

Original Investigation

Association Between Early Surgical Intervention vs Watchful Waiting and Outcomes for Mitral Regurgitation Due to Flail Mitral Valve Leaflets

Rakesh M. Suri, MD, DPhil; Jean-Louis Vanoverschelde, MD; Francesco Grigioni, MD, PhD; Hartzell V. Schaff, MD; Christophe Tribouilloy, MD; Jean-Francois Avierinos, MD; Andrea Barbieri, MD; Agnes Pasquet, MD; Marianne Huebner, PhD; Dan Rusinaru, MD; Antonio Russo, MD; Hector I. Michelena, MD; Maurice Enriquez-Sarano, MD

IMPORTANCE The optimal management of severe mitral valve regurgitation in patients without class I triggers (heart failure symptoms or left ventricular dysfunction) remains controversial in part due to the poorly defined long-term consequences of current management strategies. In the absence of clinical trial data, analysis of large multicenter registries is critical.

OBJECTIVE To ascertain the comparative effectiveness of initial medical management (nonsurgical observation) vs early mitral valve surgery following the diagnosis of mitral regurgitation due to flail leaflets.

DESIGN, SETTING, AND PARTICIPANTS The Mitral Regurgitation International Database (MIDA) registry includes 2097 consecutive patients with flail mitral valve regurgitation (1980-2004) receiving routine cardiac care from 6 tertiary centers (France, Italy, Belgium, and the United States). Mean follow-up was 10.3 years and was 98% complete. Of 1021 patients with mitral regurgitation without the American College of Cardiology (ACC) and the American Heart Association (AHA) guideline class I triggers, 575 patients were initially medically managed and 446 underwent mitral valve surgery within 3 months following detection.

MAIN OUTCOMES AND MEASURES Association between treatment strategy and survival, heart failure, and new-onset atrial fibrillation.

RESULTS There was no significant difference in early mortality (1.1% for early surgery vs 0.5% for medical management, $P=.28$) and new-onset heart failure rates (0.9% for early surgery vs 0.9% for medical management, $P=.96$) between treatment strategies at 3 months. In contrast, long-term survival rates were higher for patients with early surgery (86% vs 69% at 10 years, $P < .001$), which was confirmed in adjusted models (hazard ratio [HR], 0.55 [95% CI, 0.41-0.72], $P < .001$), a propensity-matched cohort (32 variables; HR, 0.52 [95% CI, 0.35-0.79], $P = .002$), and an inverse probability-weighted analysis (HR, 0.66 [95% CI, 0.52-0.83], $P < .001$), associated with a 5-year reduction in mortality of 52.6% ($P < .001$). Similar results were observed in relative reduction in mortality following early surgery in the subset with class II triggers (59.3 after 5 years, $P = .002$). Long-term heart failure risk was also lower with early surgery (7% vs 23% at 10 years, $P < .001$), which was confirmed in risk-adjusted models (HR, 0.29 [95% CI, 0.19-0.43], $P < .001$), a propensity-matched cohort (HR, 0.44 [95% CI, 0.26-0.76], $P = .003$), and in the inverse probability-weighted analysis (HR, 0.51 [95% CI, 0.36-0.72], $P < .001$). Reduction in late-onset atrial fibrillation was not observed (HR, 0.85 [95% CI, 0.64-1.13], $P = .26$).

CONCLUSION AND RELEVANCE Among registry patients with mitral valve regurgitation due to flail mitral leaflets, performance of early mitral surgery compared with initial medical management was associated with greater long-term survival and a lower risk of heart failure, with no difference in new-onset atrial fibrillation.

JAMA. 2013;310(6):609-616. doi:10.1001/jama.2013.8643

← Editorial page 587

+ Supplemental content at
jama.com

Author Affiliations: Mayo Clinic College of Medicine, Rochester, Minnesota (Suri, Schaff, Huebner, Michelena, Enriquez-Sarano); Université Catholique de Louvain, Brussels, Belgium (Vanoverschelde, Pasquet); University of Bologna, Bologna, Italy (Grigioni, Russo); Inserm, ERI-12, University Hospital, Amiens, France (Tribouilloy, Rusinaru); Aix-Marseille Université, Marseille, France (Avierinos); University of Modena, Modena, Italy (Barbieri); Michigan State University, East Lansing (Huebner).

Corresponding Author: Rakesh M. Suri, MD, DPhil, Division of Cardiovascular Surgery, Mayo Clinic, 200 First St, SW, Rochester, MN 55905 (suri.rakesh@mayo.edu).

Degenerative mitral regurgitation is common and can be surgically repaired in the vast majority of patients,^{1,2} improving symptoms and restoring normal life expectancy.³⁻⁶ Despite the safety and efficacy of contemporary surgical correction, an ongoing international debate persists regarding the need for early intervention⁷⁻⁹ in patients without the American College of Cardiology (ACC)/American Heart Association (AHA) guideline class I triggers (no or minimal symptoms and absence of left ventricular dysfunction). This is in part propagated by discordant views of the prognostic consequences of uncorrected severe mitral regurgitation; considered as benign by those supporting medical *watchful waiting*¹⁰ (nonsurgical observation until a distinct event is encountered) vs conveying excess mortality and morbidity (including heart failure and atrial fibrillation) by those advocating early surgical intervention.^{5,11} This controversy is reflected in current international consensus statements, in which North American documents categorize early mitral surgery as a class IIA recommendation (in favor of the procedure),¹² whereas it is a class IIB recommendation in Europe (not strongly in favor of the procedure).¹³

Watchful waiting has recently come under renewed scrutiny due to (1) emerging evidence that a growing number of centers can now achieve mitral valve repair rates of more than 95% with a low operative risk of less than 0.5% and (2) increasing recognition that awaiting incipient symptoms or ventricular dysfunction prior to intervention may be associated with excess long-term mortality and heart failure risks despite eventual “rescue surgery.”^{7,14} Analysis of large registries to assess comparative effectiveness has become a national priority.¹⁵ Although single-center data have suggested that early surgery is beneficial, the long-term consequences of currently interpreted and applied guidelines in diverse tertiary care practices are unknown.

