Is early surgery recommended for mitral regurgitation?

Early Surgery Is Recommended for Mitral Regurgitation

Maurice Enriquez-Sarano, MD; Thoralf M. Sundt III, MD

Mitral regurgitation (MR), the systolic flow reversal from the left ventricle to the left atrium, is currently the most frequent valvular heart disease.

Indications of mitral surgery, the only current approved treatment of MR, are disputed because large clinical trials in MR have not been reported and outcome studies provide the best evidence available but require careful interpretation. The benefit of surgery is uncertain in functional MR and is not addressed here. However, we illustrate here that overwhelmingly coherent cumulative evidence obtained worldwide shows that early surgery should be the preferred management approach for organic MR. This approach differs from standard guidelines, and it is essential that its principles, rationales, and conduct be fully considered.

Response by Gillam and Schwartz see p 812

Principles Guiding Early Surgery in Organic MR

Guidelines for the management of valve diseases mention class I versus class II indications as having agreed-on versus conflicting evidence/opinions. This classification is problematic for MR treatment because class I indications, based mostly on symptoms and overt left ventricular (LV) dysfunction, lead to the performance of rescue surgery (surgery for patients at considerable risk if unoperated) but do not result in optimal long-term outcomes for patients with organic MR. The concept of uniform surgical recommendations that supposedly apply equally to all centers is also problematic; recent studies have shown that the quality of surgical outcomes in MR is heterogeneous. Thus, the standard guideline framework of treatment indications, generalizable for medical therapies such as statins or aspirin, is not applicable to surgical treatment of valve diseases, particularly MR.

Data-driven principles that should guide surgical indications in organic MR are as follows. First, rescue surgery for defined symptoms or overt LV dysfunction is necessary but not desirable, and early surgery in patients without such characteristics provides the best long-term outcomes. Second, advanced repair centers with highly skilled teams (surgeon, cardiologists, echocardiographers, anesthesiologists, nursing team) and proven results are optimal for conducting early surgery. With this framework in mind, all decisions should be individualized to parameters characterizing the MR but also to comprehensive patient descriptors, particularly age, comorbidity, and personal aspirations.

Rationales for Early Surgery

Rationale 1: In Patients With Organic MR, Surgery Is Almost Unavoidable

The advent of reliable Doppler echocardiographic diagnosis of mitral valve disease allowed the clinical outcome of patients with MR to be defined. In studies of patients in their 50s at
Figure 1. Excess postoperative mortality after mitral surgery affecting patients operated on for symptoms or low EF. A and B, Observed postoperative survival (solid line) compared to expected survival (dashed line) for the specific subgroup of patients with no or minimal (class II) symptoms (A) or severe (class III or IV) symptoms (B) (both reprinted from Tribouilloy C, Enriquez-Sarano M, Schaff H, Orszulak T, Bailey K, Tajik A, Frye R. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation. 1999;99:400–405 with permission of the publisher. Copyright © 1999, the American Heart Association). After surgery for severe symptoms, survival remains lower than the expected survival (74% of expected at 10 years), whereas after surgery, in class I or II, survival is identical to that expected (104% of expected at 10 years). Thus, excess mortality persists after surgery in patients operated on with severe symptoms, whereas life expectancy is restored in patients with no or minimal symptoms. C, Echocardiographic prediction of survival after surgical correction of organic MR showing postoperative survival (solid line) compared to expected survival (dashed line) for the specific subgroup of patients with no or minimal symptoms (reprinted from Enriquez-Sarano M, Schaff H, Orszulak T, Bailey K, Frye R. Echocardio-
graphic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994;90:830–837 with permission of the publisher. Copyright © 1994, the American Heart Association). The patients with EF ≥60% display the best survival, whereas patients with EF <50% and even those with EF 50% to 59% display markedly reduced postoperative survival. Thus, mitral surgery for patients with EF <60% results in excess postoperative mortality.

Rationale 2: Class I Indications of Mitral Surgery Are Associated With Dire Outcome Consequences

Class I indications for isolated organic MR are for symptomatic patients or those with an ejection fraction (EF) ≤60% or LV end-systolic dimension ≥40 mm. Although it is satisfying to relieve symptoms by surgery, this approach implies considerable risk to patients requiring surgery because their EF has declined to <60% do not incur excess operative mortality, but late mortality is increased by 180% with EF <50% and by 80% with EF of 50% to 59% (Figure 1).7 The association of reduced preoperative EF with excess postoperative mortality has also been confirmed independently,18–20 and its association with postoperative LV dysfunction persists in the era of valve repair.21 Thus, MR surgery with either of these class I indications rescues patients from risks imposed by symptoms and low EF under medical management but is followed by considerable residual excess mortality. New data on long-term survival according to LV end-systolic dimension suggest similar excess postoperative mortality associated with end-systolic LV diameter ≥40 mm.22 Thus, rescue surgery for any class I indication is associated with excess postoperative mortality and cannot be the preferred surgical indication in organic MR.

Rationale 3: Restorative Surgery Is Possible in Most Patients With Organic MR in Western Countries

Restorative surgery is based on indications associated with postoperative restoration of life expectancy and morbidity risk. Patients with no or minimal symptoms before surgery display postoperative survival identical to that of the general population, even with operative mortality of 0.5% to 1% accounted for. Similarly, long-term postoperative survival of patients with EF ≥60% rejoins that of the general population. Thus, early surgery (no or minimal symptoms and EF
Rationale 4: Organic MR Is a Condition With Serious Outcome Consequences

Outcomes of Organic MR as a Whole

Under medical management, patients with MR resulting from flail mitral leaflets display excess mortality compared with the general population, representing the ultimate definition of a severe condition (Figure 2). In addition, in patients with no specific risk factors besides the organic MR, we observed a sudden death rate of 0.8% per year, which, although not considerable, is approximately double the spontaneous risk in the general population. This observation was contested by a prospective study conducted in Austria, which noted low mortality. However, in that small study, patients were young (by 5 to 10 years compared with other MR series and displayed smaller end-diastolic LV diameter than other organic MR studies (by 5 to 6 mm for valve prolapse and by 4 mm/m² for flail leaflets), consistent with moderate rather than uniformly severe MR. Other evidence suggests that severe organic MR is indeed associated with excess mortality. In a medically defined community, in which referral biases were minimized, asymptomatic patients with mitral prolapse incurred excess mortality directly related to the severity of MR. In addition, in a large prospective study of quantified organic MR, patients with large effective regurgitant orifice (ERO; ≥40 mm²), affirming MR severity, had excess mortality compared with the general population and with patients with a lesser degree of MR (Figure 2). A recent analysis integrating all modern “natural history” studies shows that patients with moderate to severe MR incur a 3% per year mortality compared with 6% for severe MR. Additionally, all studies show high rates of cardiac events (cardiac death, heart failure, atrial fibrillation), which in severe MR approximate 10% per year. This comprehensive examination of the literature shows that severe MR is associated with excess mortality and high morbidity. Consequently, it is essential that we define the patients at high risk who may benefit most from early surgery.

