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ORIGINAL RESEARCH

Outcomes in Mitral Regurgitation Due to Flail Leaflets

A Multicenter European Study

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OBJECTIVES The purpose of this study was to assess incidence and predictors of events associated with nonsurgical and surgical management of severe mitral regurgitation (MR) in European institutions.

BACKGROUND The management of patients with MR remains disputed, warranting multicenter studies to define clinical outcome in routine clinical practice.

METHODS The MIDA (Mitral Regurgitation International DAtabase) is a registry created for multicenter study of MR with echocardiographically diagnosed flail leaflet as a model of pure, organic MR. Our cases were collected from 4 European centers. We enrolled 394 patients (age 64 ± 11 years; 67% men; 64% in New York Heart Association functional class I to II; left ventricular ejection fraction 67 ± 10%).

RESULTS During a median follow-up of 3.9 years, linearized event rates/year under nonsurgical management were 5.4% for atrial fibrillation (AF), 8.0% for heart failure (HF), and 2.6% for death. Mitral valve (MV) surgery was performed in 315 (80%) patients (repair in 250 of 315, 80%). Perioperative mortality, defined as death within 30 days from the operation, was 0.7% (n = 2). Surgery during follow-up was independently associated with reduced risk of death (adjusted hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.21 to 0.84; p = 0.014). Benefit was largely driven by MV repair (adjusted HR vs. replacement 0.37, 95% CI 0.18 to 0.76; p = 0.007). In 102 patients strictly asymptomatic and with normal ventricular function, 5-year combined incidence of AF, HF, or cardiovascular death (CVD) was 42 ± 8%. In these patients, surgery also reduced rates of CVD/HF (HR 0.26, 95% CI 0.08 to 0.89; p = 0.032).

CONCLUSIONS In this multicenter study, nonsurgical management of severe MR was associated with notable rates of adverse events. Surgery especially MV repair performed during follow-up was beneficial in reducing rates of cardiac events. These findings support surgical consideration in patients with MR due to flail leaflets for whom MV repair is feasible. (J Am Coll Cardiol Img 2008;1:133–41)

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Mitral regurgitation (MR) is one of the most frequent valve lesions, both in Europe (1) and U.S. (2), and its prevalence is increasing, owing to the aging of the population (3,4). The best current treatment for organic MR remains uncertain (1,5,6). Studies from a single North American institution underlined the unfavorable prognosis of organic MR and the therapeutic potential of early surgical treatment (7–11). By contrast, a single-center European study (from Austria) (12) recently indicated that asymptomatic severe MR has a favorable prognosis under watchful nonsurgical management, raising profound uncertainties about the natural history of the disease and the real need for "prophylactic surgery."

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CI = confidence interval
CVD = cardiovascular death
HF = heart failure
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction
LVESD = left ventricular end-systolic diameter
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association

These conflicting results have major implications, because the American and European guidelines for the management of valvular heart disease are becoming more liberal, and mitral valve (MV) repair can now be considered in non-symptomatic patients with normal ventricular function (1,6). Because single-center studies might reflect institutional referral patterns rather than disease-specific outcomes, multicenter studies are needed to generate information applicable to everyday clinical practice.

The MIDA (Mitral Regurgitation International DAtabase) was set up specifically to facilitate multicenter study of the medical and surgical outcome of MR in routine clinical practice, and therefore all consecutive patients were enrolled irrespective of baseline characteristics. In keeping with previous studies (7–10) and current guidelines (1,13), participating centers use echocardiographically diagnosed flail leaflet (see Online Videos 1A and 1B) as a model of significant organic MR. In the present work, we evaluated data from European MIDA centers to investigate in routine practice: 1) incidence and predictors of cardiac morbidity and mortality under nonsurgical management of MR; 2) effects of MV surgery; and 3) the impact of the type of surgery on prognosis.

METHODS

Study design. The MIDA was assembled by systematically merging a series of prospectively assembled electronic institutional databases, each originally created to optimize echocardiographic reporting (MIDA centers and investigators are listed in the Appendix). For the present analysis, we considered only patients from the 4 European centers (tertiary centers at university hospitals in France [n = 2] and Italy [n = 2]). All patients provided prior informed consent for anonymous publication of their clinical data for scientific research purposes; the study was conducted in accordance with our institutional guidelines, national legal requirements, and the revised Helsinki declaration.