To understand the comparative effectiveness of early surgery vs initial medical management strategies, we analyzed patients diagnosed with flail mitral valve from the multinational Mitral Regurgitation International Database (MIDA) registry to test the null hypothesis that these therapeutic approaches are associated with similar long-term outcomes.

Methods

Study Design

All participating medical centers provided ethics and institutional review board approval for this study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Helsinki declaration. The MIDA registry systematically merged the consecutive experience with mitral regurgitation due to flail mitral valve leaflets of 6 tertiary centers: 2 in France (university hospitals in Amiens and Marseille), 2 in Italy (university hospitals in Bologna and Modena), 1 in Belgium (Brussels), and 1 in the United States (Mayo Clinic, Rochester, Minnesota). Preliminary data from the European registry have been previously published.¹⁶ Echocardiographic variables were prospectively entered.

Eligibility

Patients were enrolled in the MIDA registry if they had degenerative mitral regurgitation with a flail leaflet detected by a 2-dimensional transthoracic echocardiography from 1980 to 2004. They were eligible for our study if they had no class I surgical triggers by current guidelines (thus excluding those with current heart failure symptoms, left ventricular ejection fraction <60%, or left ventricular end-systolic diameter \geq 40 mm). Following transthoracic echocardiographic diagnosis of a flail mitral leaflet, specific eligibility criteria were the absence of (1) ischemic mitral regurgitation; (2) significant concomitant aortic valve disease, congenital heart disease, mitral stenosis, and previous valve surgery; (3) current heart failure symptoms due to mitral regurgitation defined by Framingham criteria¹⁷; (4) overt left ventricular dysfunction defined as either ejection fraction less than 60% or end-systolic diameter of 40 mm or more; and (5) contraindication to surgery due to comorbidity. Heart failure symptoms and minor subjective manifestations (minimal symptoms not attributable to heart failure) were ascertained by each patient's personal cardiologist who was also responsible for clinical decisions regarding medical management and referral for surgery.

Echocardiography

Transthoracic echocardiograms were performed within routine clinical practice, using standard methods. Left ventricular dimensions were assessed from parasternal long-axis views by 2-dimensional direct measurements or by a guided M-mode echocardiography at end-diastole and end-systole. Ejection fraction was estimated and calculated using ventricular dimensions. The severity of mitral regurgitation was assessed semiquantitatively on a scale from 1 to 4 by Doppler echocardiography according to American Society of Echocardiography criteria.¹⁸ Diagnosis of flail leaflet was based on failure of leaflet coaptation, with rapid systolic movement of the involved leaflet tip within the left atrium. Those with echocardiographic features of mitral regurgitation related to ischemic, functional, or nonflail leaflet pathology were excluded. Echocardiograms were used as collected at the time of the index echocardiography without subsequent modification and were performed both preoperatively and following surgery.

Outcomes

Early surgery was defined as performed within 3 months from diagnosis. Initial medical management was defined as medical management during the first 3 months of follow-up then either medical or surgical treatment thereafter as deemed appropriate by the patient's personal physician in routine clinical practice. The primary end point was all-cause mortality and secondary end points were heart failure and new-onset atrial fibrillation (among patients in sinus rhythm at baseline).

Follow-up

Each patient had follow-up visits with a physician within each participating center or elsewhere. Information on follow-up events was obtained by direct patient interview and clinical examination or by repeated follow-up letters and questionnaires. Documentation of testing and surgical reports were reviewed and validated by the investigators. For patients who died

during follow-up, cause of death was adjudicated by review of death certificates, physician and hospital notes, and autopsy certificate, if available.

Statistical Analysis

All analyses were performed using R programming language, version 2.15.0,¹⁹ and SAS, version 9.2. Baseline characteristics are presented as mean (SD) or median (interquartile range [IQR]) when appropriate and compared with a 2-sided *t* test or Wilcoxon rank sum test. Categorical variables were described as frequencies (%) and compared with a χ^2 or Fisher exact test. Weighted *t* and χ^2 tests were used in the case-weighted cohort. Two-sided *P* < .05 was considered statistically significant. The Kaplan-Meier method was used to calculate the survival and event rates and presented as mean (95% CI). Incidences of mortality following diagnosis were calculated (95% CI) after diagnosis using person-years. Nonoverlapping time windows of 3 to 12 months, 1 to 5 years, and 5 years or more were selected to distinguish short-term, mid-term, and long-term outcomes. Covariates in the multivariable models were selected on the basis of their known link to outcome in patients with mitral regurgitation (age, sex, comorbidity, subjective manifestations) or their guideline-based mention as a potential trigger for surgery (class II indication, atrial fibrillation, and pulmonary hypertension). Other relevant variables such as ejection fraction less than 60%, left ventricular end-systolic diameter of 40 mm or more, and heart failure symptoms are all class I triggers for surgery and were excluded, thus not requiring adjustment.

Propensity Score Matching

The propensity for early surgery was estimated using a logistic regression model (32 variables) with the response variable being surgery within 3 months (yes/no). The distribution of propensity scores in the matched cohorts is provided in eFigure 1 in the Supplement. The study groups were matched using age, sex, and the propensity for having surgery within 3 months. The parameters used were 10 years of age, exact match on sex, and a probability of 0.10 for early surgery. For each case, a control patient was randomly selected from the potential pool of candidates defined by the parameters. Bias reduction and balance between the groups of patients with early surgery and the patients with initial medical management was assessed with standardized differences of covariates. An absolute standardized difference below 0.10 indicates a small imbalance. See eFigure 2 in the Supplement for a full description of variables and comparison before and after matching. Cox proportional hazards regression models were stratified on the matched pairs.

