Chronic Mitral Regurgitation: Options for Patients in 2011

Craig R. Malloy, M.D.

Internal Medicine Grand Rounds
The University of Texas Southwestern Medical Center at Dallas
February 11, 2011

This is to acknowledge that Craig Malloy, M.D., has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Malloy will be discussing off-label uses in his presentation.

Biographical Information

Name: Craig Malloy, M.D.

Rank: Professor

Departments: Advanced Imaging Research Center
Department of Internal Medicine
Department of Radiology
Medical Service, VA North Texas Health Care System

Professorship: Richard Lange Professor of Medicine

Research: Dr. Malloy's research is focused on molecular imaging of the heart.

Chronic mitral regurgitation (MR) in adults generally is a consequence of one of three conditions: 1) degenerative disease, 2) a primary cardiomyopathy, or 3) ischemic heart disease. MR due to ischemic heart disease and degenerative disease has the potential to cause congestive heart failure, and MR due to any one of these causes may accelerate the progression of congestive heart failure. Since the population is aging and the risk of ischemic MR and other causes of left ventricular dilation increase in prevalence with age, chronic mitral regurgitation will likely be an increasing problem.

In spite of the prevalence of MR and the profound consequences of congestive heart failure, relatively few randomized studies have been performed related to management of this condition. One of the key decisions - continued medical therapy vs. surgical valve replacement for the minimally symptomatic patient - is a long known controversy yet it remains a dilemma in 2011 (3, 19, 36). Advances in technology including the gradually increasing utilization of mitral valve repair, minimally invasive surgery and newer (and as yet not available for sale in the United States) catheter-based methods only complicate the situation (12, 31, 38, 39). Yet physicians must make recommendations and patients are asked to make decisions in the context of this complex environment.

All patients with chronic MR will have a period of medical therapy, perhaps life long, and patients with minimally-symptomatic chronic MR may be managed medically for some time. Consequently the internist may have considerable contact with these patients and may be in a position to help patients with these difficult decisions. It is very important to recognize that severe MR may be present in the absence of symptoms. The purpose is to review the following: 1) the three basic etiologies of chronic severe MR, 2) the rationale for and against early surgery, 3) the potential advantages and disadvantages of recent innovations in management.

ANATOMY OF THE VALVE AND ETIOLOGY OF CHRONIC MITRAL REGURGITATION

The valve itself is a funnel-shaped sleeve that hangs from the mitral annulus and descends into the left ventricle where it is tethered by the chordae and papillary muscles. The valve has two leaflets, a tongue-shaped anterior leaflet and a somewhat narrower posterior leaflet that is divided into three scallops or segments as shown in Figure 1. The term "subvalvular apparatus" refers to the muscle of the left ventricle, the papillary muscles and the chordate tendineae. The entire apparatus of the valve is classically divided into five structures: the annulus, the mitral valve leaflets, the chordae, the papillary muscles and the supporting left ventricular myocardium. Anatomical or functional abnormalities of any one of these structures may cause mitral regurgitation.

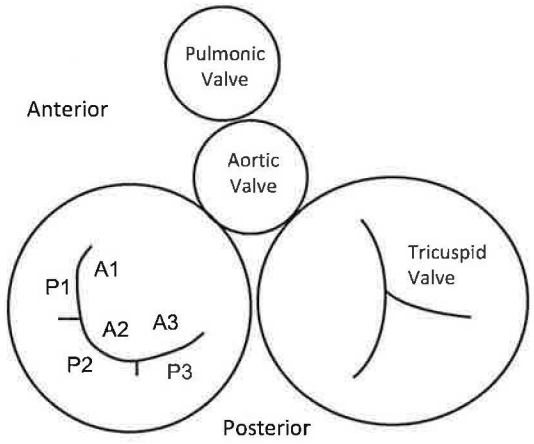

Figure 1. Anatomy of the Mitral Valve. P1, P2, and P3 refer to the scallops of the posterior leaflet; similar notation applies to the anterior leaflet, although these divisions are often not apparent.

The vocabulary related to the etiology of chronic mitral regurgitation may be confusing because terminology may refer to tissue pathology ("myxomatous degeneration"), echocardiographic findings ("mitral valve prolapse"), or a clinical syndrome ("Barlow's disease"). Adams has emphasized the importance of accurate anatomical description of MR (2, 4). As noted, abnormalities of any one of the five structures of the mitral apparatus can cause mitral regurgitation. Although it is important to have a precise anatomical diagnosis for the purpose of considering surgery or other interventions, the surgical literature divides patients into three groups. Since one of the fundamental questions is whether a patient is likely to benefit from surgery, it is worthwhile to be familiar with the terms surgeons use: degenerative, functional and ischemic MR.

Degenerative mitral valve disease refers to at least two conditions. Myxomatous degenerative disease is equivalent to Barlow's syndrome, a condition with elongated chordae resulting in failed coaption of leaflets. Fibroelastic disease results in ruptured chordae and weakening of the subvalvar apparatus.