Patients were screened for the study if they had degenerative MR with flail leaflet diagnosed with the use of two-dimensional echocardiography between 1988 and 2004 at 1 of the participating centers. Specific eligibility criteria for entry in the MIDA database were: 1) presence of an echocardiographically diagnosed flail leaflet according to validated criteria (7,14); 2) availability of a comprehensive clinical/instrumental evaluation at the time of baseline echocardiography; 3) exclusion of ischemic MR (including papillary muscle rupture); and 4) absence of significant concomitant aortic valve disease, congenital diseases or mitral stenosis, and prior valve surgery.

Echocardiography. All index transthoracic echocardiograms were performed within routine clinical practice, with standard methods (15), and prospectively entered in each of the original institutional databases. Severity of MR was assessed semiquantitatively on a scale from 1 to 4 by Doppler echocardiography (7–10,16,17). Diagnosis of flail leaflet was based on the failure of leaflet cooptation, with rapid systolic movement of the involved leaflet tip in the left atrium (7,14).

Follow-up. Follow-up collection started in January 2004 and was completed in December 2004 in 384 (98%) patients. Overall follow-up extended from baseline evaluation until study closure or last available contact (or death). During follow-up, patients were monitored by their referring physicians. The following adverse events were recorded: onset of new atrial fibrillation (AF) (with electrocardiographic evidence); heart failure (HF); total mortality; and cardiovascular death (CVD). Clinical variables were obtained by review of medical records. Events were ascertained by clinical interviews and/or by telephone calls with physicians, patients, and (if necessary) next of kin. Autopsy records and death certificates were consulted for attribution of cause of death.

Statistical analysis. Continuous variables are expressed as mean ± 1 SD and/or as median values (25th to 75th percentile). Categorical data are reported as numbers (percentages). Group comparisons were performed with the *t* test or chi-square test, as appropriate. Event rates were estimated by the Kaplan-Meier method and (for descriptive purposes) with linearized yearly rates. Event rates under nonsurgical management were calculated considering the entire follow-up of those patients who did not undergo MV surgery or the period from baseline to any MV operation (as appropriate). Rates of new AF were calculated with data from patients in sinus rhythm at baseline. We assessed the global incidence of typical MR-related events in terms of new AF, HF, or CVD (composite end point; of note, patients who had AF at baseline were considered to take into account only their contribution to incidence of HF or CVD). Post-surgical follow-up started at the time of the intervention and included the immediate post-surgical phase (unless otherwise reported).

Cox proportional hazards analysis was used to assess predictors of events under nonsurgical management; variables reaching $p < 0.10$ were entered in a multivariate model, and hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). To assess the influence of surgery on outcome, we considered the overall follow-up and performed time-dependent proportional hazards analysis within multivariate models including all baseline predictors of events.

All tests were performed with StatView 5.0.1 software (SAS Institute Inc., Cary, North Carolina) for Windows; a value of $p < 0.05$ was considered as significant.

RESULTS

Study population. The eligibility criteria were fulfilled by 394 patients, whose characteristics are summarized in Table 1. The majority of patients presented with no or minimal symptoms and normal ventricular function. The low prevalence of coronary artery disease (9%) is consistent with the organic etiology of the regurgitation. Flail leaflet was attributable exclusively to a degenerative process in 357 (91%) patients and to endocarditis in the remaining 37 (9%). Involvement was confined to the posterior leaflet in 314 (79%) patients and to the anterior leaflet in 31 (8%) and was nonspecified in 3 (1%); both leaflets were involved in 46 (12%).

Table 1. Baseline Characteristics of 394 Patients With MR Due to Flail Leaflet

Age (yrs)	64 ± 11
Male gender	265 (67%)
NYHA functional class III–IV	142 (36%)
Sinus rhythm	325 (83%)
History of coronary artery disease	33 (9%)
Left atrial dimension (mm)	48 ± 8
Left ventricular end-diastolic dimension (mm)	59 ± 8
Left ventricular end-systolic dimension (mm)	35 ± 7
Left ventricular ejection fraction (%)	67 ± 10
Grade 3–4 MR by Doppler echocardiography	381 (97%)
Vasodilators	236 (60%)
Beta-blockers	73 (19%)
Digoxin	95 (24%)
Diuretics	199 (51%)

MR = mitral regurgitation; NYHA = New York Heart Association.