Inverse Probability Weighting

Cox proportional hazards regression models^{20,21} were used for the case-weighted and inverse probability-weighted analyses to determine the effect of early surgery on outcomes. Using the same baseline characteristics for the propensity score calculation allowed case-weight estimation with a logistic regression model to predict the inverse probability of having early surgery. These case weights balanced the cohorts for an inverse probability-weighted analysis that included all patients with available data.

The proportional hazards assumption in the Cox models was assessed with Schoenfeld residuals, the model fit was evaluated with martingale and Cox-Snell residuals. The proportional hazards assumption was not satisfied for atrial fibrillation outcome. In this case, hazard ratios (HRs) are to be interpreted as an average HR throughout all event times. In addition, random-effects Cox models were used to account for potential variation between the centers. A 2-sided *P* value of < .05 was considered statistically significant.

Results

Baseline Characteristics

A total of 2097 patients were enrolled in the MIDA registry, and 1021 of those were eligible for our study. Baseline characteristics were stratified by treatment groups and by matching and weighing approaches (Table 1). Some differences, such as younger age and comorbidities, suggested less risk in the early surgery group overall. Conversely, more frequent minor subjective manifestations (minor breathlessness, chest pain or pressure, palpitations, or constitutional symptoms), class II triggers for surgery, larger left heart dimensions, and higher pulmonary pressure suggested a more severely affected early surgery group. Following propensity score matching, the differences in age and comorbidity were no longer statistically significant, but patients treated by early surgery retained slightly larger left heart dimensions and more frequent class II triggers than those subjected to initial medical management (Table 1). Similar results were observed after inverse probability weighting of treatment groups. All early surgery patients had mitral valve surgery within 3 months of diagnosis (median, 14 days) and mitral valve repair was performed in 93%. During follow-up, 339 patients with initial medical management had surgery recommended by their cardiologist (87% valve repair) at a median time of 1.65 years following diagnosis. Associated coronary bypass surgery for incidentally discovered coronary disease was performed in 22% of early vs 13% of delayed surgery (*P* = .001) groups. The distribution of the propensity scores in the 2 groups were similar (eFigure 1 in Supplement). After propensity score matching, there were no significant differences in the baseline variables used for calculation (eFigure 2 in Supplement). Absolute standardized differences below 10% indicated an adequate match.

Early Outcomes Within 3 Months of Diagnosis

Within 3 months following diagnosis, 8 patients died, 5 (1.1%) after early surgery vs 3 (0.5%) during initial medical management (*P* = .28); 9 patients developed heart failure, 4 (0.9%) after early surgery vs 5 (0.9%) during initial medical management (*P* = .96); and 30 patients developed new-onset atrial fibrillation, 24 (6.2%) after early surgery vs 6 (1.2%) during initial medical management (*P* < .001), highlighting the predisposition to early atrial fibrillation after surgery.

Long-term Survival

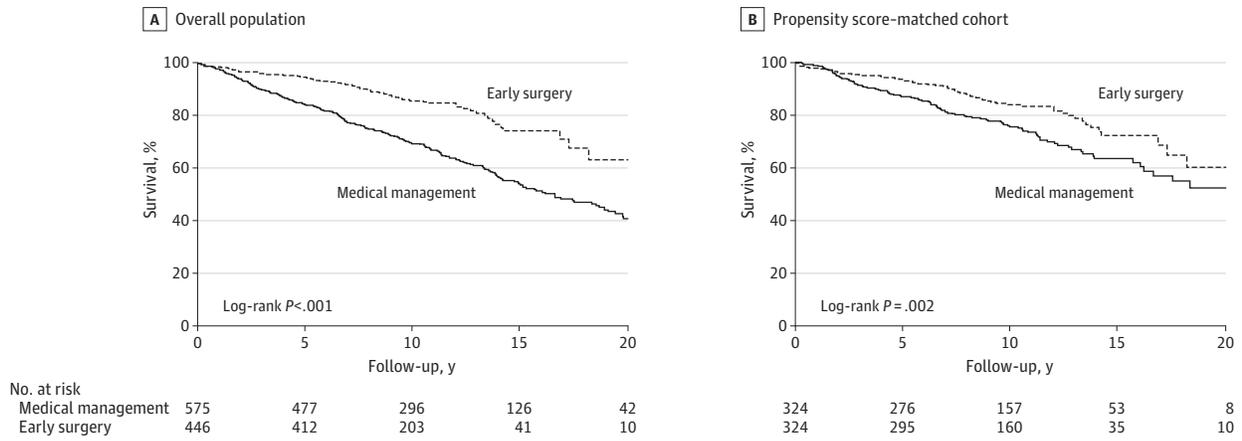
Ninety-eight percent of patients were followed up from diagnosis until death or at least 5 years. A total of 319 deaths were observed during a mean follow-up time of 10.3 years result-