Functional MR is a consequence of dilation of the left ventricle due to post infarction LV remodeling or a primary cardiomyopathy due to idiopathic dilated cardiomyopathy, viral cardiomyopathy, hypertension or other factors. By definition, the valve leaflets are normal and there is no evidence of anatomical abnormality (such as rupture) of the chordae.

Ischemic MR means that the patient has coronary artery disease and left ventricular dysfunction related either to myocardial infarction or chronic ischemia (33). Mitral regurgitation is due to altered geometry of the left ventricle. Burch initially suggested that mitral regurgitation could be due to papillary muscle dysfunction, but, aside from papillary muscle rupture, ischemia of the papillary muscle does not appear to cause MR. Rather, it may be primarily dysfunction of the left ventricle resulting in tethering of mitral leaflets that causes MR. However factors that are key to the other two diagnostic groups may also be lumped within ischemic MR. For example, chordal rupture due to altered strain on chordae is characteristic of degenerative disease, or dilation of the annulus due to extensive LV dysfunction is characteristic of functional MR. For practical purposes ischemic MR means MR in the setting of significant coronary artery disease, and all of the complexities of both degenerative and functional MR may play a role in progression.

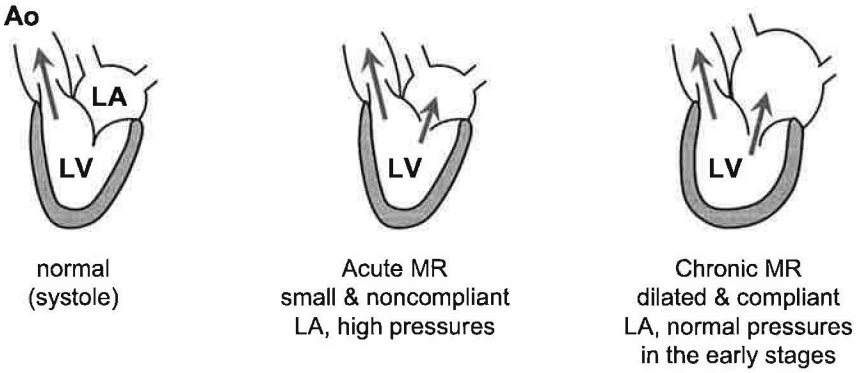

Figure 2. Influence of Acute vs. Chronic Mitral Regurgitation on the Left Ventricle and Left Atrium.

PATHOPHYSIOLOGY OF CHRONIC MR

The pathophysiology of mitral regurgitation is simple: during systole, the left ventricle ejects blood antegrade into the aorta and retrograde into the left atrium. MR is the only example of a valve lesion causing pure volume overload of the left ventricle. Aortic insufficiency is also a volume loading lesion, but early systolic pressures and coronary perfusion pressure is also affected by the disease.

Table 1. Factors Influencing the Severity of Chronic Mitral Regurgitation. The severity of MR and the ratio of forward cardiac flow (cardiac output) to backward flow are determined by several, interacting factors:

1) Size of the mitral orifice during regurgitation
2) Systemic vascular resistance opposing forward flow from the ventricle
3) Compliance of the left atrium
4) Systolic pressure gradient between the LV and the LA
5) Duration of regurgitation during systole

Initially the ventricle compensates through the Frank-Starling mechanism. As a consequence of increased preload, the left ventricle dilates and forward cardiac output is preserved because of increased stroke volume. During this period cardiac output (the sum of forward and regurgitant output) increases as needed and as a result patients may tolerate even severe chronic MR with few symptoms. During this early period – the duration is unknown – the left atrium dilates and accommodates high regurgitant volumes with little increase in pressure (Figure 2). During exercise with peripheral vasodilation the ventricle is able to increase forward output commensurate with demand. Eventually, however, the left ventricle is unable to compensate and congestive heart failure develops. With the chronic backflow of blood into the left atrium, the atrium enlarges and atrial fibrillation may develop late in the course. Pulmonary hypertension and right heart failure plus tricuspid regurgitation is also a late finding (32).

It has been suggested that patients with mitral regurgitation plus coronary artery disease are paradoxically protected from the symptoms of ischemia. This could occur because presumably angina is a consequence of an imbalance between LV wall tension during systole, a major factor in oxygen consumption, and diastolic coronary flow. If wall tension falls rapidly during systole, as happens during mitral regurgitation, then oxygen consumption is relatively low.