Mean overall duration of follow-up was 4.6 ± 3.1 years (median, 3.9 years; interquartile range, 2.2 to 6.5 years). Forty-four deaths were recorded; 32 were CVD. Estimated overall survival at 5 and 10 years was 89 ± 2% and 77 ± 4%, respectively.

Outcome under nonsurgical management. During a mean nonsurgical management of 1.4 ± 2.3 years (median, 0.4; interquartile range, 0.1 to 1.4 years), 14 patients died, 24 had new onset AF, and 40 had HF. Causes of death were left ventricular (LV) dysfunction (n = 8), unexplained sudden death (n = 2), coronary artery disease (n = 1), and noncardiac (n = 3). Estimated overall survival was 86 ± 4% at 5 years. Table 2 reports numbers, linearized rates, and estimated 5-year incidence of adverse events during nonsurgical management, and Figure 1 depicts estimated 8-year cumulative incidence of adverse events.

In univariate analysis, the following baseline variables reached at least a trend ($p < 0.10$) toward association with adverse cardiac events (AF, HF, or

Table 2. Numbers, Linearized Rates, and 5-Year Estimated Incidence of Events in Patients With MR Due to Flail Leaflet During Nonsurgical Management

Event	Events n (%)	Linearized Rates	5-Yr Incidence
New-onset AF*	24 (8%)	5.4%/yr	25 ± 5%
HF	40 (10%)	8.0%/yr	39 ± 6%
Total mortality	14 (4%)	2.6%/yr	14 ± 4%
HF/CVD	46 (12%)	9.3%/yr	42 ± 6%
AF/HF/CVD	59 (15%)	12.4%/yr	51 ± 6%

*In patients in sinus rhythm at baseline (n = 325).
AF = atrial fibrillation; CVD = cardiovascular death; HF = heart failure; MR = mitral regurgitation.

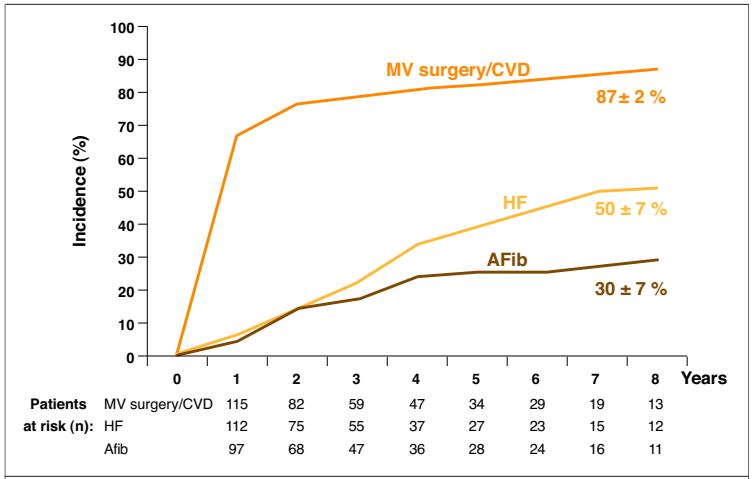


Figure 1. Long-Term Outcome of Mitral Regurgitation Due to Flail Leaflet Under Medical Treatment

Kaplan-Meier curves showing the estimated 8-year cumulative incidence of atrial fibrillation (AFib), heart failure (HF), or mitral valve (MV) surgery/cardiovascular death (CVD) during nonsurgical management of patients (n = 394) with mitral regurgitation due to flail leaflet. The results indicate that patients experienced high rates of adverse events under nonsurgical management, and surgery seemed almost unavoidable at 8 years.

CVD): age (p = 0.001), New York Heart Association (NYHA) functional class III to IV (p < 0.001), renal insufficiency (p < 0.001), left ventricular end-systolic diameter (LVESD) (p = 0.016), and left ventricular ejection fraction (LVEF) (p = 0.002). With Cox proportional hazards analysis, independent predictors of cardiac events were age (adjusted HR/year 1.03, 95% CI 1.01 to 1.05; p = 0.025); NYHA functional class (adjusted HR for class III to IV 2.93, 95% CI 1.62 to 5.32; p < 0.001), and LVEF (adjusted HR/% 0.96, 95% CI 0.93 to 0.98; p = 0.001). Notably, right ventricular systolic pressure (p = 0.48) and LVESD (p = 0.73) did not retain independent significance.