Table 1. Baseline Characteristics by Treatment Cohort

| Characteristic, % | Overall | | | | Propensity Score-Matched Cohort | | | | Inverse Probability-Weighted Cohort | | | |
|---|------------------------------|-------------------------|------------------|---------|---------------------------------|-------------------------|-----------------|---------|-------------------------------------|-------------------------|------------------|---------|
| | Medical Management (n = 575) | Early Surgery (n = 446) | Total (n = 1021) | P Value | Medical Management (n = 324) | Early Surgery (n = 324) | Total (n = 648) | P Value | Medical Management (n = 571) | Early Surgery (n = 446) | Total (n = 1017) | P Value |
| Age, mean (SD), y | 67 (13) | 62 (13) | 65 (13) | <.001 | 64 (12) | 64 (12) | 64 (12) | .75 | 65 (14) | 65 (12) | 65 (13) | .93 |
| Men | 72.1 | 73.0 | 72.8 | .56 | 76.2 | 76.2 | 76.2 | >.99 | 73.1 | 73.7 | 73.4 | .83 |
| Charlson index, mean (SD) | 0.9 (1.2) | 0.8 (1.1) | 0.8 (1.2) | .05 | 0.8 (1.2) | 0.8 (1.2) | 0.8 (1.2) | .79 | 0.8 (1.2) | 0.8 (1.1) | 0.8 (1.2) | .82 |
| Minimal subjective manifestation | 32.5 | 52.2 | 41.1 | <.001 | 40.1 | 44.1 | 42.1 | .30 | 41.0 | 41.8 | 41.3 | .80 |
| Ejection fraction, mean (SD), % | 68.6 (6) | 68.7 (6) | 68.7 (6) | .65 | 68.5 (6) | 68.2 (6) | 68.3 (6) | .46 | 68.6 (6) | 69.0 (6) | 68.8 (6) | .31 |
| Hypertension | 37.4 | 36.5 | 37.0 | .78 | 40.1 | 36.4 | 38.3 | .33 | 37.3 | 36.0 | 36.7 | .67 |
| Atrial fibrillation | 10.0 | 12.4 | 11.0 | .21 | 9.9 | 13.7 | 11.8 | .14 | 10.5 | 15.5 | 12.7 | .02 |
| Pulmonary hypertension | 11.8 | 16.8 | 14.0 | .02 | 10.8 | 17.0 | 13.9 | .02 | 11.5 | 15.2 | 13.1 | .08 |
| Class II indication | 19.1 | 27.1 | 22.6 | .002 | 18.2 | 28.7 | 23.52 | .002 | 19.3 | 28.7 | 23.4 | .001 |
| Heart rate, mean (SD), beats/min | 75 (14) | 74 (16) | 74 (15) | .28 | 74 (14) | 74 (16) | 74 (15) | .48 | 76 (17) | 75 (15) | 75 (16) | .36 |
| LVEDD, mean (SD), mm | 56.0 (6.1) | 57.7 (5.9) | 56.7 (6.1) | <.001 | 56.1 (6) | 57.6 (6) | 56.9 (6) | .004 | 56.0 (6) | 57.6 (6) | 56.7 (6) | <.001 |
| LVESD, mean (SD), mm | 32.2 (4) | 33.5 (4) | 32.8 (4) | <.001 | 32.6 (4) | 33.7 (4) | 33.1 (4) | .001 | 32.4 (4) | 33.2 (4) | 32.7 (4) | .002 |
| LVESD/BSA, mean (SD), mm/m ² | 17.6 (2.5) | 17.9 (2.6) | 17.7 (2.6) | .04 | 17.5 (2.5) | 18.0 (2.4) | 17.8 (2.5) | .03 | 17.5 (2.5) | 17.9 (2.5) | 17.7 (2.5) | .03 |
| LA diameter, mean (SD), mm | 48.0 (8.0) | 49.2 (7.6) | 48.5 (7.9) | .03 | 48.0 (7.4) | 49.3 (7.7) | 48.7 (7.6) | .04 | 48.2 (8.3) | 49.2 (7.5) | 48.6 (8.0) | .04 |
| Flail posterior | 86.0 | 87.4 | 86.6 | .52 | 86.2 | 88.5 | 87.3 | .38 | 85.8 | 89.0 | 87.1 | .14 |

Abbreviations: BSA, body surface area; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

Figure 1. Survival After Diagnosis of Mitral Regurgitation Due to Flail Mitral Leaflet According to Initial Treatment Strategy



Long-term survival following early surgery vs initial medical management overall population (A) and in the propensity score-matched cohort (B).

ing in survival of 76% (95% CI, 73%-79%) at 10 years after diagnosis and 48% (95% CI, 42%-54%) at 20 years after diagnosis (52 patients at risk at 20 years). Survival among the entire unmatched cohort for early surgery was 95% (95% CI, 92%-97%) at 5 years, 86% (95% CI, 82%-89%) at 10 years, 63% (95% CI, 51%-78%) at 20 years vs 84% (95% CI, 81%-87%) at 5 years, 69% (95% CI, 66%-73%) at 10 years, and 41% (95% CI, 35%-48%) at 20 years for initial medical management ($P < .001$), favoring early surgery (Figure 1A). Multivariable Cox models for the overall cohort (Table 2) adjusting for age, sex, Charlson comorbidity index, the presence of minimal subjective manifes-

tations, and class II triggers confirmed that early surgery was associated with higher survival (adjusted HR, 0.55 [95% CI, 0.41-0.72], $P < .001$) in the overall population. Mortality rate (per 100 person-years) was lower in patients with early surgery during all periods after diagnosis (Table 3).

Propensity score matching of early surgery and initial medical management groups yielded 648 patients (324 matched pairs, Table 1). Direct comparison of survival after diagnosis in these matched groups (with identical age and comorbidity index) confirmed higher survival after early surgery (Figure 1B) (HR, 0.52 [95% CI, 0.35-0.79], $P = .002$) showing similar advantage to that

Table 2. Patient Outcomes From Cohort Cox Regression Models

| Outcome | Overall (n = 1021) ^a | | Propensity Score-Matched Cohort (n = 648) | | Inverse Probability-Weighted Cohort (n = 1017) | |
|--------------------------------------|---------------------------------|---------|---|---------|--|---------|
| | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Overall survival | 0.55 (0.41-0.72) | <.001 | 0.52 (0.35-0.79) | .002 | 0.66 (0.52-0.83) | <.001 |
| Heart failure | 0.29 (0.19-0.43) | <.001 | 0.44 (0.26-0.76) | .003 | 0.51 (0.36-0.72) | <.001 |
| New atrial fibrillation ^b | 0.85 (0.64-1.13) | .26 | 1.28 (0.84-1.95) | .25 | 1.05 (0.81-1.37) | .72 |

Abbreviations: HR, hazard ratio.

^a Overall cohort is adjusted for age, sex, Charlson index, presence of subjective manifestations (defined as minimal symptoms not attributable to heart failure), and presence of class II indication.^b For the atrial fibrillation end point, n = 902 for the overall cohort, n = 569 for the propensity score-matched cohort, and n = 899 for the inverse probability-weighted cohort.