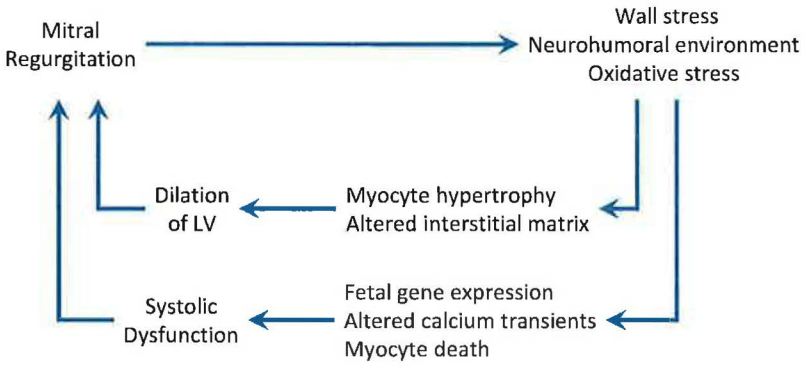

Figure 3. Effect of Mitral Regurgitation on Wall Stress, Neurohumoral Environment and Oxidative Stress. Mitral regurgitation induces a complex array of effects at the cellular level and in the interstitial environment. These changes are thought to cause dilation of the left ventricle and impaired contractility. This combination of events, in turn, may dilate the annulus or alter the geometric relations of the chordae relative to the mitral valve. The result is worsening mitral regurgitation. This Figure is redrawn from Westaby. Heart Fail Clin. 2007; 3: 139-57.

Once mitral regurgitation is established the diameter of the left ventricle at the onset of systole must increase. In the absence of any change in ventricular wall thickness, from the LaPlace relationship wall stress is increased. Furthermore, there may be systemic neuroendocrine responses. This combination of local and systemic effects is thought to generate stimuli for remodeling (ref. 51, Figure 3). The interstitial matrix and the cardiomyocytes respond to normalize wall stress. Over the long term – years – these responses are associated with decreased ventricular diastolic compliance and systolic function. Consequently, left ventricular function is further impaired, mitral regurgitation worsens because of altered geometry, wall stress escalates, and the vicious cycle causes worsening MR and heart failure (Figure 4). It is attractive to assume that this process, once initiated by severe MR, can be interrupted and perhaps reversed by surgical intervention.

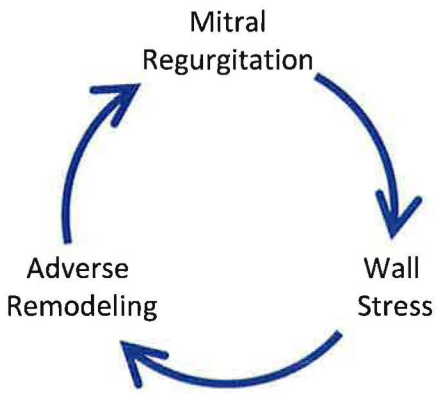

Figure 4. The Vicious Cycle of Chronic MR.

EVALUATION: IT'S ALL ABOUT THE VENTRICLE

Evaluation of a patient with suspected chronic MR should address three questions: 1) What is the etiology of mitral regurgitation? 2) What is the severity of mitral regurgitation? and 3) What is the extent of left ventricular and right ventricular dysfunction?

The symptoms of chronic MR overlap with many other conditions. Patients with chronic MR may present with symptoms of the underlying problem such as coronary artery disease or left heart failure due to a dilated cardiomyopathy. Chronic severe MR can be associated with minimal symptoms or no reported symptoms and in fact one of the difficulties in evaluation of MR is that some patients may be able to continue quite active work and travel schedules in spite of severe MR. Presumably these patients have complaint left ventricles that fill at low pressures and ejection fraction is preserved or increased. The symptoms of chronic severe MR may be minimal until left ventricular dysfunction becomes substantial. Typically patients develop symptoms of congestive heart failure including dyspnea, orthopnea and paroxysmal nocturnal dyspnea late in the course. The initial symptom is often exertional fatigue and exertional dyspnea. Atrial fibrillation can be the presenting finding, rarely associated with systemic emboli. Pulmonary hypertension is usually thought to be characteristic of mitral stenosis, but patients with mitral regurgitation may also develop pulmonary hypertension and right heart failure (27, 28).

The physical exam can demonstrate strong evidence of LV injury. In long-standing chronic severe MR the ventricle, by definition, dilates and as a result the PMI is laterally displaced, easily palpated, and diffuse. In the latter stages, a palpable S3 can be detected. The heart sounds are said to be abnormal. S1 may be soft because the high-volume antegrade flow generates high pressure between the leaflets and the LV free wall, and consequently causes the leaflets to close early. Consequently with the onset of systole, the leaflets are already nearly coapted and S1 is soft. The murmur itself is classically holosystolic because the LV pressures are higher than LA pressures throughout systole. The murmur is loudest at the LLSB and

apex, and radiates well to the axilla and sometimes to the lower left back with severe MR. An S3 is present with severe MR and LV dysfunction. Rarely, a diastolic flow murmur, reflecting high-volume antegrade flow across an otherwise normal valve, can be detected. The features of the physical exam that indicate severe MR with LV dysfunction are: lateral displacement of the PMI, an S3 (occasionally palpable), a murmur radiating to the axilla and back, and, rarely, a diastolic flow murmur.