Surgery and post-surgical outcome. The MV surgery was performed in 315 (80%) patients, on the basis of the following indications: dyspnea/HF in 215 (68%), "prophylactic surgery" in 47 (15%), LV dilation in 19 (6%), endocarditis in 13 (5%), isolated AF in 1, and various other factors in the remaining 20 (6%).

The median time (25th to 75th percentile) from the baseline echocardiogram to the MV operation was 2 (1 to 8) months. Estimated combined incidence of MV surgery/CVD at 8 years was 87 ± 2% overall (Fig. 1). Of note, patients who did not undergo surgery had severe symptoms at baseline less often (NYHA functional class III to IV: 13 of 79 [16%] vs. 129 of 315 [41%]; p < 0.001) but, in comparison with the other patients, did not display statistically significant differences in terms of age (66 ± 13 years vs. 64 ± 11 years; p = 0.095), LVEF (66 ± 8% vs. 67 ± 9%; p = 0.4), renal insufficiency (6 of 79 [8%] vs. 15 of 315 [5%]; p = 0.4), diabetes (5 of 79 [7%] vs. 27 of 315 [9%]; p = 0.6), or pulmonary disease (10 of 79 [13%] vs. 31 of 315 [10%]; p = 0.5).

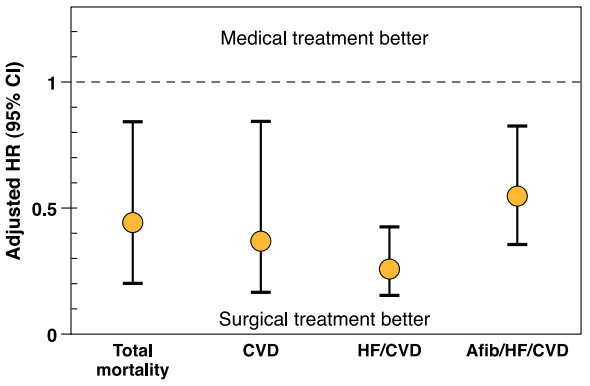
During a mean post-surgical follow-up of 4.1 ± 2.8 years (median, 3.5 years; interquartile range, 1.8 to 5.9 years), 30 patients died. Causes of death were LV dysfunction (n = 11), thromboembolisms/bleeding (n = 5), coronary artery disease (n = 3), infective endocarditis (n = 2), and noncardiac (n = 9). Perioperative mortality (defined as death within 30 days of the operation) was 0.7% (n = 2). Estimated overall survival after MV surgery was 89 ± 2% at 5 years and 79 ± 5% at 10 years. At multivariate analysis, surgery performed during follow-up was associated with a reduced risk of adverse cardiac events independently of age, NYHA functional class, and LVEF (Fig. 2).

The surgical procedure could be ascertained in all but 2 patients. The MV was repaired in 250 (80%) patients and replaced in 63 (20%). In 35 (11%) patients, a coronary artery bypass graft was also performed during MV surgery. At baseline, patients who underwent MV replacement were on average older than those who had MV repair (66 ± 10 years vs. 64 ± 11 years, p = 0.089), more often presented confined anterior leaflet involvement (13% vs. 6%, p = 0.068), and more often had AF (29% vs. 15%, p = 0.013). No significant difference between patients who received MV repair or replacement was found in terms of baseline mean LVEF or prevalence of NYHA functional class III to IV (both p > 0.49). The mean time from the echocardiogram to surgery was longer in patients who eventually underwent MV replacement (16 ± 27 months vs. 7 ± 17 months, p = 0.002). Table 3 reports numbers (linearized rates) and estimated 5-year incidence of adverse events during post-surgical follow-up according to surgical strategy. Estimated 5-year overall survival was 92 ± 2% in patients who had MV repair and 80 ± 6% in those submitted to MV replacement (p < 0.001). As can be seen from Figure 3, after adjusting for age, LVEF, end-diastolic diameter, and NYHA functional class, MV repair remained associated with remarkably better outcomes.

Subgroup analysis of asymptomatic patients with normal ventricular function. In light of current guidelines (1,6) and the finding that severe symptoms and LV dysfunction were predictors of adverse events in this and other (7) study populations, we

also evaluated clinical outcome in the subgroup of patients (n = 102) who presented with neither of these risk factors. The age of patients in NYHA functional class I and with LVEF ≥60% was 60 ± 13 years; 79 (78%) were men, 93 (92%) were in sinus rhythm, and 99 (98%) did not show signs of pulmonary hypertension (i.e., pulmonary artery systolic pressure ≥50 mm Hg [6]). Under nonsurgical management, the 5-year survival of these patients was 97 ± 3%. Linearized yearly event rates were 4.0% for AF, 5.7% for HF, and 0.4% for CVD. The combined incidence of AF, HF, or CVD at 5 years was 42 ± 8%.