Table 3. Incidence Rates of Mortality During Different Periods Following Detection in the Overall Study Population

| Time After Diagnosis | Initial Medical Management | | Early Surgery | | Rate Ratio (95% CI) | P Value | Relative Reduction of Mortality With Early Surgery, % ^b |
|--|----------------------------|-------------------|-----------------|-------------------|---------------------|---------|--|
| | No. of Patients | Rate ^a | No. of Patients | Rate ^a | | | |
| Overall | | | | | | | |
| 3-12 mo | 12 | 2.8 (1.3-4.4) | 2 | 0.6 (0-1.4) | 0.3 (0.03-0.8) | .03 | 78.6 |
| >1-5 y | 75 | 3.6 (2.8-4.5) | 17 | 1.0 (0.5-1.5) | 0.3 (0.2-0.5) | <.001 | 72.6 |
| >5 y | 158 | 4.4 (3.8-5.1) | 47 | 2.1 (1.5-2.7) | 0.5 (0.4-0.7) | <.001 | 52.6 |
| Without class II triggers for surgery ^c | | | | | | | |
| 3-12 mo | 7 | 2.0 (0.5-3.5) | 0 | 0.0 (0-0) | | .02 | |
| >1-5 y | 39 | 2.3 (1.6-3.0) | 10 | 0.8 (0.3-1.3) | 0.4 (0.2-0.7) | .001 | 64.9 |
| >5 y | 124 | 3.9 (3.2-4.6) | 30 | 1.7 (1.1-2.3) | 0.4 (0.3-0.6) | <.001 | 56.1 |
| With class II triggers for surgery ^c | | | | | | | |
| 3-12 mo | 5 | 6.4 (1.0-11.8) | 2 | 2.3 (0-5.5) | 0.3 (0.04-1.8) | .23 | 64 |
| >1-5 y | 36 | 10.9 (2.1-3.9) | 7 | 1.6 (0.4-2.8) | 0.2 (0.1-0.3) | <.001 | 85.2 |
| >5 y | 34 | 8.2 (3.1-10.8) | 17 | 3.3 (1.8-4.9) | 0.4 (0.2-0.7) | .002 | 59.3 |
| Without subjective manifestations ^d | | | | | | | |
| 3-12 mo | 8 | 2.9 (0.9-4.9) | 0 | 0.0 (0-3.0) | | .04 | |
| >1-5 y | 42 | 3.1 (2.2-4.1) | 7 | 0.9 (0.2-1.6) | 0.3 (0.1-0.6) | .001 | 70.5 |
| >5 y | 102 | 4.4 (3.5-5.2) | 18 | 1.9 (1.0-2.7) | 0.4 (0.3-0.7) | <.001 | 57.1 |
| With subjective manifestations ^d | | | | | | | |
| 3-12 mo | 4 | 2.7 (0.1-5.2) | 2 | 1.1 (0-2.6) | 0.4 (0.1-2.3) | .09 | 58.8 |
| >1-5 y | 33 | 4.6 (3.1-6.1) | 10 | 1.1 (0.4-1.8) | 0.2 (0.4-1.7) | <.001 | 76.9 |
| >5 y | 49 | 4.6 (3.3-5.9) | 29 | 2.3 (1.5-3.3) | 0.5 (1.4-3.1) | .002 | 50.8 |

^a Incidence per 100 person-years and 95% CIs.^b Percent reduction was calculated as 100 × [(initial medical management rate – early surgery rate) / (conservative rate)].^c Class II trigger defined as atrial fibrillation or pulmonary hypertension.^d Subjective manifestation defined as minor symptoms not attributable to heart failure.

observed in the overall cohort (Table 2). Inverse probability-weighted Cox models of the entire population demonstrated no significant difference in baseline characteristics (summarized in Table 1). Using the inverse probability-weighted Cox model, early surgery was again associated with longer survival (HR, 0.66 [95% CI, 0.52-0.83], $P < .001$).

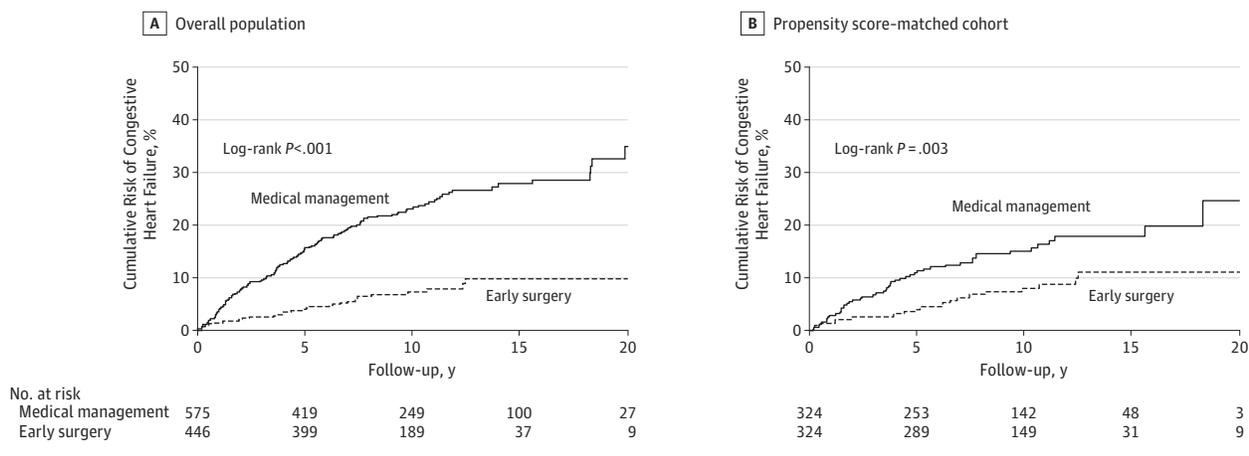
Subgroup Analysis of Long-term Survival

Among the entire study population, 231 (22.6%) patients had guideline-based class II triggers for surgery (atrial fibrillation at diagnosis or pulmonary hypertension or both) and 790 (77.4%) did not. In the absence of class II triggers for surgery, survival was better with early surgery, both overall (89% [95% CI, 85%-93%] for early surgery vs 75% [95% CI, 71%-79%] for initial medical management, $P < .001$) and in the matched cohort (87% [95% CI,

