

ORIGINAL ARTICLE

Quantitative Determinants of the Outcome of Asymptomatic Mitral Regurgitation

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ABSTRACT

BACKGROUND

The clinical outcome of asymptomatic mitral regurgitation is poorly defined, and the treatment is uncertain. We studied the effect on the outcome of quantifying mitral regurgitation according to recent guidelines.

METHODS

We prospectively enrolled 456 patients (mean [±SD] age, 63±14 years; 63 percent men; ejection fraction, 70±8 percent) with asymptomatic organic mitral regurgitation, quantified according to current recommendations (regurgitant volume, 66±40 ml per beat; effective regurgitant orifice, 40±27 mm²).

RESULTS

The estimated five-year rates (±SE) of death from any cause, death from cardiac causes, and cardiac events (death from cardiac causes, heart failure, or new atrial fibrillation) with medical management were 22±3 percent, 14±3 percent, and 33±3 percent, respectively. Independent determinants of survival were increasing age, the presence of diabetes, and increasing effective regurgitant orifice (adjusted risk ratio per 10-mm² increment, 1.18; 95 percent confidence interval, 1.06 to 1.30; P<0.01), the predictive power of which superseded all other qualitative and quantitative measures of regurgitation. Patients with an effective regurgitant orifice of at least 40 mm² had a five-year survival rate that was lower than expected on the basis of U.S. Census data (58±9 percent vs. 78 percent, P=0.03). As compared with patients with a regurgitant orifice of less than 20 mm², those with an orifice of at least 40 mm² had an increased risk of death from any cause (adjusted risk ratio, 2.90; 95 percent confidence interval, 1.33 to 6.32; P<0.01), death from cardiac causes (adjusted risk ratio, 5.21; 95 percent confidence interval, 1.98 to 14.40; P<0.01), and cardiac events (adjusted risk ratio, 5.66; 95 percent confidence interval, 3.07 to 10.56; P<0.01). Cardiac surgery was ultimately performed in 232 patients and was independently associated with improved survival (adjusted risk ratio, 0.28; 95 percent confidence interval, 0.14 to 0.55; P<0.01).

CONCLUSIONS

Quantitative grading of mitral regurgitation is a powerful predictor of the clinical outcome of asymptomatic mitral regurgitation. Patients with an effective regurgitant orifice of at least 40 mm² should promptly be considered for cardiac surgery.

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MITRAL-VALVE REGURGITATION IS common,¹ and its prevalence increases with age.¹ The management of mitral regurgitation and indications for surgery are controversial.² Previous outcome studies showed that patients with organic mitral regurgitation who have symptoms or a reduced ejection fraction are at high risk,^{3,4} warranting mitral surgery.² Conversely, the clinical outcome among patients with asymptomatic mitral regurgitation is poorly defined, and criteria defining high-risk subgroups are uncertain.² Such subgroups are important to identify as technical improvements in surgery^{5,6} — decreased operative mortality⁷ and increased repair rates⁸ — allow the restoration of patients' life expectancy.⁹ Thus, surgery may be warranted in high-risk patients with asymptomatic mitral regurgitation under medical management.

Patients with mitral-valve prolapse and higher degrees of regurgitation have been considered to be at higher risk than those with lower degrees of regurgitation,⁴ suggesting that the severity of regurgitation may provide important information on the outcome. However, standard qualitative assessment of mitral regurgitation is fraught with problems,¹⁰ and recently, American and European cardiac societies issued joint guidelines advocating the use of quantitative methods involving Doppler echocardiography and determining thresholds of severity.¹¹ However, it is not yet clear whether this approach provides meaningful information on outcomes. Thus, we designed a prospective study, enrolling patients with organic mitral regurgitation who were monitored by their independent personal physicians, to test our hypothesis that quantitative classification of regurgitation according to the regurgitant volume and effective regurgitant orifice independently predicts the outcome.

METHODS

STUDY POPULATION

Between 1991 and 2000, we prospectively enrolled patients who had at least mild holosystolic mitral regurgitation on color-flow imaging,¹² which was due to organic mitral-valve disease identified by two-dimensional echocardiography, isolated (without aortic-valve disease) and pure (without stenosis), quantitatively assessed by the authors using at least two Doppler echocardiographic methods, and asymptomatic at diagnosis. Patients were excluded if they had mitral regurgitation due to ischemic heart disease or cardiomyopathy, minimal or

early or late systolic regurgitation, structurally normal valves, associated mitral stenosis that was more than trivial, associated organic aortic or tricuspid disease, a history of valve repair or replacement, congenital or pericardial heart disease, or an ejection fraction below 50 percent.⁴ Age, sex, and the type of cardiac rhythm were not considered in the eligibility criteria. The study was approved by our institutional review board. Because the protocol was judged to pose a low risk, oral informed consent was recommended and obtained.