Mitral valve surgery was eventually performed in 70 (69%) patients after a median of 6 months. The MV was repaired in 57 (82%) and replaced in the other 13 (18%). No perioperative death was recorded. Survival 5 years after MV surgery was 90 ± 5% (100% after MV repair). Patients who underwent MV surgery within 12 months of baseline (n = 49) showed a lower risk of adverse events when compared with the patients assigned initially to medical management (n = 53, of which 21 eventually had surgery) (Fig. 4). Of note, although the relative risk of CVD was much lower than 1 with early surgical management, this end point did not reach statistical significance. Estimated 5-year overall survival was 100% in patients who underwent surgery within 12 months and 96 ± 3% in those initially assigned to medical management (p = 0.39).



End-point	Adjusted HR [95% CI] for MV surgery performed	P value
Total mortality	0.42 [0.21-0.84]	0.014
CVD	0.37 [0.17-0.84]	0.018
Heart failure (HF)/CVD	0.26 [0.16-0.42]	<0.001
Atrial fibrillation (AFib)*/HF/CVD	0.54 [0.36-0.82]	0.003

Figure 2. Independent Associations Between MV Surgical Treatment and Outcome in 394 Patients With Flail Leaflet

Time-dependent analysis shows favorable associations between MV surgery and outcome in patients (n = 394) with degenerative MR due to flail leaflet (after adjusting for age, New York Heart Association functional class, and left ventricular ejection fraction. The results support the rationale for considering MV surgery early in the course of the disease. Cases of perioperative (i.e., <30 days) AFib (n = 24) were excluded from the analysis. Point estimates of hazard ratios (HRs) are graphically depicted as **circles**, with their 95% confidence intervals (CI) **(lines)**. Abbreviations as in Figure 1.

DISCUSSION

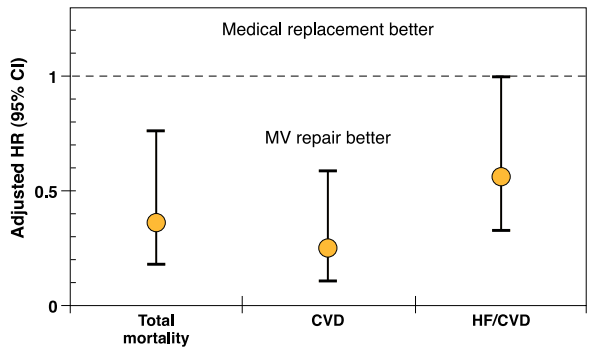
To our knowledge, this is the first multicenter study on the long-term outcome of MR diagnosed by echocardiography under nonsurgical management and during post-surgical follow-up. Whereas the results of nonsurgical management could be a cause of concern, those after MV repair seem reassuring. Patients with flail leaflet had notable cardiac morbidity and mortality, despite favorable clinical and instrumental parameters at presentation. Benefits of MV surgery were mainly seen in patients who underwent MV repair early during the course of the disease.

Outcome under nonsurgical management. Because most previous studies of MR derive from a single American center (7–11), it was unclear whether such a high rate of adverse cardiac events would be encountered in clinical practice elsewhere. Variations are to be expected in patients' characteristics between institutional settings, and differences between health care systems could influence surveillance modalities and therefore limit the external validity of results. Remarkably, a recent single-center analysis (12) of the outcome of 132 Austrian patients affected by severe organic MR—only about one-half of whom had flail leaflet—recorded a benign prognosis: at 4 years, overall survival was 96% and survival free from any indicator for surgery was 78%. These findings question the appropriateness of prophylactic surgery, as contemplated in the current guidelines (1,6). The present analysis of

Table 3. Numbers of Events in Patients With MR Due to Flail Leaflet During Post-Surgical Follow-Up and 5-Year Incidence (Linearized Rates) According to Type of Surgical Procedure