New Markers of Outcome

New markers of outcome have been recently described that require more in-depth assessment but are important in the consideration of early surgery:

- Atrial fibrillation, although known as a traditional complication of MR, is currently not mentioned as a class I indication for surgery. However, in organic MR, it is frequent and is associated with excess subsequent mortality under medical management (Figure 3). Thus, atrial fibrillation should be considered a formal indication for surgery in organic MR. Atrial fibrillation is caused and predicted by left atrial enlargement, the role of which in predicting outcome and in defining timing of surgery should be further investigated. The long-term postoperative consequences of preoperative atrial fibrillation are not well defined, and whether surgery performed for atrial fibrillation is “early” or “rescue” surgery is a matter of semantics. The essential clinical point is that the link between MR and arrhythmia should be established and surgery should be promptly considered.
The severity of MR is a major predictor of outcome in patients with mitral valve prolapse and organic MR in general. Recent guidelines emphasize the need for comprehensive assessment not limited to jet size assessment. Echocardiographic laboratories are encouraged to become proficient in MR quantification to measure regurgitant volume as a marker of volume overload and ERO as a marker of lesion severity. Multiple methods are available that allow quantitative assessment of organic MR under most clinical circumstances, and quality control allowing reliable data to be obtained is relatively simple. Quantitative assessment defines progression of MR, which color-flow imaging does not detect well. ERO $\geq 40$ mm$^2$ is associated with approximate doubling of the mortality risk (Figure 2) and quadrupling of the risk of cardiac events (Figure 3), superseding jet-based measures and marking risk of excess mortality compared with expected survival. With an ERO of 20 to 39 mm$^2$, long-term progression is associated with worsening of outcome, but for the first few years, risk is low, allowing monitoring of progression under medical management. The association of ERO with subsequent cardiac events was confirmed independently.

Hormonal activation with B-type natriuretic peptide elevation is determined by the consequences (atrial and ventricular) of the MR and not by its severity. Hormonal activation is a marker of excess risk under medical management (Figure 3). This observation has recently been independently confirmed, so hormonal activation should alert clinicians about subsequent risk under medical management.

Functional capacity can be assessed through the use of cardiopulmonary exercise with oxygen consumption measurement. Marked reduction of functional capacity ($<84\%$ of expected for age and sex) is frequent and unexpected, affecting 20% of asymptomatic patients with severe MR. Event-free survival is lower in patients who present with reduced functional capacity than in those with normal exercise capacity (Figure 3). Other indexes such as pulmonary pressure or left atrial volume are intuitively attractive but are not yet established enough relative to outcome implications and need further outcome studies. Hence, there are markers of serious outcome under medical management that allow the detection of patients at notable risk and the performance of restorative surgery that reestablishes the life expectancy of patients with organic MR.
Rationale 5: No Alternative Treatment of Organic MR Is Established

Medical treatment with angiotensin blockade has some promise in stabilizing organic MR, and β-blockade has an interesting experimental suggestion of ventricular protection, but these currently are not alternatives to surgery. Treatment of MR by percutaneous clipping of the 2 leaflets, analogous to the surgical stitch proposed by Alfieri, is currently under investigation but will apply, if successful, to a minority of bileaflet prolapse with persistent coaptation. Although investigation of other potential therapies for MR should proceed, there are no currently approved alternatives to mitral surgery for organic MR.

Rationale 6: Comparative Studies Favor Early Surgery

Randomized clinical trials are not the only way to compare therapy and are not available for all existing therapies. The benefit of surgery compared with medical management can be estimated by comparisons of patients treated a priori by early surgery or conservative management or can be estimated with a time-dependent approach that judges the risk reduction for surgery whenever it is performed. These studies, summarized in the Table, concur in demonstrating that mitral surgery markedly reduces mortality and morbidity in patients with severe organic MR defined by a specific anatomic feature—flail leaflet—or by quantitative assessment. The magnitude of risk reduction was considerable whether analyzed by direct comparison or by time-dependent method. Short of a randomized clinical trial, coherent and considerable risk reductions show that early surgery is indeed the preferred approach to severe organic MR.

Conduct of Early Surgery for Organic MR

In view of overwhelmingly coherent data obtained worldwide, we consider early surgery the preferred option for treatment of organic MR, and patients’ evaluations focus on gathering information critical to offering this option.

Process of Evaluation for Early Surgery

Process 1: Precisely Characterize the Patient’s Status

This involves standard assessment of age, comorbidity and associated non–mitral valve diseases. It also involves assess-
ment of valve reparability (cause, mechanism, and calcification of lesions), of MR severity (at best by comprehensive assessment that includes multimethod MR quantification), and of the severity of MR consequences (symptoms, signs of heart failure, atrial fibrillation, LV dimensions and EF, left atrial enlargement, pulmonary pressure, hormonal activation, functional capacity by exercise testing). This assessment requires blood tests, ECG, chest radiography, transthoracic echocardiography, and often exercise testing. Transesophageal echocardiography and LV angiogram are rarely necessary for decision making. Assessment of associated coronary disease is made usually once the surgical decision is reached.