CLINICAL ASSESSMENT AND MANAGEMENT

Each patient's history and the results of a clinical examination were recorded at baseline by his or her personal physician at our institution. Coexisting conditions were evaluated by means of the Charlson index.¹³ Congestive heart failure was diagnosed during follow-up on the basis of criteria from the Framingham Heart Study.¹⁴ Clinical management was determined independently by the patient's personal physician using all information available. Follow-up information was collected in 2002 after enrollment ended and all baseline data had been obtained.

ECHOCARDIOGRAPHIC MEASUREMENTS

Complete Doppler echocardiography was performed. Quantitative data were promptly obtained, stored in a database, and not altered throughout the study.

Quantitation of Mitral Regurgitation

Mitral regurgitation was quantified by at least two of three validated methods, and the results were averaged to calculate the regurgitant volume per beat and the area of the effective regurgitant orifice. Quantitative Doppler echocardiography is based on the measurement of mitral and aortic stroke volumes.¹⁵⁻¹⁷ Quantitative two-dimensional echocardiography is based on the measurement of left ventricular volume.^{17,18} The proximal isovelocity surface area is determined by measuring proximal-flow convergence.^{19,20} According to published guidelines, mild, moderate, and severe mitral regurgitation correspond to a regurgitant volume of less than 30, 30 to 59, and at least 60 ml per beat, respectively, and an effective regurgitant orifice of less than 20, 20 to 39, and 40 mm² or more, respectively.^{11,21}

Other Echocardiographic Measurements

Left ventricular diameters, volumes, ejection fraction, and mass were measured as recommended.²²

Left atrial volume was measured by means of an area-length method.²³ Planimetry was used to measure the mitral regurgitant jet on color-flow imaging in two planes,¹² and the ratio of the mitral regurgitant jet to the left atrial area was calculated.²⁴ The severity of mitral regurgitation was also qualitatively classified in grades (1/4 to 4/4).²⁵

STATISTICAL ANALYSIS

Unless otherwise specified, data are presented as means \pm SD or percentages. Comparisons between groups were performed with use of analysis of variance, Student's t-test, or the chi-square test, as appropriate. End points were death from any cause, death from cardiac causes, and cardiac events (defined as death from cardiac causes, congestive heart failure, or new atrial fibrillation). New atrial fibrillation was diagnosed only in patients who were in sinus rhythm at baseline. These end points were ascertained while the patients were under medical management (from diagnosis to surgery or death), and data were censored at the time of cardiac surgery if it was performed. Event rates (\pm SE) were calculated according to the Kaplan-Meier method and compared by means of the log-rank test.

We compared the observed mortality rates with the expected mortality rates using U.S. Census Bureau national life-tables and the log-rank test. Univariate and multivariate analyses of the time to events were performed with use of Cox proportional-hazards models with the effective regurgitant orifice and regurgitant volume as independent variables in continuous and categorical formats. The effect of surgery on the outcome was analyzed as a time-dependent variable with the use of proportional-hazards modeling and data from the entire follow-up period (medical and postoperative). All P values were two-sided, and values of less than 0.05 were considered to indicate statistical significance.

All authors participated in designing the study, collecting and analyzing data, and drafting and revising the manuscript.

RESULTS

BASELINE CHARACTERISTICS AND MANAGEMENT

Table 1 shows the baseline characteristics of the 456 patients enrolled, both overall and according to the effective regurgitant orifice. The majority of patients were in their 60s, were men, and had mitral-valve prolapse as the mechanism of regurgitation. The effective regurgitant orifice was deter-

mined on the basis of an average of two methods in 85 patients and three methods in 371 patients and was classified as less than 20 mm² in 28 percent of patients, 20 to 39 mm² in 28 percent, and at least 40 mm² in 43 percent, with a qualitative grade of 1/4 in 70 patients, 2/4 in 49, 3/4 in 93, and 4/4 in 244 (15, 11, 20, and 54 percent, respectively).

