

Mitral Regurgitation

Atrial Fibrillation Complicating the Course of Degenerative Mitral Regurgitation

Determinants and Long-Term Outcome

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OBJECTIVES	The study was done to define the incidence, determinants and prognostic implications of onset of atrial fibrillation (AF) during follow-up of mitral regurgitation (MR) initially in sinus rhythm.
BACKGROUND	The rates and clinical implications of AF in MR are undefined.
METHODS	We analyzed the occurrence of AF under conservative management in two populations of patients with degenerative MR in sinus rhythm at diagnosis: 1) 360 patients (65 ± 13 years, 74% men) with MR due to flail leaflets; and 2) 89 residents of Olmsted County, Minnesota (67 ± 17 years, 56% men) with grade 3 or 4 MR due to simple mitral valve prolapse (MVP) diagnosed echocardiographically.
RESULTS	In patients with MR due to flail leaflets, AF rates at 5 and 10 years were 18 ± 3% and 48 ± 6%, respectively, and the linearized rate was 5.0 ± 0.7% per year. Development of AF during follow-up was independently associated with high risk of cardiac death or heart failure (adjusted risk ratio 2.23, <i>p</i> = 0.025). The AF rate at 10 years was higher in patients ≥65 years (75 ± 10% vs. 24 ± 6%, <i>p</i> < 0.0001) and in those with baseline left atrial (LA) dimension ≥50 mm (67 ± 8% vs. 37 ± 9%, <i>p</i> < 0.001). In multivariate analysis, independent baseline predictors of AF were age and LA diameter (both <i>p</i> < 0.01). In patients with MR due to MVP, similar rates of AF (41 ± 7% vs. 44 ± 6% at nine years, <i>p</i> > 0.50) and predictors of AF (age and LA dimension, both <i>p</i> < 0.006) were noted.
CONCLUSIONS	In patients with degenerative MR in sinus rhythm at diagnosis, the incidence of AF occurring under conservative management is high and similar whether the cause of MR is flail leaflet or simple MVP. After onset of AF, an increased cardiac mortality and morbidity are both observed under conservative management. The risk of AF increases with advancing age and larger LA dimension. These data suggest that the clinical management of MR should take into account the high incidence, excess risk, and predictors of AF. (J Am Coll Cardiol 2002; 40:84–92) © 2002 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common arrhythmia (1) and is associated with an adverse prognosis (2,3). Therefore, identifying predisposing factors for AF (4–6), with the aim of improving strategies for its primary prevention, is essential.

Valvular heart diseases are associated with AF in the population (3–5), with a high population-attributable risk (6), but the specific risk of AF attached to each valvular lesion has not been well delineated (7). Furthermore, long-term risks and baseline predictors of AF in patients who were in sinus rhythm at diagnosis are poorly defined.

Mitral regurgitation (MR) is of particular interest regarding the development of AF because MR is common (8), particularly in the elderly (8), who are also at high risk for AF (6), and because MR tends to produce left atrial (LA) enlargement, a possible precursor of AF (9). In previous studies of patients with MR, those with preoperative AF

had a worse postoperative outcome than those in sinus rhythm (10). However, in patients conservatively managed, series of limited size reported a highly variable incidence of AF (7,11,12). Furthermore, the predictors of onset of AF in patients diagnosed with MR in sinus rhythm and the implications of AF for outcome under conservative (medical) management remain uncertain. Therefore, because of these conflicting or insufficient data regarding AF complicating MR, the concept of AF prevention, which may be of great importance, lacks substantiation and has not been implemented in the current guidelines regarding surgical decision making (13).

Patients with degenerative MR either with flail leaflets (14) or with simple mitral valve prolapse (MVP) represent the largest subset of candidates for MR surgery in Western countries (15), and they are an important population in which to determine the incidence and impact on outcome of AF. Also, flail leaflets (16,17) and more recently MVP (18) are reliably diagnosed by echocardiography, allowing long-term follow-up of large populations. Accordingly, in pa-

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Abbreviations and Acronyms

AF	= atrial fibrillation
BMI	= body mass index
BSA	= body surface area
CHF	= congestive heart failure
CI	= confidence interval
EF	= ejection fraction
LA	= left atrium/atrial
LV	= left ventricle/ventricular
MR	= mitral regurgitation
MVP	= mitral valve prolapse
NYHA	= New York Heart Association
RR	= risk ratio

tients who were in sinus rhythm when degenerative MR was diagnosed, we examined the long-term incidence, predisposing factors and prognostic implications of the development of AF.

SUBJECTS AND METHODS

The design of the study was a retrospective collection of cases in which the diagnosis, clinical and echocardiographic characteristics and subsequent events were independently noted (prospectively) during normal clinical care.