The transthoracic echocardiogram (TEE) provides essential information about all three factors. Although the physical exam of severe MR is characteristic, patients may have co-existing structural abnormalities. The TEE provides information on the etiology of MR such as identification of mitral valve prolapse, ruptured chordae, dilation of the annulus, regional wall motion abnormalities, redundant tissue, etc. The echo also assesses the magnitude of the mitral regurgitation. The various indicators of MR severity are summarized in Table 2. Finally, the echocardiogram provides critical information about the consequences of MR for the left ventricle, atrium, pulmonary circulation and right ventricle. As will be discussed briefly below, left ventricular dimensions and ejection fraction, estimated pulmonary artery pressures, and evidence of right heart failure are all essential information. If technical issues preclude a high quality TTE or if there is a discrepancy between the severity estimated by echo and the clinical picture, a transesophageal echocardiogram is an option, and essential if there is any chance surgery would be considered.

Table 2. Qualitative and Quantitative Parameters for Grading MR Severity. This table is modified from: Zoghbi et al. J Am Soc Echocardiogr. 2003; 16: 777-802.

	MILD	MODERATE	SEVERE
Doppler			
Jet density	faint	Dense	dense
Pulm vein flow			reversal
Quantitative			
Regurg volume	< 30 mL	30 – 60	> 60 mL
RF %	< 30 %	30 – 50	> 50 %
Effective orifice	< 0.2 cm^2	0.2 - 0.4	> 0.4 cm^2

The electrocardiogram provides useful information by suggesting other disease such as prior myocardial infarction and by demonstrating evidence of left ventricular, left atrial and right ventricular dysfunction. Specifically, atrial fibrillation (20), left ventricular hypertrophy, right ventricular hypertrophy or combined hypertrophy are all findings consistent with severe chronic mitral regurgitation. The chest x-ray is useful for detecting late features of severe MR such as pulmonary congestion, an increased cardiac silhouette and right heart failure. Rarely, mitral annular calcium can be observed which is relevant to surgery. Coronary angiography and a right heart catheterization to measure pulmonary artery pressures and pulmonary vascular resistance is necessary for evaluation of most patients with significant MR. Finally, BNP may be useful in predicting outcome (40).

With the results of these studies, one should be able to make a reasonable evaluation of the etiology, the severity of MR, and the consequences of MR for the left ventricle. The natural history and management of functional MR and ischemic MR are intertwined with the underlying cardiomyopathy or coronary artery disease, and for this reason won't be considered further (although many of the concepts developed below may be applicable). If a patient has severe MR due to degenerative disease, a critical decision is the timing of and necessity for surgery. Much of the remaining discussion will focus on the patient with normal or borderline abnormal left ventricular ejection fraction and left ventricular end systolic diameter. Often these patients have few symptoms and management is controversial.

NATURAL HISTORY OF MITRAL REGURGITATION

The natural history of chronic MR managed with medical therapy has been reported in a large number of observational studies; data from three of the best-known studies are summarized in Figure 5 (10, 41, 42). The data are reasonably consistent: adverse events such as the development of symptoms attributable to congestive heart failure or new atrial fibrillation or death occurs for the majority of patients within 5 to 7 years. However, these observations are not completely consistent with some more recent comparisons of medical vs. surgical therapy.

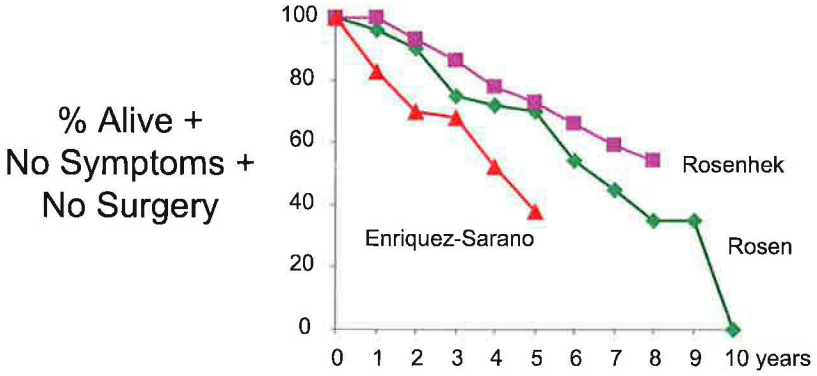

Figure 5. Natural History of Severe Chronic Mitral Regurgitation. These data are taken from three observational studies of patients managed medically: 1) Rosenhek et al. Circulation. 2006; 113: 2238-44. 2) Rosen et al. Am J Cardiol. 1994; 74: 374-80. 3) Enriquez-Sarano N Engl J Med. 2005; 352: 875-83.

It is also generally accepted that the severity of mitral regurgitation correlates with outcome. As illustrated in Figure 6, patients with progressively more severe mitral regurgitation at initial evaluation have more heart failure, cardiac death and atrial fibrillation over five years compared to patients with less severe mitral regurgitation.