When the patients were stratified according to the effective regurgitant orifice, there were significant differences in jet size, regurgitant volume, and ventricular and atrial dilatation (Table 1). As expected, a significantly higher percentage of patients with severe regurgitation were men and had mitral-valve prolapse,⁷ whereas there was no significant difference in the Charlson comorbidity index among the three groups. Clinical management after diagnosis was solely medical in 224 patients (49 percent) and was medical followed by surgery (mean, 1.2 \pm 2.0 years later) in 232 patients: 11 patients with an effective regurgitant orifice of less than 20 mm² (9 percent of this group), 58 with an effective regurgitant orifice of 20 to 39 mm² (45 percent), and 163 with an effective regurgitant orifice of at least 40 mm² (82 percent). Follow-up lasted up to 11.7 years, but the mean duration of follow-up after diagnosis was 2.7 \pm 2.9 years under medical management and 5.1 \pm 2.9 years under medical and surgical management.

SURVIVAL

There were 56 deaths among the patients whose mitral regurgitation was managed medically, with survival rates of 96 \pm 1 percent at one year and 78 \pm 3 percent at five years. In univariate analysis, the degree of mitral regurgitation strongly predicted the likelihood of survival, with a risk ratio for death from any cause of 1.21 for each 10-mm² increment in the effective regurgitant orifice (95 percent confidence interval, 1.10 to 1.32; P<0.01) (Table 2) and of 1.11 for each increment of 10 ml per beat in the regurgitant volume (95 percent confidence interval, 1.03 to 1.19; P<0.01). Among the patients with medically managed mitral regurgitation, the five-year survival rate was highest among those with an effective regurgitant orifice of less than 20 mm² (91 \pm 3 percent), intermediate among those with an effective regurgitant orifice of 20 to 39 mm² (66 \pm 6 percent), and lowest among those with an effective regurgitant orifice of at least 40 mm² (58 \pm 9 percent, P<0.01) (Fig. 1).

The observed five-year survival rates did not differ significantly from expected survival rates in the overall population (78 \pm 3 percent vs. 84 percent,

Table 1. Baseline Clinical, Left Ventricular, and Hemodynamic Characteristics of Patients with Asymptomatic Mitral Regurgitation.*

Characteristic	All Patients (N=456)	Effective Regurgitant Orifice			P Value
		<20 mm ² (N=129)	20–39 mm ² (N=129)	≥40 mm ² (N=198)	
Age (yr)	63±14	64±14	65±14	61±14	0.09
Male sex (%)	63	31	64	82	<0.01
Charlson comorbidity index	1.6±2.10	1.5±2.20	1.8±2.20	1.4±2.00	0.39
Atrial fibrillation (%)	9	10	6	10	0.45
Mitral-valve prolapse (%)	80	48	84	98	<0.01
History of hypertension (%)	39	47	40	34	<0.01
Diabetes (%)	5	6	4	4	0.61
Systolic blood pressure (mm Hg)	135±19	137±22	137±18	133±17	0.05
Diastolic blood pressure (mm Hg)	77±33	77±9	77±12	76±9	0.58
Left ventricular diastolic diameter (mm)	56±8	49±4	54±6	61±6	<0.01
Left ventricular systolic diameter (mm)	34±6	31±4	34±7	37±6	<0.01
End-diastolic volume index (ml/m ²)	108±28	80±17	103±16	129±23	<0.01
End-systolic volume index (ml/m ²)	33±130	26±100	31±120	38±140	<0.01
Ejection fraction (%)	70±8	68±9	70±8	70±8	0.06
Left ventricular mass (g)	216±64	169±54	222±55	251±54	<0.01
Left atrial volume (ml)	105±50	67±27	98±44	133±49	<0.01
Cardiac index (liters/min/m ²)	2.7±0.6	2.9±0.5	2.8±0.5	2.6±0.5	<0.01
Systolic pulmonary pressure (mm Hg)	38±11	35±7	35±9	42±13	<0.01
Mitral jet area (cm ²)	9.5±5.80	5.0±3.00	8.6±3.40	13±6.00	<0.01
Ratio of mitral jet area to left atrial area (%)	32±16	23±10	32±11	39±17	<0.01
Effective regurgitant orifice (mm ²)	40±27	11±5	31±5	64±21	—
Regurgitant volume (ml/beat)	66±40	21±10	57±13	101±29	<0.01

* Plus–minus values are means ±SD.