Patient population. Two populations of patients with degenerative MR in sinus rhythm at diagnosis were eligible for the study. The first population included patients with MR due to flail leaflets first diagnosed by two-dimensional echocardiography between January 1, 1980, and December 31, 1994, at the Mayo Clinic (Rochester, Minnesota). To determine whether AF rates and implications are similar in other patients with degenerative MR, we analyzed a second population involving patients who: 1) had MR due to MVP diagnosed between 1989 and 1995; 2) were Olmsted County, Minnesota, residents at diagnosis; and 3) had MR grade 3 or 4/4 by standard Doppler methods (all had comprehensive Doppler and color-flow imaging). In both populations, patients who had papillary muscle rupture, ischemic MR with isolated annular dilation, previous valve surgery or associated aortic or congenital disease were excluded. Patients who subsequently were identified with associated coronary disease or underwent bypass grafting at valvular surgery were not excluded.

Clinical data were obtained from medical records, and follow-up was obtained through clinical records, postal survey and telephone calls to patients, relatives or physicians. Confirmation of AF was based on electrocardiograms (12), and no unsubstantiated episode of palpitation was considered AF. Causes of death were ascertained by contacting patients' physicians and by examining death certificates and autopsy records. Associated medical conditions were assigned weights and summated as a modified comorbidity index (19).

Echocardiographic methods. Comprehensive two-dimensional echocardiography was performed (20). The

diagnosis of flail leaflets was based on failure of leaflet coaptation, with rapid systolic movement of the flail segment into the LA (16,21). The diagnosis of MVP was based on current criteria, using long-axis views of the valve (18). Severity of MR was assessed semiquantitatively on a scale of 1+ to 4+ by Doppler echocardiography (22,23). Left ventricular (LV) and LA dimensions were obtained by using M-mode echocardiography, guided by two-dimensional imaging. Ejection fraction (EF) was visually estimated in all cases and was combined with calculated values as previously reported (12,24,25). Data were used unaltered from the original prospective echocardiographic data collection by means of electronic transfer.

Statistical analysis. Continuous variables are expressed as mean \pm SD and categorical data as percentages. Group comparisons were performed with analysis of variance, standard *t* test, or chi-square test as appropriate. After diagnosis, event rates were estimated by the Kaplan-Meier method, expressed as mean \pm SE, and linearized rates were calculated as gross estimates of the hazard of AF. The main end point was occurrence of AF under conservative management, which was analyzed by censoring at the time of mitral valve surgery if eventually performed. Therefore, in all patients the time after diagnosis during which patients remained medically treated or managed was the time at risk for AF whether they had subsequent surgery or not. Identification of baseline predictors of AF was based on univariate Cox proportional hazards analysis of candidate clinical, laboratory and echocardiographic variables, with associated risk expressed as risk ratio (RR) and 95% confidence interval (CI). To account for effect of gender, body size, height, weight, body mass index (BMI), body surface area (BSA) and LV and LA sizes were used as absolute values or were normalized to the mean of each gender group. Age, gender and variables with univariate $p < 0.10$ were then tested in a multivariate model. To determine the impact of follow-up AF on subsequent outcome (death or heart failure) under conservative (medical) management, a time-dependent AF variable was tested within multivariate models (including baseline predictors) for the specific event, censoring patients at surgery (if operated on). Comparison of event rates between groups employed the two-tailed log-rank test, and between observed and expected survival the one-tailed log-rank test was used. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. MR DUE TO FLAIL LEAFLETS. From a cohort of 468 patients with the diagnosis made by echocardiography from 1980 through 1994, a total of 360 (aged 65 ± 13 years, 74% men) met eligibility criteria. At presentation, 209 of these patients (58%) were in New York Heart Association (NYHA) functional class I, 82 (23%) in class II, 52 (14%) in class III and 17 (5%) in class IV. Subsequently, 234 patients (65%) underwent surgery $2.1 \pm$