Table. Studies Reporting Direct Comparison Between Medical and Surgical Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Center</th>
<th>Analysis</th>
<th>n</th>
<th>Age, y</th>
<th>Outcomes</th>
<th>Outcome With Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ling et al,52 1997</td>
<td>Retrospective; flail leaflets</td>
<td>Single, US</td>
<td>Direct comparison</td>
<td>221</td>
<td>65</td>
<td>Survival</td>
<td>79% vs 65% at 10 y, RR=0.31; 27% vs 59% at 10 y, RR=0.38</td>
</tr>
<tr>
<td>Kang et al,11 2009</td>
<td>Prospective; quantified MR</td>
<td>Single, Korea</td>
<td>Direct comparison</td>
<td>447</td>
<td>50</td>
<td>Event-free survival</td>
<td>99% vs 85% at 7 y</td>
</tr>
<tr>
<td>Enriquez-Sarano et al,15 2005</td>
<td>Prospective; quantified MR</td>
<td>Single, US</td>
<td>Time dependent</td>
<td>456</td>
<td>63</td>
<td>Survival</td>
<td>RR=0.28 (0.14–0.55); RR=0.37 (0.17–0.79)</td>
</tr>
<tr>
<td>Grigioni et al,14 2008</td>
<td>Retrospective; flail leaflets</td>
<td>Multicenter, Europe</td>
<td>Time dependent</td>
<td>394</td>
<td>64</td>
<td>Survival</td>
<td>RR=0.42 (0.21–0.84); CVD/CHF RR=0.26 (0.08–0.89)</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; CVD, cardiovascular death; and RR, risk ratio associated with surgical management. RRs <1.0 indicate risk reduction by surgical management (values in parentheses are the 95% confidence intervals). Event rates are presented for surgical vs medical management. Analysis by direct comparison defines outcomes with surgical and medical management according to the decision made at diagnosis. Analysis using surgery as a time-dependent variable defines the change in risk provided by surgery after it is performed compared with the risk under medical management after diagnosis.

Process 2: Consider the Repair Center

The level of services of the repair center considered for the specific patient should be characterized, focusing on operative mortality, repair feasibility, and durability for the lesions described by echocardiography.

Process 3: Patient Participation

Patient participation in the decision is essential. Factual description of the patient’s status, risks, and repair possibility should be obtained, and the patient’s aspirations and point of view should be discussed.

Figure 4. Direct comparison favors early surgical management of organic MR. A. Among patients diagnosed with MR resulting from flail leaflet and all surgical candidates, better long-term survival was seen in patients treated by early surgery vs patients initially treated conservatively with the plan of proceeding to surgery if required later (reprinted from Ling L, Enriquez-Sarano M, Seward J, Orszulack T, Schaff H, Bailey K, Tajik A, Frye R. Early surgery in patients with mitral regurgitation due to partial flail leaflet: a long-term outcome study. Circulation. 1997;96:1819–1825 with permission of the publisher. Copyright © 1997, the American Heart Association). B. Among young patients in whom the severity of MR was prospectively defined by quantitative assessment, those treated by early surgery incurred much lower rates of cardiovascular events during follow-up than patients treated conservatively with the plan of proceeding to surgery if required later (reprinted from Kang DH, Kim JH, Rim JH, Kim MJ, Yun SC, Song JM, Song H, Choi KJ, Song JK, Lee JW. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation. 2009;119:797–804 with permission of the publisher. Copyright © 2009, the American Heart Association).
Specific Management of Organic MR

Rescue Surgery
Patients with symptoms attributable to MR, EF <60% or LV end-systolic dimension ≥40 mm as a result of the organic MR, should receive rescue surgery regardless of valve reparable.

Continued Follow-Up
Patients with organic MR, no symptoms, an EF ≥60% and LV end-systolic dimension ≤35 mm, sinus rhythm, normal exercise capacity (>84% of expected for age), no hormonal activation, and ERO <40 mm² can be followed up, but many will in time require surgery. The intensity of follow-up depends on the severity of MR and consequences.

Early Surgery
Patients with organic MR with no symptoms and with an EF ≥60% should be considered for early surgery if the valve is reparable in the presence of strong predictors such as an ERO ≥40 mm² or atrial fibrillation (even paroxysmal) resulting from MR. Other indicators suggestive that early surgery is warranted are end-systolic LV dimension of 36 to 39 mm,22 hormonal activation (B-type natriuretic peptide), or reduced functional capacity. Future studies should add to the list of these markers. Early surgery consideration is most appropriate in an advanced repair center. Such centers should provide operative risk of ≤1%, should have high repair rates (≥85% to 90%) and high durability of repair (≥10% reoperation rates 10 years after surgery), and should be guided by high-quality echocardiography preoperatively, intraoperatively, and postoperatively.10,52

The studies on the benefit of early surgery are dominated by highly reparable degenerative mitral disease.11,14,15,51 Whether more stringent criteria (eg, regurgitant volume ≥100 mL/beat) should apply to early surgery in patients with nonreparable valves is a hypothesis to be addressed in future studies.

The cycle of improved practice and enhanced knowledge in mitral valve disease is far from finished. Many questions remain unanswered, whether relatively simple, such as the interaction of age and prognostic markers in determining outcome and the role of left atrial enlargement or pulmonary hypertension on outcome, or more complex, such as the mechanism of myxomatous degeneration and the possible medical treatment to prevent its progression or the development of percutaneous treatment of organic MR. We are gratified that many recent improvements, such as the considerable increase in repair rates (nationally from 25% to ~55%) and marked surgery risk decline, have occurred and are ongoing. Although we call for the conduct of a clinical trial, coherent data obtained worldwide strongly suggest that the best approach to severe organic MR is to suppress it and restore life expectancy by early surgery. Hence, consideration for early surgery on the basis of appropriate criteria should always be part of the evaluation for organic MR.

Disclosures
None.

References


Response to Enriquez-Sarano and Sundt

Linda D. Gillam, MD; Allan Schwartz, MD

The argument of Drs Enriquez-Sarano and Sundt for early surgery in the absence of accepted triggers is flawed by a reliance on retrospective studies comparing patients with early surgery and those managed without a consistent trigger-driven strategy. Because many of the “medically managed” patients in these studies continued to be medically managed past triggers, these reports do not provide legitimate comparisons between early surgery and watchful waiting, the management strategy we advocate. By way of rebuttal to Dr Enriquez-Sarano and Sundt’s key arguments for early surgery, we note the following: (1) Data show that surgery is avoidable in the midterm (the majority of patients who are initially free of surgical triggers will remain so over 5 to 7 years). (2) Surgery performed as soon as agreed-on triggers, including symptoms or left ventricular dysfunction, are met has excellent outcomes. (3) We agree that early surgery is feasible with appropriate outcomes at only a limited number of centers. However, this still exposes patients to early risk of death and stroke and to recurrent mitral regurgitation. (4) We agree that mitral regurgitation may have serious consequences and that triggers may be overlooked. However, we conclude that these observations support the need for careful surveillance (watchful waiting), not early surgery. (5) Although quantifying mitral regurgitation is desirable, we note that overdiagnosis of severe regurgitation would lead to operating on patients who have less severe disease if an early surgical approach is adopted. (6) The statement that “comparative studies all show a marked benefit of early surgery” is not supported by the data.
“Is early surgery recommended for mitral regurgitation?”