P=0.21) or in the group with an effective regurgitant orifice of less than 20 mm² (91±3 percent vs. 86 percent, P=0.12). However, the actual survival rates were significantly lower than the expected rates in the group with an effective regurgitant orifice of 20 to 39 mm² (66±6 vs. 84 percent, P=0.04) and the group with an effective regurgitant orifice of at least 40 mm² (58±9 vs. 78 percent, P=0.03).

In multivariate analysis, survival was independently predicted by increasing age (P<0.01), the presence of diabetes (P<0.01), and a greater effective regurgitant orifice (adjusted risk ratio per 10-mm² increment, 1.18; 95 percent confidence interval, 1.06 to 1.30; P<0.01). After adjustment for age, sex, the presence or absence of diabetes and atrial fibrillation at baseline, and the ejection fraction (and even the Charlson comorbidity index), the effective regurgitant orifice independent-

ly predicted survival, with an adjusted risk ratio for death from any cause of 1.20 for each 10-mm² increment (95 percent confidence interval, 1.07 to 1.34; P<0.01) and of 2.90 for an effective regurgitant orifice of at least 40 mm², as compared with one of less than 20 mm² (95 percent confidence interval, 1.33 to 6.32) (Table 2).

Regurgitant volume was less strongly predictive of survival after adjustment for age and the presence or absence of diabetes (P=0.04) and even less so after adjustment for age, sex, the presence or absence of diabetes and atrial fibrillation, and the ejection fraction (P=0.06). The qualitative grade of mitral regurgitation, jet area, and ratio of the jet to the left atrial area were predictive of survival on univariate analysis (all P≤0.05) but not on multivariate analysis (all P>0.30). Furthermore, nested models showed that quantitative classification based

Table 2. Risk of Death from Any Cause, Death from Cardiac Causes, and Cardiac Events among Patients with Asymptomatic Mitral Regurgitation under Medical Management.*

Type of Analysis	Death from Any Cause		Death from Cardiac Causes		Cardiac Events	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Unadjusted						
Per 10-mm ² increment in ERO	1.21 (1.10–1.32)	<0.01	1.29 (1.15–1.42)	<0.01	1.22 (1.13–1.30)	<0.01
Adjusted for age and presence or absence of diabetes						
Per 10-mm ² increment in ERO	1.18 (1.06–1.30)	<0.01	1.26 (1.12–1.40)	<0.01	1.20 (1.11–1.29)	<0.01
Adjusted for age, sex, ejection fraction, and presence or absence of diabetes and atrial fibrillation						
Per 10-mm ² increment in ERO	1.20 (1.07–1.34)	<0.01	1.30 (1.13–1.47)	<0.01	1.25 (1.15–1.35)	<0.01
ERO, 20 to 39 mm ² †	2.58 (1.25–5.40)	0.01	3.10 (1.15–8.53)	0.03	2.57 (1.41–4.68)	<0.01
ERO ≥40 mm ² †	2.90 (1.33–6.32)	<0.01	5.21 (1.98–14.40)	<0.01	5.66 (3.07–10.56)	<0.01

* Cardiac events were defined as death from cardiac causes, congestive heart failure, and new atrial fibrillation. CI denotes confidence interval, and ERO effective regurgitant orifice.

† The reference group was made up of the patients with an effective regurgitant orifice of less than 20 mm².

on the effective regurgitant orifice significantly increased the predictive value of models that used qualitative grading or jet measures (all $P < 0.01$).

Among the patients with medically managed mitral regurgitation, 35 died of cardiac causes, with a five-year mortality rate of 14 ± 3 percent overall and 3 ± 2 percent among those with an effective regurgitant orifice of less than 20 mm², 20 ± 6 percent among those with an effective regurgitant orifice of 20 to 39 mm², and 36 ± 9 percent among those with an effective regurgitant orifice of at least 40 mm² ($P < 0.01$) (Fig. 2). In multivariate analysis, the effective regurgitant orifice predicted the adjusted risk of death from cardiac causes (Table 2). Regurgitant volume also predicted the risk of death from cardiac causes (adjusted risk ratio per increment of 10 ml per beat, 1.17; 95 percent confidence interval, 1.05 to 1.30; $P < 0.01$) but with a slightly lower χ^2 (52 vs. 57). In nested models including the qualitative or jet-related grade of mitral regurgitation, the quantitative classification of the effective regurgitant orifice had superior predictive power (all $P < 0.01$).