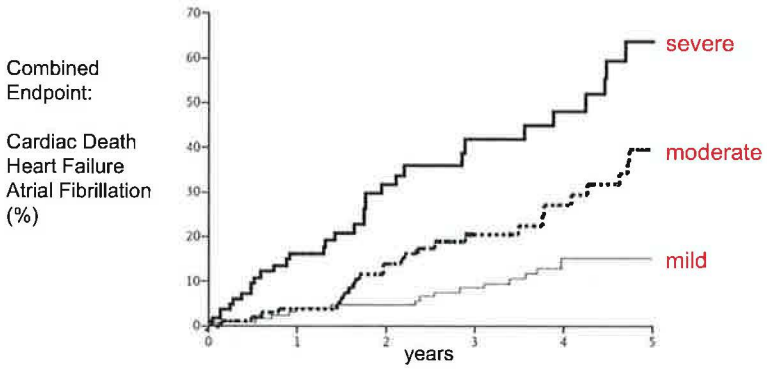

Figure 6. Natural History of Chronic Mitral Regurgitation as a Function of Severity. Patients were managed medically. Data redrawn from Enriquez-Sarano N Engl J Med. 2005; 352: 875-83.

In summary, with medical management of severe mitral regurgitation, much of the literature reports a relentless downhill course with progressive symptoms and premature death. Furthermore, the poor prognosis correlates with the severity of MR.

THE MITRAL REGURGITATION HYPOTHESIS

The "mitral regurgitation hypothesis" is this: If the severity of mitral regurgitation is reduced, then patients live longer. According to this hypothesis, if we can move an asymptomatic patient from severe MR to mild MR by whatever means, then the patient will move from the "severe" survival curve shown in Figure 6 to the "mild" survival curve. The assumption is that MR causes an environment including wall stress or neurohumoral condition that drives progression of the MR even in the absence of significant symptoms. This attractive hypothesis guides much of our thinking in management of chronic MR. Does the evidence support this hypothesis?

OPTION #1: MEDICAL THERAPY

Medical therapy is focused on the underlying condition if MR is due to ischemic heart disease or a dilated cardiomyopathy. In general there are very few studies of medical management of mitral regurgitation and those are limited by the small numbers of patients (29, 30). A framework for thinking about medical therapy is to target the regurgitant volume per unit time as estimated by the Toricelli relationship, also termed the orifice equation, which describes flow across a round orifice (14). In the following it is assumed that the systolic ejection period is approximately fixed across physiological heart rates, a good assumption in adult humans. This approach, while simplistic, does allow us to think about the hydraulic effects of medical therapy:

$$\text{regurgitant flow per minute} \propto (\text{heart rate}) \cdot (\text{orifice area}) \cdot (\sqrt{(\text{LVP} - \text{LAP})})$$

where LVP is left ventricular systolic pressures and LAP is left atrial pressures during systole. According to this equation, the volume of mitral regurgitant flow per unit time is determined by three factors. *First*, the magnitude of the pressure gradient across the valve is simply the difference between left ventricular systolic pressures and left atrial pressure. Since LV systolic pressures are determined by arterial pressures (in the absence of aortic stenosis or dynamic outflow tract obstruction), the regurgitant volume is sensitive to the gradient between systemic pressures and pressure in the left atrium during systole. However because of the square root in the relationship modest changes in the gradient do not correspond to a dramatic effect in the regurgitant volume. Second, the size of the regurgitant orifice is a factor. Occasionally the size of the regurgitant orifice may be more-or-less fixed, for example in a perforated leaflet due to endocarditis or trauma. If MR is functional and due to dilation of the annulus, then the orifice area may be sensitive to ventricular volumes. Ischemic MR causing intermittent regional wall motion abnormalities could also cause variations in the orifice. The implication is straightforward: manage ventricular dilation due to volume overload with diuretics and treat ischemia. Third, the fraction of time the ventricle spends in systole is a factor. Again, the implication is simple: if the patient is in atrial fibrillation, convert to sinus rhythm and control tachycardias.

In general, the basics of medical therapy - control hypertension, control heart rate and reduce pulmonary congestion - probably have a beneficial effect on reducing the effective orifice area, reducing the duration of systole, and reducing the magnitude of the systolic pressure gradient. There is no doubt that medical therapy improves both symptoms and survival in patients with decompensated mitral regurgitation and heart failure. However, among asymptomatic or minimally symptomatic patients with severe MR, it is less clear that medical therapy reduces the severity of MR.

Angiotensin Converting Enzyme Inhibitors

Table 3. Summary of Studies of Angiotensin Converting Enzyme Inhibitors or A2 Blockers in Chronic MR. The studies by Marcotte and by Wisenbaugh were randomized; the number of patients randomized to ACEIs is shown. RF, regurgitant fractions.