Event	n (%)	5-Yr Incidence (Linearized Rates)	
		Replacement (n = 63)	Repair (n = 250)
Total mortality	30 (10%)	20 ± 6% (5.3%/yr)	8 ± 2% (1.5%/yr)*
CVD	21 (7%)	16 ± 5% (4.6%/yr)	6 ± 2% (0.8%/yr)*
HF	29 (10%)	6 ± 3% (2.2%/yr)	13 ± 3% (2.5%/yr)
HF/CVD	46 (15%)	21 ± 6% (6.3%/yr)	16 ± 3% (3.2%/yr)*

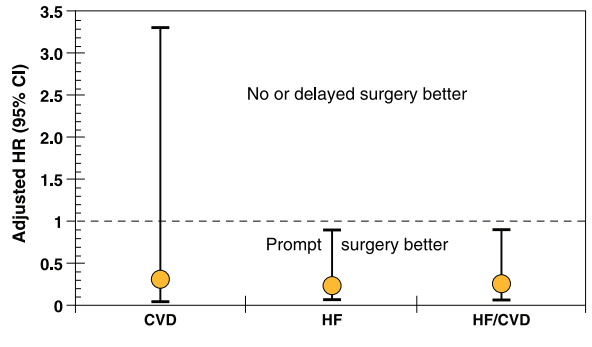
*Difference statistically significant (i.e., <0.05) between mitral valve repair versus replacement. Abbreviations as in Table 2.



End-point	Adjusted HR [95% CI] for MV repair performed	P value
Total mortality	0.37 [0.18-0.76]	0.007
Cardiovascular death (CVD)	0.24 [0.10-0.58]	0.002
Heart failure (HF)/CVD	0.58 [0.33-1.00]	0.051

Figure 3. Independent Associations Between Surgical Strategy and Outcome in 313 Patients With Flail Leaflet Undergoing MV Surgery

Time-dependent analysis shows favorable associations between MV repair (vs. replacement) and outcome in patients (n = 313) with degenerative MR due to flail leaflet (after adjusting for age, New York Heart Association functional class, and left ventricular end-diastolic diameter and ejection fraction). Mitral valve repair currently seems to be the strategy of choice in degenerative MR. Point estimates of HRs are graphically depicted as **circles**, with their 95% CI **(lines)**. Abbreviations as in Figures 1 and 2.



End-point	Adjusted HR [95% CI] for early surgery performed	P value
Cardiovascular death (CVD)	0.38 [0.05-3.33]	0.386
Heart failure (HF)	0.20 [0.05-0.89]	0.035
HF/CVD	0.26 [0.08-0.89]	0.032

Figure 4. Independent Associations Between Therapeutic Strategy and Outcome in 102 Asymptomatic Patients With LVEF ≥60%

Time-dependent analysis in asymptomatic patients with normal ventricular function (n = 102) (after adjusting for age) shows favorable associations between prompt surgery (vs. no or delayed surgery) and HF and the combined end point HF/CVD (only CVD failed to reach statistical significance). Mitral valve repair in asymptomatic patients with normal ventricular function seems to prevent cardiac morbidity. Prompt surgery was defined as an operation performed <12 months after echocardiography (delayed surgery as ≥12 months). Point estimates of HRs are graphically depicted as **circles**, with their 95% CI **(lines)**. Abbreviations as in Figures 1 and 2.

data pooled from several European centers was based on a larger sample size (12). We found a total annual mortality under medical treatment approaching 3%, with notable linearized annual rates of AF (5.4%) and HF (8.0%) (Table 2). Thus, MR due to flail leaflet seemed to be associated with serious morbidity and mortality (Fig. 1). This study's focus on routine clinical practice implied inclusion of all consecutive patients with MR. Because the inclusion of patients meeting consensus guidelines for surgery might conceivably have contributed to the high incidence of events under nonsurgical management (ultimately leading to an overestimate of the related risks), we also performed a subgroup analysis of lower-risk patients. Remarkably, adverse cardiac events were also rather common among asymptomatic patients who presented with normal ventricular function (freedom from CVD or any indication for surgery at 5 years was only 58%).