82%-92%] for early surgery vs 82% [95% CI, 77%-87%] for initial medical management, $P = .04$) at 10 years. With class II triggers, survival was better with early surgery, both overall (76% [95% CI, 68%-85%] for early surgery vs 44% [95% CI, 36%-55%] for initial medical management, $P < .001$) and in the matched cohort (75% [95% CI, 66%-86%] for early surgery vs 48% [95% CI, 37%-64%] for initial medical management, $P < .001$) at 10 years. The long-term mortality rate was lower after early surgery over all periods examined (Table 3).

Minimal subjective manifestations were noted at initial consultation in 451 patients (41%) and absent in 570 (59%). In the absence of subjective manifestations, survival was better with early surgery, both overall (87% [95% CI, 82%-92%] for early surgery vs 71% [95% CI, 67%-76%] for initial medical management, $P < .001$) and in the matched cohort (84% [95% CI, 78%-

Figure 2. Heart Failure Incidence After Diagnosis of Mitral Regurgitation Due to Flail Mitral Leaflet According to Initial Treatment Strategy



Long-term heart failure risk following early surgery vs initial medical management overall (A) and in the propensity score-matched cohort (B).

90%] for early surgery vs 78% [95% CI, 72%-85%] for initial medical management, $P = .04$ at 10 years. With subjective manifestations, survival was similarly better with early surgery, both overall (85% [95% CI, 80%-90%] for early surgery vs 66% [95% CI, 59%-73%] for initial medical management, $P < .001$) and in the matched cohort (84% [95% CI, 78%-90%] for early surgery vs 73% [95% CI, 65%-81%] for initial medical management, $P = .03$) at 10 years. The long-term mortality rate was lower after early surgery over all periods examined (Table 3).

When analysis was restricted to patients surviving 3 months after diagnosis, long-term survival was again higher after early surgery (at 10 years, 86% [95% CI, 83%-90%] for early surgery vs 70% [95% CI, 66%-74%] for initial medical management; at 20 years, 57% [95% CI, 41%-77%] for early surgery vs 41% [95% CI, 35%-48%] for initial medical management; $P < .001$). In patients surviving 3 months after diagnosis who were propensity score-matched, long-term survival was greater following early surgery at 10 years (85% [95% CI, 80%-89%] vs 75% [95% CI, 71%-81%] following initial medical management, $P < .001$).

Heart Failure Incidence

During follow-up, 167 patients incurred at least 1 incident episode of heart failure representing a rate of 16% (95% CI, 14%-19%) at 10 years and 27% (95% CI, 20%-33%) at 20 years. In the overall cohort, heart failure was less frequent after early surgery (7% [95% CI, 5%-10%] for early surgery vs 23% [95% CI, 19%-27%] for initial medical management at 10 years and 10% [95% CI, 6%-14%] for early surgery vs 35% [95% CI, 27%-42%] for initial medical management at 20 years, $P < .001$, Figure 2A). Multivariable Cox models for the overall cohort (Table 2) adjusting for age, sex, Charlson index, minimal symptoms, and class II triggers confirmed an independent protective effect associated with early surgery upon late heart failure risk (adjusted HR, 0.29 [95% CI, 0.19-0.43], $P < .001$).

In propensity score-matched cohorts, cumulative incidence of heart failure was again lower after early surgery (8% [95% CI, 5%-11%] for early surgery vs 15% [95% CI, 11%-19%] for initial medical management at 10 years and 11% [95% CI,

6%-15%] for early surgery vs 24% [95% CI, 13%-34%] for initial medical management at 20 years, Figure 2B), with HR, 0.44 (95% CI, 0.26-0.76), $P = .003$.

Inverse probability-weighted analysis also demonstrated the independent association of early surgery with freedom from late heart failure (Table 2; HR, 0.51 [95% CI, 0.36-0.72], $P < .001$).

Subgroup Analysis of Heart Failure Incidence

Early surgery was followed by lower unadjusted cumulative rates of heart failure at 10 years, both in patients with class II triggers (14% [95% CI, 6%-21%] for early surgery vs 38% [95% CI, 26%-48%] for initial medical management, $P < .001$) or without them (5% [95% CI, 3%-8%] for early surgery vs 20% [95% CI, 16%-24%] for initial medical management, $P < .001$). The adjusted HRs of heart failure associated with early surgery were lower at 10 years than medical management in patients with class II triggers (0.29 [95% CI, 0.14-0.55], $P < .001$) or without (0.29 [95% CI, 0.17-0.48], $P < .001$). Early surgery was also followed by lower cumulative rates of heart failure at 10 years, both in patients with minimal subjective manifestations (7% [95% CI, 4%-11%] for early surgery vs 24% [95% CI, 17%-30%] for initial medical management, $P < .001$) or without them (7% [95% CI, 3%-11%] for early surgery vs 23% [95% CI, 18%-27%] for initial medical management, $P < .001$). Adjusting for baseline characteristics, early surgery was associated with a significant reduction of heart failure risk both with (adjusted HR, 0.33 [95% CI, 0.18-0.57], $P < .001$) and without (adjusted HR, 0.23 [95% CI, 0.11-0.41], $P < .001$) baseline minor (non-heart failure) subjective manifestations.