Seventy-four patients died during the follow-up period (medical and postoperative). The five-year survival rate was 85 ± 2 percent overall and did not differ significantly from the rate expected in the general population among those with an effective regurgitant orifice of less than 20 mm² (91 ± 3 percent vs. 86 percent, $P = 0.19$), those with an effective regurgitant orifice of 20 to 39 mm² (81 ± 4 percent vs. 85 percent, $P = 0.61$), or those with an effective

regurgitant orifice of at least 40 mm² (85 ± 3 percent vs. 86 percent, $P = 0.80$), reflecting normalization of the life expectancy among the groups with an effective regurgitant orifice of 20 mm² or more after accounting for postoperative survival rates.

CARDIAC EVENTS

During medical follow-up, 91 patients had a cardiac event (death from cardiac causes, congestive heart failure, or new atrial fibrillation), with one-year and five-year rates of 7 ± 1 percent and 33 ± 3 percent, respectively. The five-year rates of cardiac events differed significantly according to both the effective regurgitant orifice (15 ± 4 percent among those with an effective regurgitant orifice of less than 20 mm², 40 ± 7 percent among those with an effective regurgitant orifice of 20 to 39 mm², and 62 ± 8 percent among those with an effective regurgitant orifice of at least 40 mm²; $P < 0.01$) (Fig. 3) and the regurgitant volume (17 ± 4 percent among those with a regurgitant volume of less than 30 ml per beat, 32 ± 6 percent among those with a volume of 30 to 59 ml per beat, and 55 ± 7 percent among those with a volume of at least 60 ml per beat; $P < 0.01$). The effective regurgitant orifice was a powerful predictor of the risk of cardiac events on univariate analysis (risk ratio per 10-mm² increment, 1.22; 95 percent confidence interval, 1.13 to 1.30; $P < 0.01$) and along with age ($P < 0.01$), the presence of diabetes ($P < 0.01$), and the presence of atrial fibrillation ($P = 0.05$), was an independent predictor of risk.

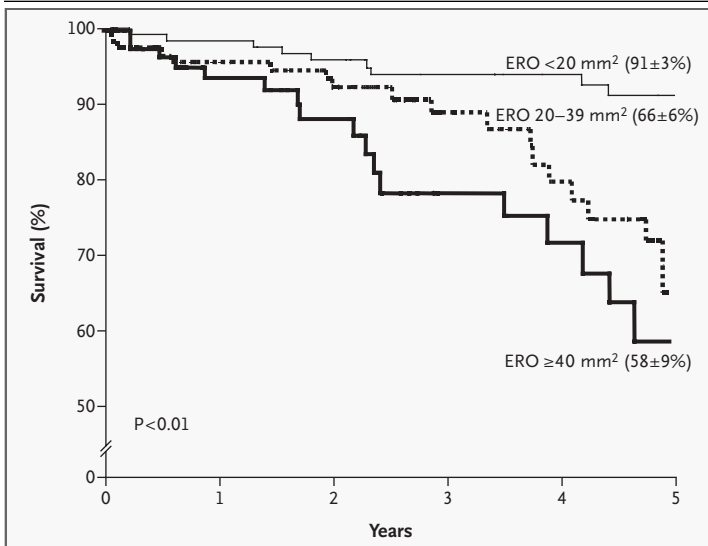


Figure 1. Kaplan–Meier Estimates of the Mean (\pm SE) Rates of Overall Survival among Patients with Asymptomatic Mitral Regurgitation under Medical Management, According to the Effective Regurgitant Orifice (ERO). Values in parentheses are survival rates at five years.