**Primum Non Nocere**

*The Case for Watchful Waiting in Asymptomatic “Severe” Degenerative Mitral Regurgitation*

*Linda D. Gillam, MD; Allan Schwartz, MD*

“The physician must... have two special objects in view with regard to disease, namely, to do good or to do no harm” —Hippocrates

The optimal surgical treatment for severe mitral regurgitation resulting from degenerative disease (flail or prolapse caused by myxomatous change or fibroelastic deficiency) is mitral repair.2–5 Although the decision to intervene on a symptomatic patient is relatively straightforward, current guidelines also define other triggers for surgery in patients who are asymptomatic.6,7 In the absence of symptoms, left ventricular (LV) dysfunction, defined as an LV ejection fraction (LVEF) of 30% to 60% or an LV end-systolic diameter (LVESD) of ≥40 mm6 (>45 mm7), is a class I indication. Class IIa indications in the asymptomatic patient with preserved LV function include atrial fibrillation and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg after exercise). It is also deemed reasonable (class IIa6 or IIb7) to regard the presence of severe mitral regurgitation as a sole and sufficient indication for surgery provided that the likelihood of repair is high (≥90%)6 and operative risk is low.7 This last recommendation has generated considerable debate because no randomized controlled trial has defined the best treatment for asymptomatic patients with severe degenerative mitral regurgitation. Proponents of prophylactic repair favor an aggressive surgical approach, whereas opponents lobby for a strategy of close medical follow-up until conventional triggers are met (watchful waiting). Here, we present our argument for watchful waiting.

**Response by Enriquez-Sarano and Sundt see p 821**

The Burden of Proof

Because by definition a strategy of prophylactic surgery in asymptomatic patients cannot improve their sense of well-being, it must be associated with better surgical and/or clinical outcomes relative to a triggered strategy. It is our position that this benefit has not been established. Moreover, the recommendation for prophylactic surgery assumes that methods for quantifying mitral regurgitation in this patient population are reliable, that the ability to predict reparability is robust, that repair is a definitive (durable) solution, and that the surgical resources exist to offer technically adequate repair to the population in question. Here, we present data to argue that each of these assumptions is erroneous. Finally, we emphasize that although ≈40% to 50% of initially asymptomatic patients followed up for 5 to 8 years will develop...
conventional triggers for surgery, roughly equal numbers will not. Thus, the notion that surgery is inevitable in patients with severe degenerative mitral regurgitation over at least a midterm time frame is not justified.

Watchful Waiting Versus Prophylactic Surgery: The Outcomes Data

Because there has been no prospective trial randomizing asymptomatic patients with severe degenerative mitral regurgitation to either watchful waiting or early surgery, a critical evaluation of existing data is in order. There has been only 1 prospective trial in which a clearly defined trigger-driven strategy has been evaluated. As reported by Rosenhek et al, this approach, called watchful waiting, involves close clinical and echocardiographic follow-up, with surgery triggered by the onset of symptoms, a change in LVEF and/or LVESD to meet the guideline-specified thresholds, the onset of atrial fibrillation, or the development of pulmonary hypertension. In this study, 132 consecutive asymptomatic patients with severe degenerative mitral regurgitation were enrolled. Notably, the diagnosis of severe regurgitation was based on an integrated approach as recommended by the American Society of Echocardiography rather than a single parameter such as effective regurgitant orifice. All patients were in sinus rhythm with an LVEF $\geq 60\%$ and an LVESD $\leq 45$ mm (the trigger dimension in the European Society of Cardiology guidelines) and had a pulmonary artery systolic pressure of $\leq 50$ mm Hg as determined echocardiographically. Patients were followed up in a valvular heart disease clinic with serial history, physical examination, and echocardiographic evaluation at 12-month intervals after the stability of the findings was confirmed. This interval was decreased to 3 to 6 months if echocardiographic findings showed a significant change or moved close to thresholds for surgery. Surgery was advised if symptoms, atrial fibrillation, or echocardiographic triggers occurred. This approach defines watchful waiting.

Survival free of any trigger for surgery was 55% at 8 years with no significant difference between patients with and without flail (Figures 1 and 2). Survival in the overall group, 91% ± 3%, was not different from expected survival calculated from age- and gender-matched mortality rates in the Austrian general population (Figure 3). This remained true in the subgroup of 58 patients with flail leaflet who had an 8-year survival of 92% ± 4%. Over an estimated median follow-up of 69.2 months, there were 8 deaths: 2 deaths in patients who had met triggers but refused surgery, 1 death in a patient with myocarditis, and 3 noncardiac deaths (1 stroke, 2 cancer) in patients who had not developed triggers. Importantly, there were no sudden deaths in patients without triggers for surgery (1 patient who refused surgery had sudden death). The repair rate was 83%. Although there were no operative deaths, there were 2 late postoperative deaths (1 stroke and 1 myocardial infarction, both in patients who had undergone mechanical mitral valve replacement). All patients had good functional status after surgery (23 asymptomatic, 4 in New York Heart Association class I, and 8 in New York Heart Association class II). Four patients had postoperative LV impairment (2 with mitral
replacement and normal preoperative function, 2 with coronary artery bypass graft surgery and mitral repair and mild preoperative LV impairment.

There are 4 key points to be taken from this study. First, in this series, watchful waiting conveyed no survival disadvantage. Second, surgical outcomes with this strategy were excellent. Third, more than half the patients were still free of triggers for surgery at the 8-year follow-up. Finally, repair rates at this excellent center were <90%. In aggregate, these data provide strong support for a watchful waiting strategy.