Author	Ref.	drug	pub. date	patients	duration (mo)	RF
Gupta	22	enalapril	2001	40	6	no
Marcotte	35	lisinopril	1997	12/23	12	-6%
Dujardin	9	losartan	2001	28	4	-11%
Harris	24	ramipril	2005	26	6	no
Wisenbaugh	52	captopril	1994	12/28	6	no
Schön	43	quinipril	1994	12	12	-42%
Høst	25	ramipril	1997	11	1	-18%
Tischler	46	enalapril	1998	11	6	-17%

The theoretical rationale for use of angiotensin converting enzyme inhibitors is strong. ACE inhibitors reduce systolic loading on the ventricle and consequently reduce the LV - LA gradient. Further, reduced LV pressures may reduce the diameter of the annulus and thereby reduce regurgitant flow. ACE inhibitors may also be beneficial because of effects on ventricular remodeling and possible slowing of ventricular dilation during increased wall stress. We know from the SAVE trial that post-MI remodeling of the left ventricle was attenuated by ACEIs. The SOLVD study showed that among patients with LV dysfunction but without heart failure, ACEIs slowed progression of LV dilation. Since valve tethering is a consequence of abnormal left ventricular geometry and tethering may cause significant MR, it would be reasonable to presume that ACEIs may have long-term benefit and even reverse the severity of MR.

Unfortunately, when the primary problem is severe degenerative MR, the actual benefit of ACEIs is uncertain. A small number of studies in patients with MR have evaluated the long-term effects of ACE inhibitor and angiotensin 2 receptor blockers. Some have observed a small reduction in MR severity with treatment. Ramipril has been favored in some studies because it has a long half-life and a high affinity for myocardial tissue ACE. The intent is to inhibit both systemic and myocardial tissue ACE and thereby protect against remodeling and dilation of the ventricle. Among some normotensive patients, a small decrease in the severity of MR has been described, but this has not been universally observed (Table 3).

Beta Adrenergic Blockers

The theoretical rationale for beta adrenergic blockade is similarly reasonable. Volume overload due to MR results in neuroendocrine activation similar to heart failure. Beta blockers added to ACEI therapy reduce the rate of LV dilation and the combination, among patients with mild heart failure, reverses LV remodeling. Among patients with severe heart failure and chronic MR the combination of beta blockers and ACEIs reduced the severity of MR. Beta blockade in patients with heart failure is associated with increased survival, so it is reasonable to examine a possible benefit in patients with MR. This hypothesis was examined and supported in a large observational cohort of patients with severe MR and normal ejection fraction (50). Chart review found that among patients on beta blocker therapy, mortality was reduced. However, this was a retrospective observational study; a randomized controlled trial is not available.

OPTION #2: SURGICAL REPAIR OR REPLACEMENT OF THE VALVE

Mitral valve replacement cures mitral regurgitation and it remains a widely-used surgical therapy for mitral regurgitation. The operations are more-or-less standard and there is an enormous literature on the durability, importance of anticoagulation the relative benefits of tissue vs. mechanical valves. Years ago it was widely thought that valve replacement caused an inevitable deterioration of LV function, but preservation of the subvalvular apparatus has improved post operative LV function.

Unlike mitral valve replacement which refers to a specific operation regardless of the etiology, mitral valve repair targets the specific anatomical cause of the mitral regurgitation (7, 8). Repair of a redundant floppy posterior leaflet is relatively simple and associated with a very high rate of success. The promised advantages of mitral valve repair are widely-publicized, including: 1) no need for anticoagulation, 2) low rates of thromboembolism, 3) excellent durability, and 4) resistance to endocarditis. The mortality for mitral valve repair is low, much less than 3% and in some large series, 0% or 1%. If feasible, mitral repair is preferred over a prosthetic valve (15, 16).

Mitral valve repair consists of three procedures in various combinations. First, the valve leaflets themselves may be restructured by excising redundant tissue. In some instances after excision of portions of the posterior leaflet, the leaflet itself may be disconnected from the annulus and reattached to shrink to circumference of the annulus. Whether or not this procedure is performed, a supporting ring is almost universally sutured into the annulus to reduce the circumference of the annulus and thereby improving coaption of the leaflets, and preventing further dilation. Chordae may also be repaired or reimplanted, as needed. Surgeons are also using annuloplasty for management of tricuspid regurgitation and right heart failure more frequently.

In the 1990s Otavio Alfieri suggested suturing the central portion of the middle scallop of the posterior leaflet to the middle edge of the anterior leaflet (34). This procedure, now known as the "Alfieri Stitch", creates permanent coaption of the middle portion of the leaflets and generates a double-orifice mitral valve. His group is not a strong proponent of this repair particularly in the absence of annulo-plasty, but the procedure remains in use by experienced surgical teams for a small number of patients (44, 45).

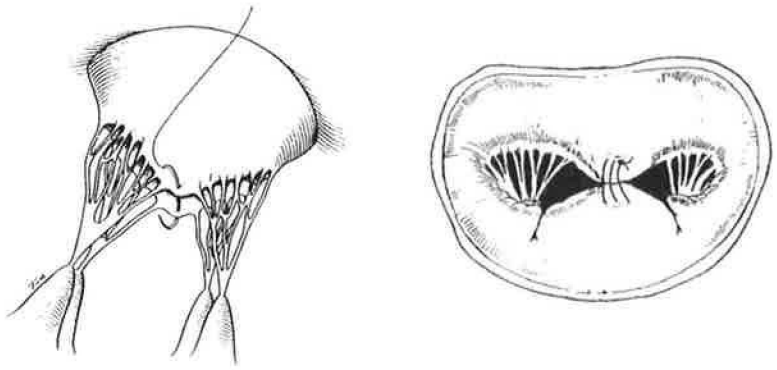

Figure 7. The Alfieri Stitch. The coapting surfaces of the middle scallops of the anterior and posterior leaflets are sutured together, creating a double-orifice mitral valve.