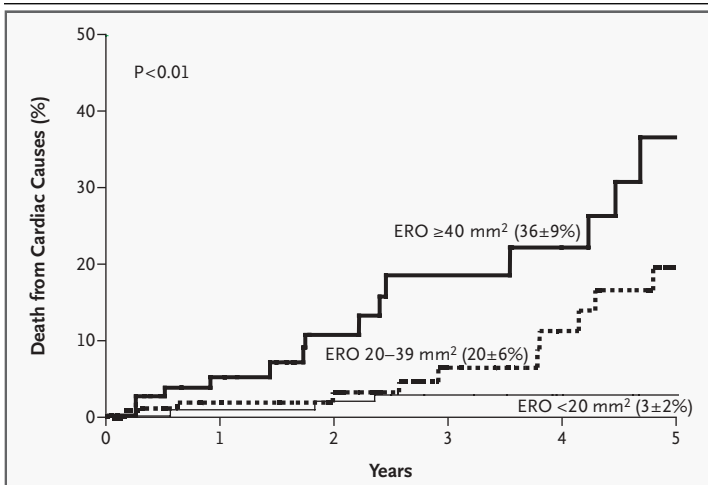


Figure 2. Kaplan–Meier Estimates of the Mean (\pm SE) Rates of Death from Cardiac Causes among Patients with Asymptomatic Mitral Regurgitation under Medical Management, According to the Effective Regurgitant Orifice (ERO). Values in parentheses are survival rates at five years.

After adjustment for age, sex, the presence or absence of diabetes and atrial fibrillation, and the ejection fraction, the effective regurgitant orifice remained independently predictive of the risk of cardiac events (Table 2). Similarly, the regurgitant volume predicted the risk of cardiac events (unad-

justed risk ratio per increment of 10 ml per beat, 1.15; 95 percent confidence interval, 1.09 to 1.21; $P < 0.01$; adjusted risk ratio per increment of 10 ml per beat, 1.18; 95 percent confidence interval, 1.10 to 1.25; $P < 0.01$; and adjusted risk ratio for a volume of at least 60 ml per beat as compared with a volume of less than 30 ml per beat, 4.50; 95 percent confidence interval, 2.40 to 8.60; $P < 0.01$). The moderate range of regurgitant volume (30 to 59 ml per beat) showed borderline significance (risk ratio for the comparison with a volume of less than 30 ml per beat, 1.80; 95 percent confidence interval, 0.97 to 3.30; $P = 0.06$). The qualitative grade and jet area were predictive of the risk of cardiac events on univariate analysis (both $P < 0.01$) but not on multivariate analysis (both $P > 0.25$). In nested models, the predictive power of the quantitative classification of the effective regurgitant orifice was superior to that afforded by the qualitative grade or jet area (both $P < 0.01$).

SURGERY AND CLINICAL OUTCOME

Among the 232 patients who underwent cardiac surgery, 2 underwent isolated coronary bypass and 230 underwent mitral surgery (valve repairs in 209 and valve replacements in 21, with 38 associated coronary-bypass graft procedures). The appearance of symptoms was the indication for surgery in 94 patients. In 91 other patients, the presence of marked left ventricular dilatation (end-systolic diameter of at least 40 mm, end-diastolic diameter of at least 65 mm, or both), atrial dilatation (volume of at least 100 ml), or both contributed to the indication for surgery. Thus, physicians' and patients' preference led to surgery in only 47 patients. The Charlson comorbidity index was similar in patients who underwent surgery and those who did not ($P = 0.51$).

The five-year rates of freedom from surgery and from death or cardiac surgery were 46 ± 3 percent and 36 ± 3 percent, respectively. Excluding patients who underwent cardiac surgery within 90 days after the diagnosis of mitral regurgitation, the 5-year rates of freedom from surgery and from death or cardiac surgery were 63 ± 3 percent and 49 ± 3 percent, respectively. These rates were 94 ± 3 percent and 86 ± 4 percent, respectively, among those with an effective regurgitant orifice of less than 20 mm^2 ; 55 ± 6 percent and 36 ± 6 percent, respectively, among those with an effective regurgitant orifice of 20 to 39 mm^2 ; and 27 ± 6 percent and 16 ± 4 percent, respectively, among those with an effective regurgitant orifice of at least 40 mm^2 ($P < 0.01$).