In a study often quoted in support of prophylactic mitral surgery, Enriquez-Sarano et al10 prospectively enrolled 456 patients with asymptomatic degenerative mitral regurgitation and an LVEF ≥50% from 1991 to 2000. Complete history, physical examination, and quantitative echocardiographic assessment of regurgitant volume and effective regurgitant orifice were performed. Subsequent management was by the patient’s personal physician with no prespecified triggers for surgery and no prespecified methodology or schedule for clinical and echocardiographic follow-up. Forty-nine percent of patients were treated medically. Outcome data were obtained retrospectively in 2002.

The major observation of the study was a strong association between the severity of regurgitation as assessed by effective regurgitant orifice and both cardiac death and all-cause mortality in patients managed medically. For patients with severe mitral regurgitation (effective regurgitant orifice ≥40 mm²), the 5-year survival rate was only 58±9% compared with a 78% survival predicted from US Census Bureau national life tables. In this group, 5-year cardiac mortality was 36±9%, and the 5-year cardiac event rate (cardiac death, congestive heart failure, and/or atrial fibrillation) was 62±8%.

However, it would be wrong to assume that all patients with severe mitral regurgitation who were managed medically did not meet criteria for surgery during the follow-up period. Importantly, although all were asymptomatic at baseline, they did not necessarily remain asymptomatic over the period that was retrospectively reviewed. In particular, it is not known how many cardiac deaths occurred in patients who had developed triggers for surgery before death. At a minimum, patients (the number was not specified) who developed congestive heart failure were presumably symptomatic. In addition, other patients had other abnormalities that would be triggers for surgery in the current or 1998 guidelines11 even at baseline. For example, at baseline, 5% (10 of 198) had atrial fibrillation, and baseline values for LVESD (37±6 mm) and pulmonary artery systolic pressure (42±13 mm Hg) indicate that these patients who also met LVESD and pulmonary artery systolic pressure thresholds. Additionally, although the study included patients with LVESD between 50% and 60%, these patients would be considered to have depressed LV function and therefore would be candidates for surgery according to both 199811 and current6 guidelines. This observational study simply does not provide data on the natural history of medically managed patients who remained asymptomatic and did not meet surgical triggers.

The impact of prophylactic surgery is also difficult to discern from this study because, of the 232 patients who underwent surgery, 41% did so for symptoms and 39% did so for marked LV and/or atrial dilatation. Although 20% of patients had surgery based on “physicians’ and patients’ preference,” it is possible that some of them had atrial fibrillation and/or elevated pulmonary artery systolic pressure. Follow-up data are not broken down by indication for surgery.

In aggregate, the authors are to be commended for pointing out the association between the severity of mitral regurgitation as assessed with quantitative echocardiography and outcomes. However, this study provides no basis for arguing that prophylactic surgery rather than watchful waiting is better for asymptomatic patients with severe mitral regurgitation who do not meet conventional triggers.

Earlier observational studies from the same group have also been presented as supporting prophylactic surgery. Although they fall short from this perspective when critically evaluated, they do provide some information relevant to the present debate. Ling et al12 evaluated outcomes in 221 patients with flail mitral leaflets diagnosed by echocardiography (1980 to 1989). All patients were presumed to have severe regurgitation and were “eligible for operation” as determined by their treating physicians. It should be noted that this study preceded the 1998 American College of
Cardiology/American Heart Association (ACC/AHA) guidelines and that indications for surgery in this study group were not specified. Outcomes were compared between 63 who underwent surgery within 1 month of diagnosis and 158 who were initially treated medically (80 of whom later had surgery). The early surgery group was younger and had fewer comorbidities. Thirteen percent of patients in the medical treatment group were in New York Heart Association class III or IV heart failure, and 18% had atrial fibrillation.

Overall, patients with an early surgical strategy did better than those initially managed medically, with overall 10-year survival rates of 79±8% and 65±5%, respectively. However, in the context of the present discussion, it is impossible to identify patients who would be considered asymptomatic and without triggers in either the early surgery or initially medically managed groups, precluding a comparison of prophylactic surgery and watchful waiting in these patients. It is interesting that repair rates in both the early and late surgery groups were low by current standards but comparable (67% and 66%, respectively), suggesting that even then, delaying surgery did not reduce the likelihood of repair.

In another retrospective study, Grigioni et al13 reviewed the prevalence of sudden death in 345 patients with flail leaflet and presumed severe regurgitation diagnosed echocardiographically (1980 to 1994). Importantly, functional status and other clinical and echocardiographic variables were defined only at the time of diagnosis because limited follow-up data were available. The mean age was 67±12%. At 5 and 10 years, sudden death rates were 8.6±3% and 18.8±4%, respectively, with a yearly linearized rate of 1.8%. Univariate baseline predictors of sudden death were functional class, atrial fibrillation, coronary disease, smoking, serum creatinine, LVEF, LVESD, and left atrial dimension. With baseline functional status only, the linearized rate of sudden death in New York Heart Association class I patients was only 1.0%, even though 53% of the cases of sudden death occurred in patients who were no longer asymptomatic at the time of sudden death. Moreover, the linearized rate of sudden death in patients in New York Heart Association class I or II and in sinus rhythm with an LVEF ≥60% and no history of sudden death was 0.8% per year. Thus, even in a relatively old patient population, the risk of sudden death in asymptomatic patients without conventional triggers for surgery was low.

More recently, Grigioni et al14 reported outcomes in an observational study of 394 patients with flail leaflets and presumed severe mitral regurgitation from 4 European sites of the Mitral Regurgitation International Database (MIDA). Although patients were enrolled prospectively on the basis of baseline echocardiograms, no follow-up echocardiographic data were reported, and all clinical data were acquired retrospectively by chart review and telephone calls. Mitral surgery was performed at the discretion of the treating cardiologist. Of the 315 patients who underwent surgery (perioperative mortality defined as death within 30 days of surgery was 0.7%; n=2), only 15% did so for prophylaxis. The most common indication for surgery was symptoms (68%), with LV dilatation (dimension unspecified) accounting for 6% and endocarditis for 5%.