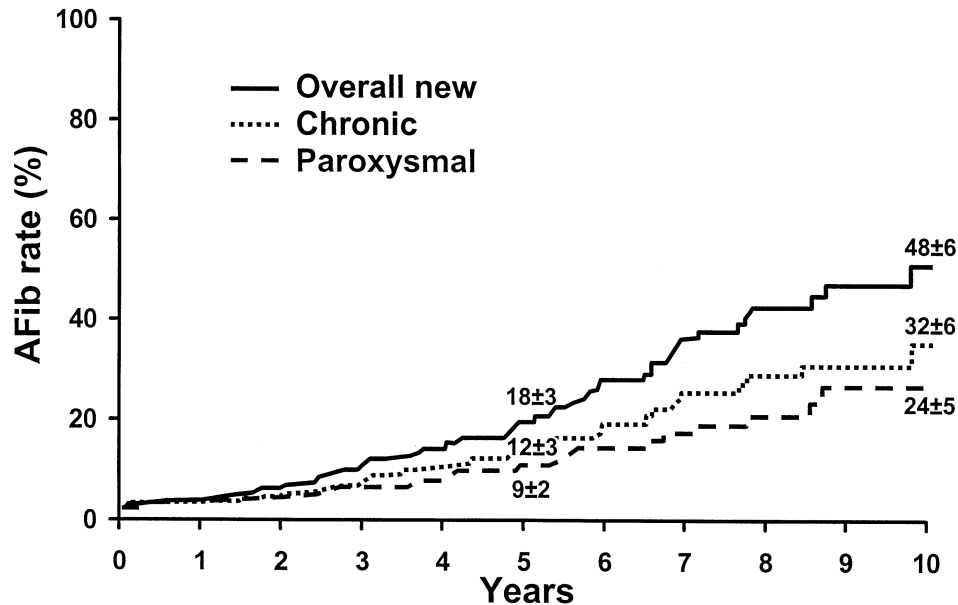


Figure 1. Incidence of atrial fibrillation (AFib) under conservative (medical) management among patients with mitral regurgitation due to flail leaflets diagnosed with the patient in sinus rhythm. The overall rates of new atrial fibrillation and of permanent and paroxysmal atrial fibrillation are presented as Kaplan-Meier curves.

2.9 years after diagnosis. Of the patients initially in NYHA functional class III or IV, 55 underwent surgery; 14 were not operated on because all had improved clinically after receiving medical treatment ($n = 14$) and also were not surgical candidates ($n = 4$) or refused surgery ($n = 2$). The presumed cause of flail leaflet was idiopathic in 295 patients, infective endocarditis in 58 patients, trauma in 5 patients and miscellaneous causes in 2 patients. The LV systolic and diastolic diameters, EF and wall thickness were 35 ± 6 and 60 ± 7 mm, $64 \pm 9\%$ and 11 ± 1 mm, respectively. The LA diameter was 50 ± 8 mm. Among the 330 patients in whom MR was graded by Doppler echocardiography, 277 (84%) had grade 3+ or 4+/4+ regurgitation. Follow-up was complete for 357 patients (99%).

MR DUE TO MVP. Among 645 residents of Olmsted County, Minnesota, diagnosed with MVP between 1989 and 1995, 89 had severe MR (grade 3 or 4) and were in sinus rhythm at diagnosis. Compared with patients with flail leaflets, those with MVP had similar age (67 ± 17 vs. 65 ± 13 years, $p = 0.22$), comorbidity ($p = 0.38$), NYHA functional class (III to IV in 19 vs. 19%, $p = 0.90$) and BMI (24.2 ± 4 vs. 24.5 ± 4 , $p = 0.50$). However, patients with MVP had slightly lower EF (61 ± 11 vs. $64 \pm 9\%$, $p = 0.03$), had smaller LA (46 ± 10 vs. 50 ± 8 mm, $p = 0.002$) and were more often women (44 vs. 26%, $p = 0.02$). During follow-up, 35 patients (39%) underwent surgery 3.7 ± 2.8 years after diagnosis.

Incidence of AF. MR DUE TO FLAIL LEAFLETS. During follow-up under medical management (38 ± 40 months), 56 patients experienced AF and 304 remained in sinus rhythm. At 5 and 10 years, overall rates of AF were $18 \pm 3\%$ and $48 \pm 6\%$, respectively (Fig. 1). Yearly linearized rate of

AF was $5.0 \pm 0.7\%$. The mean time to occurrence of AF was 52 ± 32 months. The initial episode of AF was paroxysmal in 25 patients, representing a 10-year rate of $24 \pm 5\%$, but subsequent recurrence was $49 \pm 12\%$ at 1 year and $56 \pm 12\%$ at 2 years. The first episode of AF was permanent in 31 patients. Accounting for recurrence of AF, the 10-year rate of permanent AF was $32 \pm 6\%$. After surgery in the 234 patients, the total rate of AF was 6% at 3 months and $37 \pm 5\%$ at 10 years.

MR DUE TO MVP. Under medical management, 19 patients incurred AF, with an incidence rate similar to that of patients with flail leaflets (at 9 years $41 \pm 9\%$ vs. $44 \pm 6\%$, $p = 0.67$). When all 449 degenerative MR patients were combined, the 5-year and 10-year rates of AF were $18 \pm 3\%$ and $47 \pm 5\%$, respectively. Of note, survival under conservative management was similar whether MR was due to MVP or flail leaflets (9-year, 61 ± 8 vs. $60 \pm 5\%$; $p = 0.70$), with 5-year and 10-year survival under conservative management for all degenerative MR of $78 \pm 3\%$ and $52 \pm 5\%$, respectively.