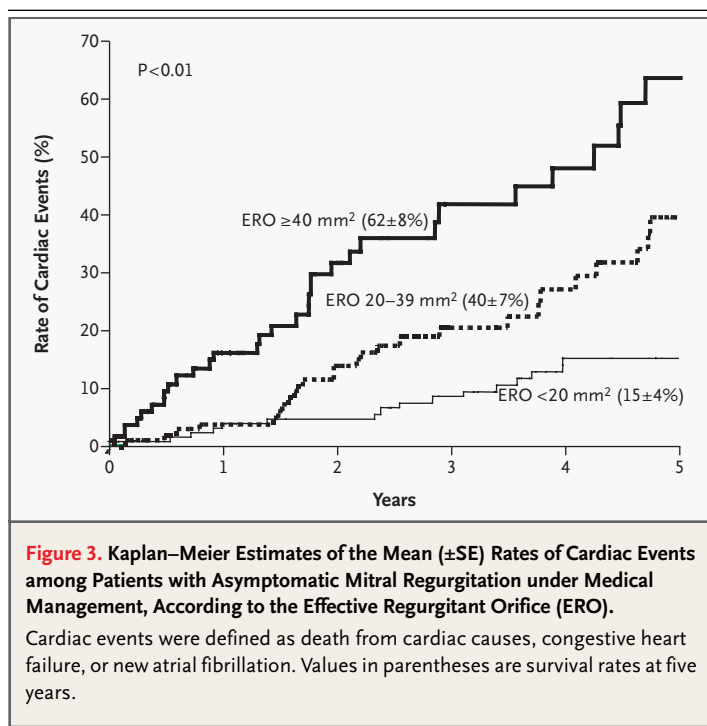
Eighteen patients died after surgery, two during the 30-day postoperative period (1 percent). Cox proportional-hazards analysis with surgery as the time-dependent variable showed that surgery was associated with a decreased subsequent risk of death on univariate analysis (risk ratio, 0.32; 95 percent confidence interval, 0.18 to 0.54; $P < 0.01$); in a multivariate analysis with adjustment for age, sex, the presence or absence of diabetes and atrial fibrillation, the effective regurgitant orifice, and the ejection fraction (risk ratio, 0.28; 95 percent confidence interval, 0.14 to 0.55; $P < 0.01$); and after additional adjustment for the Charlson comorbidity index (risk ratio, 0.35; 95 percent confidence interval, 0.18 to 0.68; $P < 0.01$).

Cox proportional-hazards modeling that included a term for the interaction between the effective regurgitant orifice and surgery demonstrated a larger survival benefit associated with surgery for larger effective orifices (adjusted risk ratio per 10-mm² increment in the effective regurgitant orifice, 0.73; 95 percent confidence interval, 0.56 to 0.95; $P = 0.02$).

Similarly, the risk of death from cardiac causes after surgery was reduced on univariate analysis (risk ratio, 0.41; 95 percent confidence interval, 0.22 to 0.77; $P < 0.01$) and multivariate analysis (adjusted risk ratio, 0.31; 95 percent confidence interval, 0.14 to 0.68; $P < 0.01$). With the use of separate time-dependent variables for coronary-bypass and mitral surgery, the adjusted risk ratio for death from any cause was 0.16 (95 percent confidence interval, 0.07 to 0.36; $P < 0.01$) and 0.14 for death from cardiac causes (95 percent confidence interval, 0.05 to 0.39) after mitral surgery, demonstrating a reduction in risk with mitral surgery. With respect to cardiac events, surgery was associated with an increased risk of new atrial fibrillation (adjusted risk ratio, 5.95; 95 percent confidence interval, 3.38 to 10.46; $P < 0.01$) but a decreased risk of congestive heart failure (adjusted risk ratio, 0.37; 95 percent confidence interval, 0.17 to 0.79; $P < 0.01$) following the intervention.

DISCUSSION

We conducted a prospective study of the clinical outcomes among patients with asymptomatic organic mitral regurgitation using quantitative measurements of the effective regurgitant orifice and regurgitant volume. One important finding is that the quantitative grading of mitral regurgitation according to recent guidelines¹¹ is a powerful predic-



tor of the clinical outcome of medical management. This classification's prognostic power superseded that of all semiquantitative indexes. Indeed, the rates of death from any cause, death from cardiac causes, and cardiac events with the use of medical management were independently determined by the effective regurgitant orifice. Patients with medically managed asymptomatic mitral regurgitation who had an effective regurgitant orifice of at least 40 mm² had an excess risk of death from any cause, a risk of death from cardiac causes that was more than five times that among patients with mild regurgitation, and a risk of cardiac events that was close to six times as high. In this group of patients the five-year probability of death or late cardiac surgery was 84 percent, suggesting that surgery is almost inevitable. Patients with an effective regurgitant orifice of 20 to 39 mm² had complication rates that were initially low but subsequently rose over time. Cardiac surgery, despite its associated increase in the risk of atrial fibrillation, markedly reduced the risk of heart failure and death and normalized the patients' life expectancy. Therefore, quantitative grading of mitral regurgitation according to recent guidelines permits risk stratification of patients with isolated, asymptomatic, organic mitral regurgitation and should be part of the clinical decision-making process.