Of relevance to the present discussion are the 102 patients who were asymptomatic and had “normal LV size and function,” LVEF ≥60%. The methods for assessing LVEF and size and the threshold for abnormal size are not provided. It should be noted that at least 10% of these patients met other triggers for surgery on entry because only 92% were in sinus rhythm and 2% had estimated pulmonary artery systolic pressure >50 mm Hg. Mitral surgery (repair in 82%) was eventually performed in 69% of these patients, and although the indications for surgery are not specified, it is likely that, as for the group at large, the onset of symptoms was the major driver. Although the study does not allow a comparison of prophylactic surgery and watchful waiting, the estimated overall 5-year survival of patients initially assigned to medical management (96%) was not statistically different from that of those who underwent surgery within 12 months. This, then, is another study demonstrating good outcomes in patients undergoing surgery for conventional triggers.

Earlier this year, Kang et al15 reported a single nonrandomized study of 447 consecutive patients who, on entry, were considered to have severe degenerative mitral regurgitation on the basis of proximal isovelocity surface area (PISA)–defined echocardiographic criteria (19% flail, 81% prolapse). At baseline, patients were asymptomatic and free of triggers for surgery by the 1998 ACC/AHA guidelines.11 (These differ from the 2006 guidelines in that the LVESD trigger was 45 rather than 40 mm.)

One hundred sixty-one patients underwent early elective surgery as determined by the treating physician and patient choice (94% repair, no operative mortality). Patients in the remaining group (n=286) were followed up yearly with clinical and echocardiographic evaluation and were referred for surgery if they developed dyspnea, atrial fibrillation, or an echocardiographic trigger. On the basis of an intention-to-treat analysis, the estimated actuarial 7-year cardiac mortality was 0% in the early operated group and 5±2% in the triggered group. However, it is notable that in the early surgery group, 3 deaths resulting from stroke and infection were, as is the convention, considered noncardiac despite possible associations between these conditions and valve surgery.16 In addition, in the triggered group, 6 of 12 deaths occurred in patients who developed triggers and did not undergo surgery, and 1 of 12 occurred as a result of postoperative heart failure. Although there were 3 sudden deaths over 7 years of follow-up among 207 patients who did not reach triggers, the approximate risk appears to be <0.5% per year, similar to that noted in the Mayo series.13 The authors also used propensity-matched pairs to consider event-free survival. Event was defined as a composite of operative mortality, cardiac death, repeat mitral valve surgery, and hospitalization for congestive heart failure. Event-free survival was 85.4±4% at 7 years in the triggered group versus
99±1% in the prophylactic group. However, in addition to the previously noted reservations about the classification of deaths as cardiac versus noncardiac, events that would likely occur more frequently in the prophylactically operated patients (recurrent/residual mitral regurgitation not leading to repeat surgery, embolic events, bleeding complications resulting from anticoagulation) were not included in the analysis, and because congestive heart failure is a trigger for surgery, it is gratuitous that it would be less frequent in the prophylactic group. In addition, it appears that all 17 patients lost to follow-up were in the prophylactic surgical group. For these patients, classifiable events were likely not adequately captured because the only source of information was the Korean national registry of vital statistics. It is uncertain whether the presumed failure to include these patients in the propensity-matched analysis biased event rates. Finally, postoperative follow-up by annual clinic visit or phone call without specified serial echocardiograms would tend to underestimate the incidence of recurrent mitral regurgitation.

A principal argument for prophylactic surgery has been the supposed inevitability of the development of triggers. How, then, about the possibility of doing harm? One might assume that predicting reparability is straightforward. However, data suggest that this is not the case. First, surgical expertise is variable, and even lesions routinely repairable in some institutions (P2 flail/prolapse) may not be repaired at others. Indeed, Jung et al22 reported in the Euro Heart Survey that the absence of local expertise in mitral repair was the reason for valve replacement rather than repair in 32.5% of cases. In addition, the echocardiographic expertise to accurately localize the pathology may not be available, and even in expert hands, disease involving the medial (A3, P3) and lateral (A1, P1) scallops may be missed even with newer 3-dimensional transesophageal echocardiography capability. Consequently, even in expert hands, reparability is not always predictable.

For example, in the Rosenhek et al8 series in which all institutions had excellent imagers and surgeons, only 83% of valves thought to be repairable were indeed repaired. In the Grigioni et al14 series of flail leaflets, the overall repair rate was 80% (82% in those initially asymptomatic with LVEF ≥60%). Similarly, if one assumes in the Kang et al15 series that prophylactic surgery was carried out only on patients deemed likely to have reparable valves, only 94% of valves considered repairable were actually repaired.

Larger real-world series such as the Society of Thoracic Surgeons National Adult Cardiology database of procedures performed from January 2000 to December 2007 reveal that only 69% of patients with isolated mitral regurgitation undergo mitral repair (versus replacement),24 although this is trending upward.25 The report of the 2001 Euro Heart Survey22 indicates that only 46.5% of mitral interventions are repairs. Although these data argue for referral to surgical centers of excellence for mitral surgery, this is often impossible because of patient and/or family preference and insurance restrictions. Moreover, cardiologists and surgeons are often reluctant to admit that their centers have suboptimal results for a procedure as common as mitral repair.

Thus, even in the best of centers, up to 20% of patients sent for prophylactic repair will have mitral valve replacement with its associated higher operative mortality (see below) and poorer long-term outcomes. Surely this risk is not justifiable in patients who are asymptomatic and free of conventional triggers.

**Predicting Repair Is an Imperfect Science**

A number of studies have reported the superiority of repair over mitral valve replacement2,14-19 for patients with degenerative mitral regurgitation, underlying the recommendation that prophylactic surgery be considered only in patients with ≥90% probability of repair.6 Because transesophageal echocardiography can delineate the nature (prolapse, flail) and extent (involved scallops) of degenerative mitral regurgitation20 and the likelihood of repair is related to these parameters,21 one might assume that predicting reparability is straightforward. However, data suggest that this is not the case. First, surgical expertise is variable, and even lesions routinely repairable in some institutions (P2 flail/prolapse) may not be repaired at others. Indeed, Jung et al22 reported in the Euro Heart Survey that the absence of local expertise in mitral repair was the reason for valve replacement rather than repair in 32.5% of cases. In addition, the echocardiographic expertise to accurately localize the pathology may not be available, and even in expert hands, disease involving the medial (A3, P3) and lateral (A1, P1) scallops may be missed even with newer 3-dimensional transesophageal echocardiography capability. Consequently, even in expert hands, reparability is not always predictable.