Determinants of AF. MR DUE TO FLAIL LEAFLETS. For descriptive purposes, baseline characteristics of the patients who had AF under conservative management compared with those who remained in sinus rhythm under conservative management and with those who remained in sinus rhythm until they underwent mitral surgery are presented in Table 1 (left panel). Although these groups were different globally, few variables were different between the group with AF and that with persistent sinus rhythm under conservative medical management (as opposed to the surgical group). In particular, age and LA size were different. Of note, a history of myocardial infarction was not observed

Table 1. Baseline Characteristics of Patients With MR Due to Flail Leaflets and Association With Subsequent Development of AF

	Baseline Characteristics According to Outcome				Association With Time to AF†		
	Patients With Follow-Up AF Under Medical Management (n = 56)	Patients in SR Under Continuous Medical Management (n = 103)	Patients in SR Until Mitral Surgery (n = 201)	p Value	Risk Ratio	95% CI	p Value
Age (yrs)	70 ± 9	70 ± 12	61 ± 13*	0.0001	1.046	1.022–1.072	0.0001
Male gender	66%	74%	76%	0.37	0.67	0.39–1.19	0.14
NYHA functional class III to IV	5%	13%	26%*	0.0001	2.06	0.48–6.04	0.29
Hypertension	27%	31%	30%	0.84	0.96	0.54–1.79	0.89
Comorbidity index <2	66%	66%	81%*	0.008	0.52	0.30–0.94	0.045
BSA (m ²)	1.85 ± 0.22	1.80 ± 0.23	1.88 ± 0.20	0.01	1.05	0.34–3.49	0.93
BSA normalized by gender	1.02 ± 0.10	0.97 ± 0.10*	1.01 ± 0.08	0.001	8.86	0.49–2.18	0.15
BMI (kg/m ²)	25.1 ± 4.6	24.0 ± 4.1	24.6 ± 3.4	0.15	1.03	0.96–1.09	0.36
Smoking	34%	47%	41%	0.29	1.20	0.70–2.13	0.51
Serum creatinine (mg/dl)	1.3 ± 1.1	1.4 ± 1.1	1.1 ± 0.3*	0.04	1.26	0.87–1.57	0.18
Total cholesterol (mg/dl)	214 ± 77	207 ± 96	210 ± 46	0.88	1.00	0.99–1.003	0.70
History of MI	5%	13%	4%	0.02	1.06	0.39–4.36	0.92
Ejection fraction (%)	64 ± 9	63 ± 10	64 ± 8	0.36	0.994	0.96–1.03	0.75
LVS (mm)	34 ± 6	34 ± 7	36 ± 6	0.02	0.99	0.94–1.04	0.70
LVD (mm)	60 ± 8	56 ± 6*	62 ± 7	0.01	1.008	0.96–1.047	0.70
LA (mm)	50 ± 8	46 ± 7*	51 ± 8	0.0001	1.064	1.027–1.10	0.0006
WT (mm)	11 ± 1	11 ± 1	11 ± 1	0.20	1.12	0.89–1.39	0.34
Severe MR	78%	70%	93%*	0.0001	1.33	0.70–2.74	0.39

*Denotes $p < 0.05$ in comparison with patients in whom AF developed under conservative management. †Time to AF is for events occurring under conservative management. Continuous variables are expressed as mean ± SD and categorical variables as percentages.

AF = atrial fibrillation; BMI = body mass index; BSA = body surface area; CI = confidence interval; LA = left atrial diameter; LVD = end-diastolic left ventricular diameter; LVS = end-systolic left ventricular diameter; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; SR = sinus rhythm; WT = end-diastolic wall thickness.

with higher prevalence at diagnosis in patients who developed AF during conservative follow-up (Table 1). This result is consistent with the prevalence of coronary disease in the 191 patients who underwent coronary angiography at any point during follow-up (10/33 or 30% in patients with AF, 2/4 in patients without AF and followed conservatively and 45/154 or 30% in patients who remained in sinus rhythm until surgery [$p = 0.69$]). However, compared with all patients who remained in sinus rhythm, those who had AF remained under conservative management (instead of undergoing surgery) more often (at five years, 64 ± 6 vs. $37 \pm 3\%$; $p < 0.001$) and for a longer time ($2,162 \pm 1,283$ days from diagnosis vs. $1,062 \pm 1,239$ days, $p < 0.0001$).