Mitral valve surgery is generally offered to patients with severe MR and overt symptoms because of anticipated high mortality with medical therapy. Once surgery is performed and MR is eliminated, one might expect the vicious cycle described above to be interrupted. However, although symptoms are not sensitive to the severity of MR, patients who undergo surgery for a symptom indication incur high mortality rates in spite of successful surgery, as shown in Figure 8. Excess mortality of NYHA class III and IV patients was observed in all subgroups examined in this study including pre-operative ejection fraction and whether the patient had valve repair or replacement (48).

Since patients who undergo surgery for symptoms continue to suffer high mortality, it would be useful to identify markers of risk that add information to symptom status and would identify patients at risk for long term mortality (47). Reduced preoperative LV ejection fraction is a predictor of mortality, as is left ventricular end systolic diameter (LVESD), as shown in Figure 4. This parameter is one that distinguishes recommendations for surgery in North America vs. in Europe.

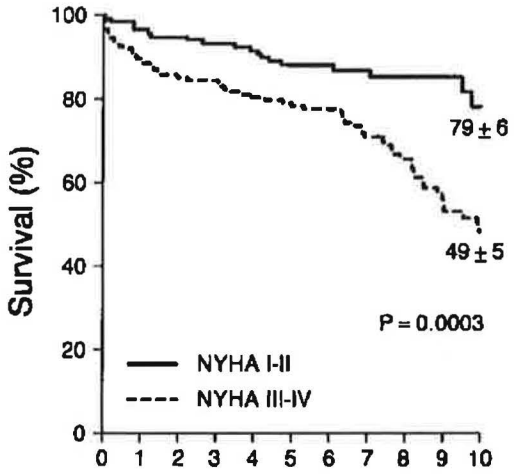

Figure 8. Postoperative survival among patients in NYHA class I or II and patients in class III or IV. This difference in outcome was also observed when patients were stratified for ejection fraction < 60 % or ≥ 60%. Data from Tribouilloy et al. Circulation. 1999; 99: 400-5.

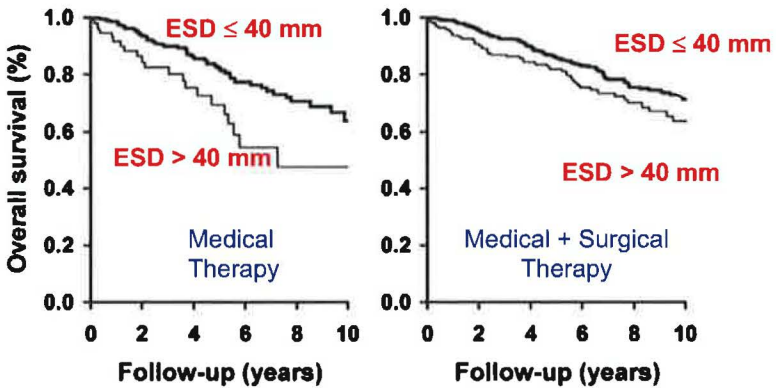

Figure 9. Survival According to Left Ventricular End Systolic Dimension in Patients With MR. The left panel shows outcome with medical management and the right panel shows outcome with surgery and medical management. Data from: Tribouilloy et al. J Am Coll Cardiol. 2009; 54: 1961-8.

A number of studies have addressed the question of proper timing of mitral valve surgery among patients with severe but asymptomatic MR (10, 26, 42). Data from one of the most influential reports are shown in Figures 10 and 11. In this study, consecutive asymptomatic patients with severe degenerative mitral regurgitation were followed with serial clinical and echo exams. Patients were referred for surgery when symptoms occurred or when asymptomatic patients developed left ventricular dysfunction, atrial fibrillation, or pulmonary hypertension. This study confirmed (see Figure 10) the relentless course of mitral regurgitation. However, with this treatment strategy and with support from a surgery team with 0% operative mortality, overall survival was excellent as shown in Figure 11. These investigators reported that postoperative outcome was good.