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**Operative Morbidity and Mortality**

Surgical mortality with mitral repair in centers of excellence is very low (0% to 1%),14,15 and in the recent study of trends in
mitral valve surgery based on the Society of Thoracic Surgeons National Adult Cardiology database of procedures (2000 to 2007), a mortality rate of 1.2% for isolated mitral valve repair (n=28,140) was noted.24 However, surgical mortality in patients with valve replacement, a not-uncommon outcome even if repair is planned, is much higher (3.8%).24

Hospital procedural volume influences both surgical mortality and the likelihood of repair versus replacement.26 Gammie et al26 used the Society of Thoracic Surgeons database to perform a retrospective review of outcomes for 13,614 patients undergoing elective valve surgery. Unadjusted mortality was 3.08% in the lowest-volume quartile (1 to 35 cases per year) versus 1.1% in the highest-volume quartile (>140 cases per year). Conversely, the rates of mitral repair were lowest in the lowest-volume quartile (48%) versus >77% in the highest-volume quartile. The higher rates of mitral replacement and its attendant higher mortality rates accounted for some but not all of the higher mortality in the low-volume centers.

Exposure to operative morbidity must also be considered when one is considering prophylactic surgery because most patients would not require surgery under watchful waiting for 5 to 10 years.8,18 Because of its impact on quality of life and mortality, ischemic stroke is particularly concerning. Russo et al16 reported a retrospective study of 1344 consecutive patients who underwent surgery for isolated mitral regurgitation (repair, n=897; mechanical valve replacement, n=231; and biological valve replacement, n=216) and identified ischemic strokes occurring early (<30 days), midterm (30 to 180 days), and long term (>180 days.) In the early perioperative period, the relative risk of stroke compared with population-expected rates was 41 with no significant differences between the types of mitral valve surgery. Between 30 and 180 days, the relative risk was still high in all groups (1.7 overall), returning to a level closer to the risk in the general population beyond 180 days. Expressed differently, the early risk of ischemic stroke was 2% overall and slightly >1% in patients undergoing repair. Particularly disturbing is the fact that stroke symptoms fully resolved in only 18%. Although the observational study of Avierinos et al27 reported a 2.2 lifetime relative risk of ischemic neurological events in patients with mitral prolapse, this was attributable at least in part to cardiac surgery and atrial fibrillation. It is clear, therefore, that the risk of stroke with surgery is much higher than it is with watchful waiting.

For patients who, despite the best of intentions, undergo mitral replacement rather than repair, additional causes of operative morbidity, including hemorrhagic complications related to anticoagulation18 and endocarditis, must also be considered. Overall rates of valve-related complications after mitral valve replacement are 1% to 2% per year.19,28

**Mitril Repair Is Not a Permanent Solution**

It is tempting to view mitral repair as a definitive and durable treatment for degenerative mitral regurgitation. However, even in the best centers, this is clearly not true (the Table).17,20–31 Prospective data on the recurrence of regurgitation after repair with serial complete echocardiographic follow-up are limited, but it is clear that studies that use reoperation as the sole metric for recurrence of regurgitation significantly underestimate repair failure.15,20–31

David et al11 reported their experience with 701 patients undergoing mitral repair between 1981 and 2001 and compared outcomes in those with anterior, posterior, and bileaflet prolapse. Overall survival at 12 years was 75±5% with no differences between groups. However, freedom from operation at 12 years was 96±2% for posterior, 88±4% for anterior, and 94±2% for bileaflet prolapse, with anterior prolapse an independent predictor of reoperation. Importantly, freedom from moderate to severe mitral regurgitation at 12 years was 80±4% for posterior, 65±8% for anterior, and 67±6% for bileaflet prolapse.

Similar results were reported by Flameng et al.29,30 In that series of 348 patients undergoing repair for degenerative mitral regurgitation, at the 10-year follow-up, survival was 80.1% and freedom from operation was 94.4%. However, freedom from 3 to 4+ regurgitation was only 82.2% at 5 years and 64.9% at 10 years, with a linearized recurrence rate of 3.2% per year.30 When corrected for risk factors related to surgical technique, there was no difference in recurrence between patients with diffuse myxomatous disease (Barlow disease) and localized fibroelastic deficiency, findings similar to those of David et al.31

Therefore, there is a significant risk of recurrent mitral regurgitation and reoperation over the same time period that many patients being treated with watchful waiting will not meet surgical triggers. Certainly, particularly for prophylactic surgery, the rate of recurrent mitral regurgitation is a better marker of surgical effectiveness than reoperation.

**Pitfalls in the Diagnosis of “Severe” Mitral Regurgitation**

In deciding the best strategy for managing patients with asymptomatic mitral regurgitation, the accuracy and reproducibility of grading severity become critical if it is the sole trigger for surgery. In its recent “Recommendations for Evaluation of the Severity of Native Valvular Regurgitation With Two-Dimensional and Doppler Echocardiography,” the American Society of Echocardiography emphasized a multifaceted approach that includes both imaging evidence of volume overload (left atrial and ventricular enlargement) and the use of multiple Doppler tools. These include jet area by color-flow mapping, measurement of the vena contracta, calculation of effective regurgitant orifice and regurgitant volume using the PISA method, calculation of regurgitant volume by continuity equation, assessment of pulmonary venous flow (searching for systolic blunting or flow reversal), and diastolic transmitral flow (looking for a heightened E wave).
Reliance on 1 method alone has the potential to overestimate the severity of regurgitation, an unacceptable possibility if the diagnosis of severe regurgitation will result in surgical intervention. However, in many laboratories, jet area alone is used to diagnose severe regurgitation. This approach is particularly troublesome when applied to jets that are nonholosystolic because many occur with degenerative mitral regurgitation. A jet area measured on a single frame may significantly overestimate severity when regurgitation is limited to a short portion of systole. Added to this is the potential for errors in machine settings (gain and Nyquist limit) that may artificially increase jet dimensions.

The potential for overdiagnosing severe regurgitation in patients with degenerative disease is compounded by the fact that theoretically more robust PISA methods for quantification are also flawed when jets are eccentric (constrained) and/or nonholosystolic. As reported by Enriquez-Sarano et al,35,36 these features are common with degenerative mitral regurgitation and will result in the overestimation of severity by PISA methods. Although correction factors have been proposed,36,37 they are not routinely used.

