.** Mitral valve surgery improves symptoms and outcome in symptomatic patients with severe chronic MR, particularly with valve repair (3,4). Class I indications for surgery are based on symptoms or LV dysfunction in current guidelines (3,4). Nevertheless, optimal timing of surgery in organic MR remains debated (3,4,7–9). Indeed, patients operated on after they become symptomatic or after developing LV dysfunction incur excess mortality after surgery (5,6) so that such rescue surgery leaves patients with less than optimal result. Thus, ongoing research aims at defining markers of outcome that are associated with notable risk under medical management but do not affect post-operative outcome and allow life expectancy restoration after surgery. Recent data demonstrated improvement of outcome after surgery, particularly valve repair, resulting in restoration of life expectancy in patients with severe MR (2,8,9), even in patients asymptomatic before surgery (8). The present study confirms beneficial effects of mitral surgery on mortality and cardiac events, emphasizing patients with marked LA enlargement and importantly, shows that LA enlargement does not imply untoward post-operative outcome. Thus, in contrast to symptoms or low EF, LA index  $\geq 60$  ml/m<sup>2</sup> is a high-risk marker allowing restorative surgery without excess post-operative risk.

In clinical practice, our data suggest that LA index  $\geq 60$  ml/m<sup>2</sup> should be included among novel markers of risk in organic MR in conjunction with MR severity quantitation (8) as part of comprehensive risk assessment. In view of the risk attached to marked LA enlargement and of outcome improvement provided by surgery, we believe that patients with severe MR and LA index  $\geq 60$  ml/m<sup>2</sup>, even those asymptomatic, should be considered for mitral surgery, particularly if valve repair is feasible. Conversely, patients

with moderate MR incur initially lower risks (8) and LA index  $\geq 60$  ml/m<sup>2</sup> should lead to close follow-up to detect MR progression.

**Study limitations.** Our study strength relies on triple quantitative assessment of LV, LA, and MR with prospective enrollment of patients with organic MR in sinus rhythm. Atrial fibrillation is an important determinant of LA remodeling per se, which we excluded and the role of LA enlargement in patients with MR and AF will require future studies.

Clinical management was determined independently by patient's personal physicians without investigators' interference. Regular follow-up, touted as key to good outcome (7), was obtained in all patients, at Mayo Clinic or with their home physicians, and is representative of routine medical care.

Left atrial enlargement is caused by MR and may be considered a surrogate for MR severity. However, LA enlargement integrates not only MR degree but also other measures of the valve disease severity (14). The crucial point is that LA index, irrespective of this supposed "surrogate" nature, predicted survival and cardiac events, adjusting for known predictors of outcome in organic MR, including Charlson comorbidity index and quantitation of MR severity. In that respect adjustment by ERO did not affect results (HR for LA index  $\geq 60$ : 2.48,  $p = 0.036$  for mortality and 3.98,  $p < 0.0001$  for cardiac events). Overfitting may cause detection of spurious predictors of outcome, but the prospective and hypothesis-driven natures of our study that used few adjusting variables concur to suggest overfitting risk as minimal. Thus, we believe that LA enlargement is indeed an integrator of MR consequences rather than a surrogate, which should be used for risk stratification and clinical decisions in routine practice.

## Conclusions

In this large population of patients with chronic organic MR in sinus rhythm, LA enlargement is a strong and independent predictor of outcome under medical management, even after adjustment and stratification by regurgitant volume. Patients with LA index  $\geq 60$  ml/m<sup>2</sup> incur excess mortality and frequent cardiac events whereas those with LA index 30 to 59 ml/m<sup>2</sup> tend to present with notable cardiac events. Mitral valve surgery results in improved outcome, particularly in patients with a LA index  $\geq 60$  ml/m<sup>2</sup>. Thus, LA volume measurement should be a part of routine echocardiographic examination and be integrated into the clinical decision making process in patients with organic MR.

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**Key Words:** mitral regurgitation ■ left atrium ■ echocardiography ■ left atrial volume ■ mitral valve surgery ■ prognosis.