The MIDA registry has the advantage of taking flail leaflet as a model of pure, severe chronic MR (7–10). As well as being a specific sign of severe MR according to current guidelines (1,13), flail leaflet is a frequent cause of surgical MR (3,4,7,13). Studies using different models of MR have generated highly variable 5-year survival figures (ranging from 27% to 97%) (7). In addition to sample size considerations (18–22), discrepancies can also be related to enrolment of patients with varying degrees of regurgitation (18,23,24). Of note, patients enrolled in the Austrian series (12) had generally smaller ventricular dimensions (likely reflecting less severe consequences of MR) than the present cohort. The favorable outcome recorded in the Austrian study (12) might also be related to the significantly younger mean age of the patients (55 ± 15 years). The mean age of the present study population (64 ± 11 years) is consistent with the demographic data of patients enrolled in the large Euro Heart Survey on Valvular Heart Disease (mean age 64 ± 14 years) (4) and therefore likely provides a better reflection of current routine clinical practice.

Surgery and post-surgical outcome. In the present study, MV surgery generally seemed to be almost inevitable in the medium term (Fig. 1). Interestingly, the proportion of surgical interventions that could be considered "prophylactic" was rather similar to that reported in the European survey (4), likely reflecting a growing awareness of the severity of natural history of MR. The MV surgery performed during follow-up was independently associated with a reduced risk of total mortality (p =

0.014), CVD ($p = 0.018$), HF/CVD ($p < 0.001$), and AF/HF/CVD ($p = 0.003$) (Fig. 2). Notably, early surgical treatment was also associated with a reduced risk of cardiac morbidity in nonsymptomatic patients with normal ventricular function (Fig. 4). This is, to our knowledge, the first multicenter study to provide evidence of the benefits of MV surgery (25–27). Although previous single-center studies indicated that early surgical treatment might be warranted, the specific characteristics of the setting raised uncertainties on the applicability of the surgical results to clinical practice elsewhere (28,29). In the present series, the operative mortality (defined as death within 1 month of the operation) was <1%, a finding in line with a recent survey by the European Society of Cardiology (4). This reassuring figure might be related to the patients' generally favorable clinical/instrumental parameters at the time of the intervention and the large proportion of MV repairs. Of note, no perioperative death was recorded among asymptomatic patients with normal ventricular function. Taken together, these findings seem to support early consideration of surgery, before aging and hemodynamic deterioration can increase the surgical risk.

We found that the cardiac surgeon was able to repair the MV in 80% of cases. The feasibility of a repair seems to have been an incentive for earlier surgical treatment (patients undergoing MV repair had more favorable baseline characteristics). Nevertheless, clear benefits of MV repair were also evident at multivariate analysis (Fig. 3), indicating that MV repair is advantageous irrespective of patients' baseline characteristics. The lower rates of adverse events (Table 3) also support the MV repair strategy. Some evidence exists that the advantages of MV repair could be driven by favorable effects on ventricular function (25). However, in the present study, the greatest benefits of MV repair were observed in nonsymptomatic patients presenting normal LV function (who displayed excellent survival at 5 years).

Can the findings of this study tell us anything about optimal timing of MV surgery? Although positive results of early surgical treatment might seem attractive, the potential advantages seem largely to depend on the ability to achieve MV repair. In highly selected institutions, MV repair is successful in 90% of cases (27,29), but in the wider European Survey, only approximately 50% of interventions succeeded (4). Whether a policy of referring patients with severe organic MR to major centers characterized by greater skill in MV repair and lower mortality rates (28) is ultimately feasible and beneficial remains an open question (1,6). Notably, in the European survey, over 30% of decisions to select MV replacement were determined by lack of locally available MV repair facilities (4).

Because this is not a randomized study, no firm conclusion can be made regarding whether nonsymptomatic patients with severe MR and normal LV function should undergo prompt surgical treatment. For instance, 1 selection bias concern could regard hidden reasons for denying surgery (of note, we were unable to detect major baseline differences in comorbidities between surgically and nonsurgically treated patients). Nevertheless, the results of this multicenter study do provide suggestive evidence in favor of early consideration of surgery when MV repair is feasible. The rationale for such an approach is based on: 1) the high incidence of adverse events under medical treatment; 2) the generalized necessity of surgery in the medium term; 3) the low surgical risk; and 4) the more favorable long-term outcome when the intervention is performed in an early phase of the disease.

Study strengths and limitations. A limitation of the present study was that, whereas echocardiographic data were prospectively collected, clinical and nonechocardiographic data were obtained by review of medical records and supplemented by interviews and telephone calls with patients, relatives, and physicians. Nevertheless, the consistency of our results with previous series enrolling MR due to flail leaflets (7) argues in favor of the study's internal validity. Quantitative assessment of MR was not obtained, but restriction to patients with flail leaflet (1,13) and the consistency of ventricular diameters with previous series enrolling severe MR by quantitative assessment (11) suggests effective exclusion of moderate regurgitation. Of note, incidence of AF might have been underestimated in the absence of routine periodic loop monitor surveillance.