Therefore, it is essential to analyze the end point of time to occurrence of AF under conservative management with the Cox proportional hazards method (Table 1, right panel). The baseline clinical predictors of time to AF were age ($p < 0.0001$) and comorbidity ($p = 0.045$), with borderline effect of female gender ($p = 0.14$). Incidence of AF was higher in patients ≥ 65 years versus < 65 years ($75 \pm 10\%$ vs. $24 \pm 6\%$ at 10 years, $p < 0.0001$, Fig. 2). Yearly rates of AF in patients ≥ 65 years and < 65 years were $6.9 \pm 1.1\%$ and $2.8 \pm 0.7\%$, respectively ($p < 0.0001$).

The LA dimension was the only echocardiographic variable ($p = 0.0004$) predictive of time to AF. Of note, severe MR was neither more prevalent nor associated with shorter time to AF (Table 1). Incidence of AF was higher with LA dimension ≥ 50 mm versus < 50 mm (at 10 years,

$67 \pm 8\%$ vs. $37 \pm 9\%$; $p < 0.0001$; Fig. 3). Yearly rates of AF with LA ≥ 50 mm and < 50 mm were $8.4 \pm 1.6\%$ and $2.9 \pm 0.7\%$, respectively ($p < 0.0001$). The predictive power of uncorrected LA dimension was not improved by normalizing LA diameter by gender and was superior to that of the LA diameter normalized to BSA, which was only marginal ($p = 0.08$). The LV EF or diameters (normalized or not to BSA) showed no association with AF. Also, patients with and without MR grade 3 or 4 had similar rates of AF (at 10 years, $44 \pm 7\%$ vs. $49 \pm 14\%$, respectively; $p = 0.40$).

MR DUE TO MVP. The only baseline predictors of AF were age and LA diameter, with RRs (age: RR [95% CI] = 1.05/year [1.03 to 1.07], $p < 0.0001$; LA diameter: 1.07/mm [1.04 to 1.10], $p < 0.0001$) very similar ($p > 0.12$) to those of patients with flail leaflet (Table 1, right panel).

MULTIVARIATE ANALYSIS. In MR due to flail leaflets, using original baseline variables, age and LA dimension were the only independent predictors of AF, and female gender showed a borderline trend (Table 2A). Similarly, in the entire population of degenerative MR (combining flail leaflets and MVP), age ≥ 65 years and LA ≥ 50 mm were predictors of AF (Table 2B) independently of gender. However, LA size was smaller in women than in men (47 ± 8 vs. 50 ± 9 mm, $p = 0.007$ overall), which may potentially bias the effect of LA size and gender on incidence of AF. Therefore, first, multivariate models were repeated separately in men and women. In both genders, adjusting for

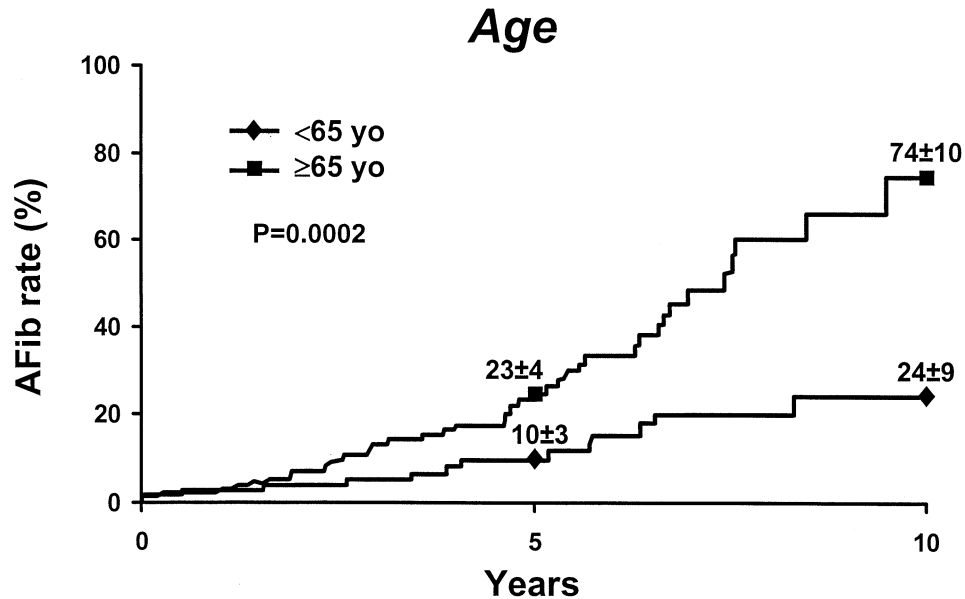


Figure 2. Atrial fibrillation (AFib) rate in patients with mitral regurgitation due to flail leaflets diagnosed with the patient in sinus rhythm, according to age at diagnosis, <65 or ≥65 years old (yo). Note the considerably higher rate in older patients.

age, the absolute LA size (adjusted RR = 3.17 and 1.73 per 10-mm increment, $p < 0.0001$ and $p = 0.007$ in women and in men, respectively) was independently predictive of AF.