These concerns are not simply hypothetical. In the ACORN trial,38 an inclusion criterion for mitral valve surgery was clinical indication for mitral valve surgery. Yet, core laboratory assessment found that 41% of patients thus identified had only 0 to 2+ regurgitation. In the Everest I trial of a transcatheter mitral clip, the core laboratory failed to find 3 to 4+ regurgitation in 38% of patients labeled as having such by the referral site.39

### Defining Watchful Waiting

In this argument against prophylactic surgery for patients with asymptomatic mitral regurgitation and none of the conventional triggers, it should be clear that we are strongly

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**Table. Durability of Mitral Repair**

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>n</th>
<th>Combined Survival, % (y)</th>
<th>Freedom From Reoperation, % (y)</th>
<th>Combined, % (y)</th>
<th>Freedom From MR (3–4+), % (y)</th>
<th>Combined, % (y)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Combined, Anterior</td>
<td>Posterior</td>
<td>Both</td>
<td>Combined, Anterior</td>
<td>Posterior</td>
<td>Both</td>
</tr>
<tr>
<td>Mohy et al17</td>
<td>1980–1995</td>
<td>679</td>
<td>42 (15)</td>
<td>72 (15)</td>
<td>89 (15)</td>
<td>80 (19)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Flameng et al29</td>
<td></td>
<td>242</td>
<td>91 (8)</td>
<td></td>
<td>94 (8)</td>
<td>83 (5); 71 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>David et al31</td>
<td>1981–2001</td>
<td>701</td>
<td>88 (12)</td>
<td>96 (12)</td>
<td>94 (12)</td>
<td>65 (12)</td>
<td>80 (12)</td>
<td>67 (12)</td>
</tr>
<tr>
<td>Suri et al32</td>
<td>1980–1999</td>
<td>1173</td>
<td>42 (15)</td>
<td></td>
<td>90* (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flameng et al30</td>
<td></td>
<td>348</td>
<td>80 (10)</td>
<td></td>
<td>94 (10)</td>
<td>65 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newcomb et al33</td>
<td></td>
<td>183</td>
<td>92 (10)</td>
<td></td>
<td>93 (10)</td>
<td>80 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvador et al34</td>
<td>1986–2006</td>
<td>555</td>
<td>84 (15)</td>
<td></td>
<td>92 (15)</td>
<td>85 (15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MR indicates mitral regurgitation.

*Graph only; no numbers in text.

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advocating close clinical and echocardiographic follow-up of these patients. As described by Rosenhek et al., such watchful waiting includes clinical and echocardiographic follow-up at least annually. After an initial evaluation, follow-up at shorter intervals (3 to 6 months) is advisable to establish stability. Similarly more frequent follow-up is warranted if there are changes compared with previous measurements or if measurements are close to the predefined cutoffs.

Quantitative echocardiography (as opposed to visual assessment of ventricular size and LVEF) in a laboratory capable of acquiring high-quality images is essential. Because there is consensus that symptomatic patients with severe mitral regurgitation should undergo surgery, a critical assessment of functional status is an essential part of patient evaluation and management. Arguably, the onset of subtle symptoms may be easier to identify in patients who are followed up longitudinally by the same physician and/or the same clinic. A standard set of questions on the ease with which certain activities are performed may be helpful because patients may slowly scale back on activities to avoid excessive dyspnea and remain “asymptomatic.” Formal exercise stress testing with reference to age- and gender-predicted achievable exercise times may be helpful.

Summary

Despite current enthusiasm for prophylactic surgery in patients with asymptomatic severe degenerative mitral regurgitation, existing data suggest that watchful waiting is the preferred strategy. In revisiting the words of Hippocrates, there are no convincing data that prophylactic surgery can be construed as “doing good” because excellent outcomes have been shown with a watchful waiting strategy. In addition, the short- and long-term risks of mitral surgery, coupled with the risk that mild to moderate regurgitation may be inappropriately labeled as severe, translate to a very real possibility of doing harm. Only randomized prospective trials will resolve this intense debate. However, for now, “primum non nocere” is best translated as “watchfully wait and operate only when conventional triggers are met.”

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Disclosures

None.

References

Response to Gillam and Schwartz

Maurice Enriquez-Sarano, MD; Thoralf M. Sundt III, MD

Drs Gillam and Schwartz defend passive mitral regurgitation (MR) management with 1 study and ignore its limitations. They neglect population-based data and criticize studies with larger samples, well-defined MR severity, and prospective enrollment. Yet these studies’ conclusions are consistent: MR patients medically managed in clinical practice incur excess mortality and high morbidity. Drs Gillam and Schwartz recommend strict obedience to unproven criteria. The first study of the impact of left ventricular end-systolic dimension on MR survival was just published. It shows excess mortality with left ventricular end-systolic dimension ≥40 mm under medical management but also after surgery (thus, guidelines should be changed for <40 mm). Hence, the concept that patients with MR who have not reached guideline-based thresholds are safe is erroneous. Drs Gillam and Schwartz ignore the dire long-range consequences of performing surgery for class III to IV symptoms or left ventricular dysfunction, the value of novel risk markers, and the inevitability of surgery. Some surgeons cannot provide acceptable early MR surgery, but almost 1 in 4 Society of Thoracic Surgeons centers achieves outstanding results. The discussion of MR severity is confusing. Simply put, comprehensive assessment is a must, but it is essential to recognize 3 large outcome studies finding effective regurgitant orifice strongly predictive of outcome. Thus, fear of short-term risks and errors should not stop rigorous quality control, deliberate referrals, and proactive action to avoid long-range risks of catastrophic inaction. Drs Gillam and Schwartz claim close follow-up as sufficient on the basis of the same small study but fail to provide their data despite their large volume (New York Health Department, 2006; 267 mitral replacements, 423 repairs). Thus, surgical indications and compliance with their recommendations in their own center are unknown. Our experience is well known, reported, and coherent with other large centers, and we are gratified by outcomes achieving life-expectancy restoration for patients with MR.
Early Surgery Is Recommended for Mitral Regurgitation
Maurice Enriquez-Sarano and Thoralf M. Sundt III

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