Mitral regurgitation enlarges the left atrium,²³ which increases atrial compliance enough to normalize left atrial pressure, even in the presence of severe regurgitation.²⁶ Therefore, most patients are asymptomatic at diagnosis,³ a circumstance that led to the belief that asymptomatic mitral regurgitation is benign.²⁷ More recent natural-history studies raised the possibility that the clinical course of initially asymptomatic organic mitral regurgitation may be more complicated than once thought.^{3,28,29} Hence, clinical management is difficult and subject to controversy.^{2,30} Delaying surgical correction until symptoms appear is problematic, since the outcome may be suboptimal at that stage,⁹ with an excess risk of postoperative mortality and left ventricular dysfunction.³¹ Hence, it has been suggested that surgery for organic mitral regurgitation should be considered while patients are asymptomatic.^{7,32} This approach is supported by the high feasibility,³³ low risk,⁸ and excellent long-term results^{5,6} of valve repair, but it requires the identification of subgroups of patients with mitral regurgitation who are at high risk under medical management.³⁰ In previous studies,³ patients with symptoms or a reduced ejection fraction had a poor outcome. However, the approach to risk stratification for the majority of patients who did not have these characteristics is uncertain.²⁸

Recently, American and European cardiac societies have emphasized the value of a quantitative assessment of mitral regurgitation,¹¹ on the basis of previous validation studies.¹⁵⁻²⁰ Recommendations describe methods of measuring the regurgitant orifice and volume and propose a grading scheme,¹¹ but there have been no data on whether these measures influence outcome and may be used for risk stratification among patients with asymptomatic mitral regurgitation.

Although both the regurgitant volume and the orifice predict the outcome of mitral regurgitation, the effective regurgitant orifice appears to be a better predictor of survival. These two variables are strongly but not linearly related and are complementary.¹⁷ The regurgitant volume represents the transformation of left ventricular energy into kinetic energy, whereas the size of the orifice translates into both kinetic and potential energy (left atrial pressure),³⁴ establishing a mechanistic link to the development of heart failure. Irrespective of these novel concepts, evidence is accumulating that these measures have independent prognostic importance³⁵ and should be routinely evaluated.

The identification of severe mitral regurgitation

was previously based on physiological¹⁷ and angiographic²¹ data. Our data clearly show that patients with a regurgitant volume of at least 60 ml per beat or an effective regurgitant orifice of at least 40 mm² have a poor outcome with medical management alone and should be considered to have severe mitral regurgitation.

The effective regurgitant orifice is a major determinant of survival after diagnosis and, therefore, must be determined at diagnosis.¹¹ Patients with an effective regurgitant orifice of at least 40 mm² had considerable rates of complications and death with the use of medical management in our study and represent a high-risk group despite the absence of symptoms and the ostensibly benign presentation. These patients should mainly be the ones who are considered for prompt surgery, especially if valve repair appears feasible. Conversely, patients with an effective regurgitant orifice of 20 to 39 mm² have a low risk of death and cardiac events within the first few years after diagnosis and may initially be followed medically. The rates of cardiac complications subsequently increase, possibly because of progression of regurgitation,³⁶ and such patients require careful follow-up and repeated quantitative assessment of the degree of regurgitation.

Mitral surgery is associated with a considerably decreased subsequent risk of mortality and heart failure.³⁷ The reduction in the risk of death associated with surgery is greater among patients with a larger effective regurgitant orifice than among those with a smaller effective orifice and results in normalization of the life expectancy.⁹ These data provide a firm basis for considering surgery in patients with asymptomatic mitral regurgitation who have an effective regurgitant orifice of at least 40 mm². However, since the risk of atrial fibrillation increased after surgery, a clinical trial of surgery in such patients is essential.

Our prospective study demonstrates that quantitative assessment of mitral regurgitation according to recent guidelines is a powerful predictor of the clinical outcome among patients with isolated, asymptomatic organic mitral regurgitation. Patients with an effective regurgitant orifice of at least 40 mm² have a significantly increased risk of death and of cardiac events and should promptly be considered for cardiac surgery, since surgery considerably reduces the rate of death from cardiac causes, decreases the risk of heart failure, and normalizes life expectancy.

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