Second, multivariate analysis was repeated in the entire population using LA diameter normalized to gender, showing that age and LA remained independently predictive of AF incidence (Table 2C) and that gender was not associated with AF after diagnosis. Symptoms, comorbidity, history of myocardial infarction, all risk factors for coronary disease and cause of degenerative MR (MVP vs. flail leaflets) were not independently predictive of AF (all $p > 0.40$).

Impact of onset of AF on mortality and morbidity. In MR due to flail leaflets, during conservative follow-up 67

deaths (44 [66%] cardiovascular) occurred. At 10 years, the observed survival rate was lower than the expected survival of the general population of same age and gender ($53 \pm 5\%$ vs. 64% , $p = 0.051$). Using time-dependent analysis, onset of AF during follow-up was associated with an increased risk of subsequent death (RR = 3.42, 95% CI = 1.7 to 6.7, $p < 0.0001$). Multivariate analysis confirmed that new AF during follow-up was independently (of age, NYHA functional class at baseline and EF) associated with increased mortality (adjusted RR = 2.02, $p = 0.056$) (Fig. 4).

Similarly, 78 patients with flail leaflets experienced congestive heart failure (CHF) under conservative management. Onset of new AF during follow-up was associated with a higher risk of CHF (RR = 3.23, 95% CI = 1.59 to

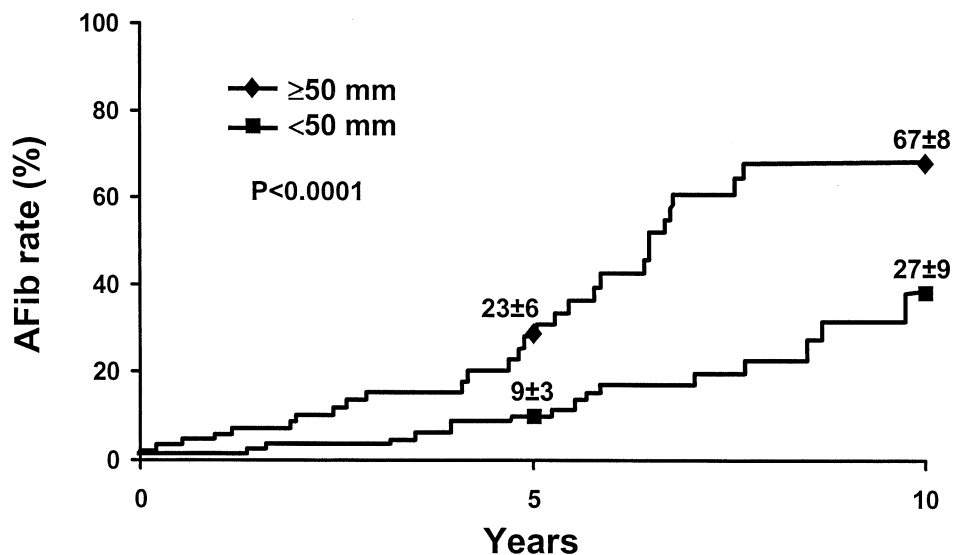


Figure 3. Atrial fibrillation (AFib) rate in patients with mitral regurgitation due to flail leaflets diagnosed with the patient in sinus rhythm, according to left atrial diameter at diagnosis <50 or ≥50 mm. Note the considerably higher rate in patients with a markedly dilated left atrium.

Table 2. Multivariate Predictors of Atrial Fibrillation

Variable	Unit	Risk Ratio	95% CI	p Value
A. Models Using Original Variables in Patients With MR Due to Flail Leaflets				
Age	Per year	1.044	1.02-1.08	0.002
Gender	Per female	1.85	0.98-3.40	0.057
LA	Per mm	1.08	1.04-1.12	0.0002
B. Models Using Original Variables in All Patients With Degenerative MR				
Age	≥ 65 years	2.76	1.64-4.86	0.0001
Gender	Per female	1.47	0.89-2.37	0.14
LA	≥ 50 mm	2.77	1.72-4.45	0.0001
C. Models Using Normalized Variables in All Patients With Degenerative MR				
Age	≥ 65 years	3.26	1.79-6.36	0.0001
Gender	Per female	1.30	0.75-2.20	0.34
LA-normalized	Per 10% increase	1.46	1.25-1.68	0.0001

CI = confidence interval; LA = left atrial diameter; LA-normalized = LA/(mean LA of patient gender) (10% increase in LA-normalized is 5.0 mm in men and 4.7 mm in women); MR = mitral regurgitation.