CONCLUSIONS

In the setting of this multicenter study, nonsurgical management of patients with pure, severe organic MR due to flail leaflet diagnosed by echocardiography was associated with a high cardiac morbidity and mortality. Surgical treatment of MR seemed to be almost unavoidable in the medium term and was generally safe and beneficial. These considerations might be seen to support the role of early surgery.

However, the potential benefits of MV surgery seemed largely to depend on the ability to repair the valve, and this observation underlines the extreme importance of carefully evaluating feasibility in individual patients.

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REFERENCES

1. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007; 28:230–68.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.
3. Olson LJ, Subramanian R, Ackermann DM, Orszulak TA, Edwards WD. Surgical pathology of the mitral valve: a study of 712 cases spanning 21 years. Mayo Clin Proc 1987;62:22–34.
4. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.
5. Lung B, Gohlke-Barwolf C, Tornos P, et al. Recommendations on the management of the asymptomatic patient with valvular heart disease. Eur Heart J 2002;23:1252–66.
6. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2006;48:e1–148.
7. Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflet. N Engl J Med 1996;335:1417–23.
8. Ling LH, Enriquez-Sarano M, Seward JB, et al. Early surgery in patients with mitral regurgitation due to flail leaflets: a long-term outcome study. Circulation 1997;96:1819–25.
9. Grigioni F, Enriquez-Sarano M, Ling LH, et al. Sudden death in mitral regurgitation due to flail leaflet. J Am Coll Cardiol 1999;34:2078–85.
10. Grigioni F, Avierinos JF, Ling LH, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002;40: 84–92.
11. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352:875–83.
12. Rosenhek R, Rader F, Klaar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238–44.
13. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
14. Mintz GS, Kotler MN, Segal BL, Parry WR. Two-dimensional echocardiographic recognition of ruptured chordae tendineae. Circulation 1978; 57:244–50.
15. Tajik A, Seward J, Hagler D, Mair D, Lie J. Two-dimensional real-time ultrasonic imaging of the heart and great vessels, technique, image orientation, structure identification, and validation. Mayo Clin Proc 1978;53:271–303.
16. Abbasi AS, Allen MW, DeCristofaro D, Ungar I. Detection and estimation of the degree of mitral regurgitation by range-gated pulsed Doppler echocardiography. Circulation 1980;61: 143–7.
17. Helmcke F, Nanda NC, Hsiung MC, et al. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75:175–83.
18. Munoz S, Gallardo J, Diaz-Gorrin JR, Medina O. Influence of surgery on the natural history of rheumatic mitral and aortic valve disease. Am J Cardiol 1975;35:234–42.
19. Hochreiter C, Niles N, Devereux RB, Kligfield P, Borer JS. Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. Circulation 1986;73:900–12.
20. Rosen SE, Borer JS, Hochreiter C, et al. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. Am J Cardiol 1994;74: 374–80.
21. DePace NL, Mintz GS, Ren JF, et al. Natural history of the flail mitral leaflet syndrome: a serial 2-dimensional echocardiographic study. Am J Cardiol 1983;52:789–95.
22. Hammermeister KE, Fisher L, Kennedy W, Samuels S, Dodge HT. Prediction of late survival in patients with mitral valve disease from clinical, hemodynamic, and quantitative angiographic variables. Circulation 1978; 57:341–9.
23. Wilson MG, Lim WN. The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life. I. Prognosis with special reference to survivorship. Circulation 1957;16: 700–12.
24. Rapaport E. Natural history of aortic and mitral valve disease. Am J Cardiol 1975;35:221–7.
25. Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. Circulation 1995;91:1022–8.
26. Gillinov AM, Cosgrove DM, Blackstone EH, et al. Durability of mitral valve repair for degenerative disease. J Thorac Cardiovasc Surg 1998;116: 734–43.
27. Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. Circulation 2001;104:I1–7.
28. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–37.
29. Braunberger E, Deloche A, Berrebi A, et al. Very long-term results (more than 20 years) of valve repair with carpentier's techniques in nonrheumatic mitral valve insufficiency. Circulation 2001;104:I8–11.

APPENDIX

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APPENDIX

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