New Atrial Fibrillation

Among those in sinus rhythm at diagnosis ($n = 902$), new-onset atrial fibrillation occurred in 227 patients overall, corresponding to a cumulative rate of 25% (95% CI, 22%-28%) at 10 years and 41% (95% CI, 33%-47%) at 20 years. Importantly, despite the early postoperative observation of excess atrial fibrillation in the early surgery group, the long-term incidence was without significant difference between cohorts ($P = .33$, eFigure 3A in Supplement). Following propensity score-matching, new late-onset atrial fi-

brillation risk was also similar between early surgery and initial medical management groups at 5, 10, 15, and 20 years ($P = .89$, eFigure 3B in Supplement).

All 3 multivariable Cox models (for the overall population, propensity score-matched cohort, and the inverse probability-weighted cohort) confirmed that treatment strategy was not influential upon the incidence of new atrial fibrillation (Table 2). Random effects Cox models that accounted for potential variations between centers produced similar results. Furthermore, no subgroup showed a detectable difference in new atrial fibrillation incidence between treatment strategies (all subgroups, $P > .20$).

Discussion

This multicenter, international registry of consecutive patients diagnosed in routine practice with mitral valve regurgitation due to flail mitral leaflets is, to our knowledge, the largest in the world permitting analysis of the comparative effectiveness of early surgery vs initial medical management of patients without traditional class I triggers for surgery. In most instances initial medical management was selected by each patient's personal physician, demonstrating the degree of perceived equipoise regarding the 2 available management strategies following a new diagnosis of severe mitral regurgitation due to flail mitral valve leaflets. Our study shows that early mitral valve surgery was not associated with excess short-term (3 months) mortality or heart failure but did carry a small increased risk of early atrial fibrillation. Long-term, the results are coherent by all methods used (direct comparison, adjusted comparison, propensity score matching, inverse probability weighting) that early surgical correction of mitral valve regurgitation was associated with a significant survival benefit (total mortality decrement of approximately 40%) and diminished heart failure risk (reduction of approximately 60%). Furthermore, the lasting benefit of early surgery appeared to be sustained 20 years following diagnosis and observed in subgroups with or without class II triggers for surgery, and with or without (non-heart failure-related) minor subjective manifestations. These findings emanate from institutions that together provide a very high rate of mitral valve repair (>90%) with low operative mortality, emphasizing that such results might also be achieved in routine practice at many advanced repair centers.

In the absence level I evidence from a randomized trial, it is necessary to study the consequences of current international mitral regurgitation management strategies using alternative means. The National Heart, Lung, and Blood Institute has recently endorsed the pursuit and publication of comparative effectiveness research as a national priority in response to health care reform and national stimulus legislation¹⁵ to better inform medical decision making and improve health care outcomes.²² Large clinical registries, such as MIDA, have been championed as essential in delivering the evidence necessary to facilitate these initiatives, in the absence of or due to the limited feasibility of randomized clinical trials. The MIDA registry includes the mandated and standardized collection of clinical data of patients with severe mitral regurgitation caused by flail leaflets and as such "may better represent the diversity of patients, pro-

viders, and practice settings found in contemporary clinical care."¹⁶ One method to limit selection bias in registries is to restrict the study population "to newly treated patients...eligible for either therapy" to "narrow any pretreatment differences between patients receiving alternative therapies." The analyses performed in our report thus pivoted on the stratification of patients into early surgical correction of mitral valve regurgitation vs initial medical management groups to determine the effect of the treatment strategies on long-term patient outcomes.

Current American College of Cardiology and American Heart Association guidelines state as a class IIA recommendation that mitral valve surgery may be offered to those with severe mitral regurgitation if the likelihood of repair is high (>90%) and operative risk is low.¹² Level I evidence does not currently exist to inform the management of cardiac care professionals, and it will be some time until current study results are available.²³ The present data substantiate the opportunity to improve long-term patient survival and diminish late heart failure risk in those with mitral regurgitation due to flail mitral leaflets through early referral for surgical correction where appropriate expertise exists.

Limitations

Access to high-quality medical management, echocardiographic surveillance, and surgical care were provided in accordance with center-specific standards of clinical practice and following individual interpretation of international heart valve guidelines.^{12,13} As such, the current report presents a realistic overview of those who are likely to benefit from surgical intervention at these sites but are not currently mandated to consider it under current international guidelines governing the management of patients with severe degenerative mitral regurgitation without class I triggers. We selected 3 months as the window for performance of early surgical intervention based on clinical observation of the practicalities of patients making arrangements to schedule and undergo mitral valve surgery. Even with early surgery defined as occurring within 1 or 6 months following diagnosis in exploratory models, surgical intervention was still associated with better outcomes than initial medical management (at 1 month: adjusted risk of death, 0.51 [95% CI, 0.37-0.70, $P < .001$]; heart failure, 0.36 [95% CI, 0.23-0.57, $P < .001$]; and atrial fibrillation, 0.66 [95% CI, 0.47-0.92, $P = .01$]; at 6 months: adjusted risk of death, 0.46 [95% CI, 0.35-0.61, $P < .001$]; heart failure, 0.30 [95% CI, 0.20-0.44, $P < .001$]; and atrial fibrillation, 0.94 [95% CI, 0.71-1.25, $P = .67$]).

Watchful waiting is an admittedly vague term because a rigorous protocol of clinical and echocardiographic follow-up may have (theoretically) altered results; however, we are unable to speculate whether this may have been the case. Classification of mitral regurgitation severity by semiquantitative assessment was permitted in order to include those with long-term follow-up, while quantitative assessment is more routinely performed in the current era.

In addition, although propensity score matching and inverse probability weighting adjusts for known interactions, while unlikely, residual confounding cannot be ruled out. Although these results were derived from a population of patients with flail mitral valve leaflets, they may not apply to those with other etiologies of mitral valve disease.

Conclusion

The advantages associated with early surgical correction of mitral valve regurgitation were confirmed in both unmatched and matched populations, using multiple

statistical methods. Among patients with mitral valve regurgitation due to flail mitral leaflets, prompt surgical intervention within 3 months following detection was associated with greater long-term survival and lower heart failure risk, even in the absence of traditional class I triggers for surgery.