6.58, $p = 0.001$). In multivariate analysis, new AF was independently (adjusting for baseline age, NYHA functional class and EF) associated with CHF (adjusted RR = 2.26, $p = 0.032$) whether AF was initially permanent or paroxysmal ($p = 0.09$). Rates of cardiac death and CHF at 5 and 10 years were $31 \pm 3\%$ and $59 \pm 5\%$, respectively, and were independently higher after new AF (adjusted RR = 3.13, $p = 0.0009$). When examined in all patients with degenerative MR, AF during follow-up remained associated with higher rate of subsequent CHF (adjusted RR [95% CI] = 4.85 [2.89 to 8.14], $p < 0.0001$) and of CHF or cardiac death (adjusted RR [95% CI] = 4.37 [2.74 to 6.97], $p < 0.001$).

DISCUSSION

The present study shows that AF is a common complication in patients with degenerative MR while they are conservatively managed, occurring at a linearized rate of 5% per year. The incidence of AF is similar whether MR is due to flail leaflets or MVP. The onset of AF is independently associated with an increased risk of adverse cardiac death and heart failure. With advancing age, the risk of AF increases markedly. The LA dimension in sinus rhythm is also a major independent predictor of subsequent AF under conservative management. The high frequency and severe consequences of the development of AF and its association with LA size suggest that consideration should be given to preventing LA enlargement and to incorporating LA size in the clinical decision-making process in patients with MR. **AF in patients with MR.** Atrial fibrillation is a common arrhythmia associated with an adverse prognosis (2,3). In the population, valvular disease is a risk factor for AF (4,6), but the incidence and implications of AF in specific valvular diseases remain uncertain. Such data are particularly important in MR because of the current high prevalence of MR (8) and of the uncertainties regarding the implications of AF in its management (13).

Although mild functional MR is common in primary AF (26), in MR due to organic valve diseases AF has been variably reported as rare (7,11) or relatively frequent (12) in small series that did not permit definition of determinants and outcome implications of AF. In the present study of patients with isolated pure degenerative MR due to MVP or flail leaflets, and who were conservatively managed after diagnosis in sinus rhythm, AF occurred frequently—in almost half the patients at 10 years, corresponding to a linearized rate of 5% per year. This rate includes permanent

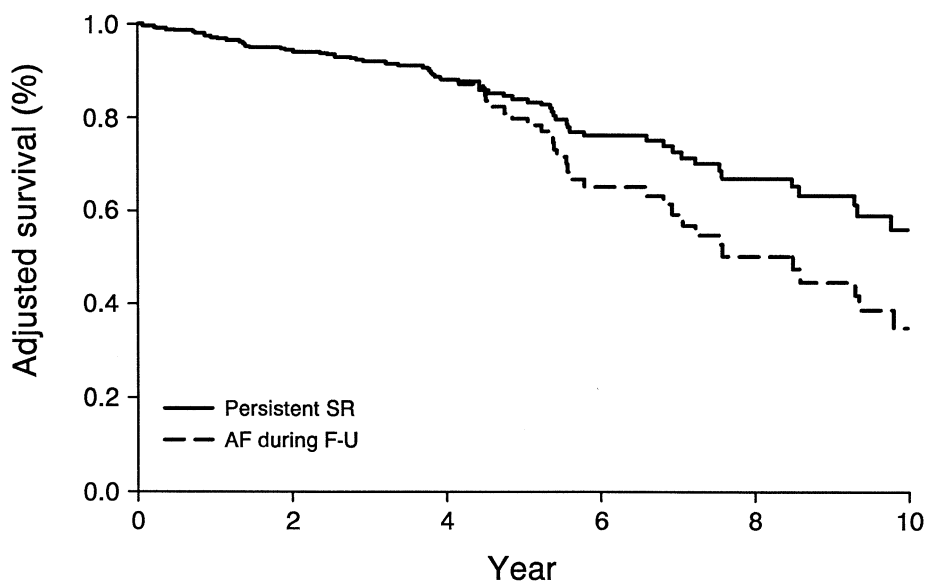


Figure 4. Survival of patients with mitral regurgitation due to flail leaflets adjusted for age, gender, ejection fraction and symptoms at baseline, and separating at the fourth year after diagnosis those patients with and those without postdiagnosis atrial fibrillation. Note the excess mortality in patients with follow-up atrial fibrillation. SR = sinus rhythm; AF = atrial fibrillation; F-U = follow-up.

and paroxysmal AF, but combining these two forms is justified by previous reports and by our present data, suggesting that the prognosis of these two forms of AF may not be distinguishable (27).

Moreover, the high recurrence of AF after a first episode suggests that distinguishing paroxysmal from permanent AF is moot and that any AF should be considered a harbinger of clinical complications. Indeed, in the present series, we noted—to our knowledge for the first time—that the occurrence of AF in patients with MR is independently associated with an increased risk of death and heart failure under conservative management. After occurrence of AF, the risk of death or CHF more than doubles, even adjusting for baseline predictors of outcome. The grave prognosis of AF justifies defining the determinants of AF during follow-up.

Factors predisposing to AF in patients with MR. In the population, advancing age is linked with higher rates of AF (4,6,28). A link between AF and coronary disease has been suggested (29) but most often denied (30,31), and this was not observed in our series. The mechanism by which aging influences the occurrence of AF remains unclear, but it may be related to structural or functional properties of atrial tissue (32). Nevertheless, AF is also frequent in younger patients with MR initially in sinus rhythm, occurring in almost one-fourth of them at 10 years and suggesting that other predisposing factors may lead to AF.

We observed a trend for slightly higher risk of AF in women. This trend, noted previously (6,33) although not consistently (34), was insignificant, particularly when gender differences in LA size were accounted for. Also, identical rates of AF were noted in MR due to flail leaflets and MVP, showing that AF is a complication of MR and not of a specific mitral lesion. Nevertheless, the lack of significant association between degree of MR and AF rate in patients with flail leaflet probably reflects a rapid progression of MR and of LA enlargement in these patients (35).

Thus, an important observation of this study is that LA enlargement is not a benign compensatory phenomenon in MR but leads to AF and its complications. A large atrial size has long been noted with chronic AF (36). However, this study demonstrates that in patients with degenerative MR in sinus rhythm at diagnosis, LA enlargement precedes and predisposes to the development of AF (4,5,9). Because AF seems to result from micro-re-entrant circuits (37), LA anatomic and electrical properties contribute to the arrhythmia (9). Left atrial enlargement preceding AF may be related to larger regurgitant volume (38) or to alterations of atrial myocardium (39), or to both, but in any case, LA dilation disturbs impulse propagation, leading to AF (5). Indeed, LA dimension remains independently predictive of AF, even after controlling for other markers of volume overload, such as LV size and function. Therefore, the clinical implications of these data should be considered.

Clinical implications. Occurrence of AF was independently related to excess mortality and morbidity under

conservative management, in contrast to the fact that AF in asymptomatic patients with MR is labeled a class II indication for surgery (13). In view of the present results and the high maintenance of sinus rhythm if surgery is performed promptly after the onset of AF (40), it appears reasonable that recent onset of AF be considered a class I indication for surgery. Indications for the MAZE procedure (41) in MR with AF are not fully defined, but the relatively low additional risk of the atrial procedure suggests that such a combination can be considered (42).

Prevention of AF in MR is important. Prevention of LA enlargement has not yet been demonstrated. Early surgery appears to prevent cardiovascular morbidity (43) and may minimize complications related to marked LA enlargement (44), but its role in preventing AF is uncertain. The role of vasoactive treatment in MR has not been defined (13,45), but it may reduce LA size (46). In view of our data, clinical trials testing possible prevention of LA enlargement and AF in MR are needed.

Study limitations. Only AF demonstrated by electrocardiogram was considered. Thus, brief or unrecorded AF episodes may have been ignored. This approach, justified by potential misclassifications (6), was used in population studies of AF (5,6,9).

The echocardiographic diagnosis of flail leaflet (16,17) and MVP (18) at different dates has become reliable and widely accepted and, therefore, the two populations are not totally simultaneous and their results are presented separately. Remarkably, the rates, predictors and impact of AF are identical, showing the robustness of the present data, which can be applied to all degenerative MR. For clinical outcome, a referral bias is often possible. However, in both uni- and multivariate analyses, AF rates were similar ($p = 0.67$ and $p = 0.47$) in community-based MVP and flail leaflet patients, and adjustment for comorbidity did not affect the results ($p > 0.40$), suggesting a low probability of referral bias.

The link between LA enlargement and subsequent AF may be questioned. However, LA size is also a marker of subsequent AF in the general population (5,6,9), of subsequent heart failure in MR (12), and even of subsequent mortality after surgery (47). Importantly, LA size normalized to BSA was a less powerful predictor of AF than was the absolute LA diameter or LA simply normalized to the mean by gender.

Conclusions. Patients with degenerative MR diagnosed in sinus rhythm, while under conservative management, incur subsequent AF frequently, in close to half of them at 10 years. The occurrence of AF is independently associated with a higher rate of subsequent adverse cardiac events. These findings suggest that prompt surgical consideration should be given to patients with severe MR in whom AF develops. Advancing age and LA enlargement at baseline are major predisposing factors for the development of AF. Therefore, the degree of LA enlargement, as a predictor of subsequent AF, should be taken into account when surgery

is considered in patients with degenerative MR in sinus rhythm, and the possibility of preventing progression of LA enlargement should be evaluated in controlled trials in patients with MR.

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