ARTICLE INFORMATION

Author Contributions: Dr Enriquez-Sarano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Suri, Vanoverschelde, Grigioni, Avierinos, Russo, Enriquez-Sarano.

Acquisition of data: Suri, Vanoverschelde, Grigioni, Tribouilloy, Avierinos, Barbieri, Pasquet, Russo, Enriquez-Sarano.

Analysis and interpretation of data: Suri, Vanoverschelde, Grigioni, Schaff, Tribouilloy, Avierinos, Huebner, Rusinaru, Russo, Michelena, Enriquez-Sarano.

Drafting of the manuscript: Suri, Grigioni, Avierinos, Huebner, Enriquez-Sarano.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Suri, Huebner, Rusinaru, Enriquez-Sarano.

Obtained funding: Enriquez-Sarano.

Administrative, technical, or material support: Suri, Barbieri, Enriquez-Sarano.

Study supervision: Suri, Grigioni, Schaff, Tribouilloy, Avierinos, Barbieri, Pasquet, Russo, Michelena, Enriquez-Sarano.

Drs Enriquez-Sarano and Suri contributed equally to this work.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Suri reports receiving grant funding from Edwards Lifesciences, Sorin Group, and St Jude Medical and support for travel and accommodations from Sorin Group and serving on the eligibility committee for the Abbot COAPT trial. Dr Grigioni reports receiving payment for lectures from Edwards Lifesciences. Dr Enriquez-Sarano reports serving as a board member for Valtech and receiving grant funding from Abbott Vascular.

MIDA Investigators: Christophe de Meester, Patrick Montand, Fabien Chenot, Bernhard Vancraeynest, and Gebrine El-Khoury (Brussels, Belgium); Elena Bararesi, Marinella Ferlito, Claudio Rapezzi, Angelo Branzi, Carlo Savini, and Roberto Di Bartolomeo (Bologna, Italy); Roberta Lugli, Francesca Mantovani, Chiara Manicardi, Francesca Bursi, and Maria Garzia (Modena, Italy); Catherine Szymansky, Gilles Touati, Thierry Caus, Jean Paul Remadi, Franck Levy, and Faouzi Trojette (Amiens, France); Jean-Francois Avierinos (Marseille, France); and Douglas Mahoney (Rochester, Minnesota).

Additional Contributions: We thank Zhuo Li, MSc, for expert statistical analysis, Diane Wilke, RN, for expert data abstraction, and Doug Mahoney, MSc (Mayo Clinic), for expert statistical analysis including population matching. They received a salary from their institution.

REFERENCES

1. Suri RM, Burkhart HM, Daly RC, et al. Robotic mitral valve repair for all prolapse subsets using techniques identical to open valvuloplasty: establishing the benchmark against which percutaneous interventions should be judged. *J Thorac Cardiovasc Surg*. 2011;142(5):970-979.
2. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation*. 2007;115(7):881-887.
3. 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(9):875-883.
4. Grigioni F, Tribouilloy C, Avierinos JF, et al; MIDA Investigators. Outcomes in mitral regurgitation due to flail leaflets: a multicenter European study. *JACC Cardiovasc Imaging*. 2008;1(2):133-141.
5. Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation*. 2009;119(6):797-804.
6. 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(6):1819-1825.
7. Enriquez-Sarano M, Sundt TM III. Early surgery is recommended for mitral regurgitation. *Circulation*. 2010;121(6):804-811.
8. Gillam LD, Schwartz A. Primum non nocere: the case for watchful waiting in asymptomatic "severe" degenerative mitral regurgitation. *Circulation*. 2010;121(6):813-821.
9. Rosenhek R. Watchful waiting for severe mitral regurgitation. *Semin Thorac Cardiovasc Surg*. 2011;23(3):203-208.
10. Rosenhek R, Rader F, Klar U, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113(18):2238-2244.
11. Montant P, Chenot F, Robert A, et al. Long-term survival in asymptomatic patients with severe degenerative mitral regurgitation: a propensity score-based comparison between an early surgical strategy and a conservative treatment approach. *J Thorac Cardiovasc Surg*. 2009;138(6):1339-1348.
12. 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 (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists; endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114(5):84-231.
13. 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(2):230-268.
14. Gillinov AM, Mihaljevic T, Blackstone EH, et al. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? *Ann Thorac Surg*. 2010;90(2):481-488.
15. Hlatky MA, Douglas PS, Cook NL, et al. Future directions for cardiovascular disease comparative effectiveness research: report of a workshop sponsored by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol*. 2012;60(7):569-580.
16. Tribouilloy C, Grigioni F, Avierinos JF, et al; MIDA Investigators. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: a long-term follow-up multicenter study. *J Am Coll Cardiol*. 2009;54(21):1961-1968.
17. Lloyd-Jones DM, Larson MG, Leip EP, et al; Framingham Heart Study. Lifetime risk for developing congestive heart failure. *Circulation*. 2002;106(24):3068-3072.
18. Agricola E, Oppizzi M, De Bonis M, et al. Multiplane transesophageal echocardiography performed according to the guidelines of the American Society of Echocardiography in patients with mitral valve prolapse, flail, and endocarditis. *J Am Soc Echocardiogr*. 2003;16(1):61-66.
19. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2012.
20. Hernán M, Brumback B, Robins J. Marginal structural models to estimate the joint causal effect of nonrandomized treatments. *J Am Stat Assoc*. 2001;96(454):440-448.
21. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550-560.
22. Concato J, Peduzzi P, Huang GD, et al. Comparative effectiveness research: what kind of studies do we need? *J Investig Med*. 2010;58(6):764-769.
23. Tietge WJ, de Heer LM, van Hessen MW, et al. Early mitral valve repair versus watchful waiting in patients with severe asymptomatic organic mitral regurgitation: rationale and design of the Dutch AMR trial, a multicenter, randomised trial. *Neth Heart J*. 2012;20(3):94-101.