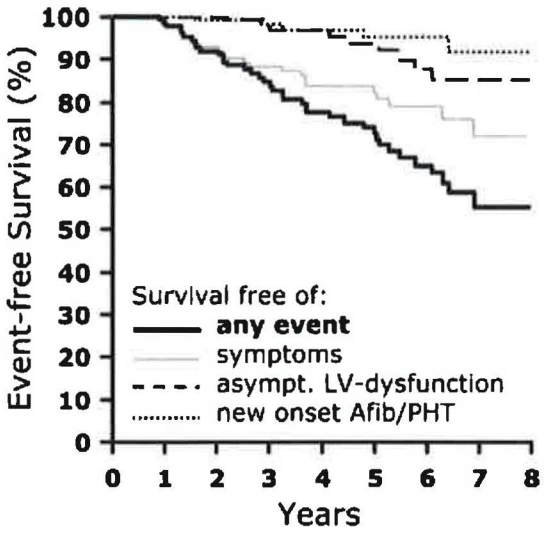

Figure 10. Event Free Survival During Watchful Waiting. After 8 years about 60% had developed an indication for surgery, left ventricular dysfunction, pulmonary hypertension, atrial fibrillation or symptoms. Figure from Rosenhek et al. Circulation. 2006; 113: 2238-44.

In contrast to the conclusions by Rosenhek and colleagues, two other major studies evaluated a strategy of watchful waiting in severe asymptomatic mitral regurgitation (10, 26). All three studies are summarized in Table 4. These studies share a number of features. First, they are not randomized. Some patients with asymptomatic severe MR were selected for surgery by their physicians and others were assigned to medical therapy with close follow up. Since all patients had a TEE, valve morphology was known and there may have been (or likely there were) technical features that suggested a difficult operation that may have swayed assignment to watchful waiting.

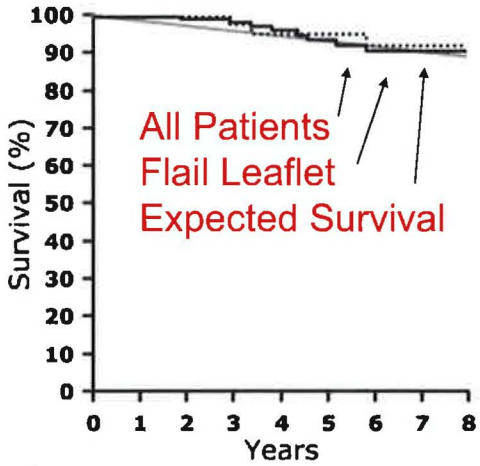

Figure 11. Survival of patients with asymptomatic severe degenerative MR. Survival of patients managed according to a watchful waiting strategy did not differ from expected cumulative survival, and a subset with flail leaflet did not differ. Perioperative and postoperative deaths for those patients who required valve replacement during follow-up are included. Data from Rosenhek et al. Circulation. 2006; 113: 2238-44.

A second common feature is that patients followed medically crossed over to surgery because of symptoms at a variable rate ranging from 41% to 94%. This means that in spite of watching, the patients deteriorated. The typical symptoms and findings of MR - left heart failure, atrial fibrillation, pulmonary hypertension and right heart failure - are

not trivial and sometimes are permanent in spite of valve surgery. It is attractive to assume that surgery will reliably reverse early adverse events, but this is not the case.

Third, it is also true that some patients can have a benign course. In the Kang study, 85% of patients in the watchful waiting group were free of cardiac events at 7 years. However, some of these patients had urgent surgery, perhaps indicating that unexpectedly rapid deterioration may occur.

Finally, surgical mortality was 1% or less in all three studies in spite of the fact that in some instances patients were quite ill at the time of surgery. For example, in the Kang study, more than 1/3 who had watchful waiting but needed surgery had been admitted because of congestive heart failure. Some of these patients may not have been optimal candidates for surgery at the time of surgery.

Table 4. Comparison of Three Studies of Mitral Valve Surgery and Medical Therapy for Severe Chronic Mitral Regurgitation. Data are from: Kang et al. Circulation. 2009; 119: 797-804; Rosenhek et al. Circulation. 2006; 113: 2238-44; and Enriquez-Sarano et al. N Engl J Med. 2005; 352: 875-83.

First Author	**Kang**	**Rosenhek**	**Enriquez-Sarano**
Reference	26	42	10
Publication Date	2009	2006	2005
Country	Korea	Austria	USA
Number of pts	286	132	198
Duration (years)	11	7	9
Mitral surgery in f/u (%)	19	26	82
Symptomatic at surgery	94	69	41
Surgical mortality (%)	0	0	1
Event-free survival	85% (7 y)	55% (8 y)	38% (5 y)
Recommended management strategy	Early Surgery	Watchful Waiting	Early Surgery

The conflicting conclusions of these studies, all from outstanding centers, may illustrate a problem that is worth a brief mention. Adams and Anyanwu have commented on clinical and methodological pitfalls "that limit generalization of results from most studies of mitral valve repair" (1). Although this editorial focused on surgical management of ischemic mitral regurgitation, most of the comments are generally relevant to reading the surgical literature. Four pitfalls and limitations in surgical reports of mitral valve repair were identified.

First, it is relatively common that data on the etiology of mitral regurgitation is not well-described and the preoperative evaluation is inconsistent. For example, ischemic mitral regurgitation can produce a number of different anatomical variants that require different surgical approaches, yet these are typically not described. Furthermore, echocardiographic assessment is inconsistent or incomplete. In some instances left ventricular ejection fraction is simply evaluated by eye. *Second*, preferences by the patient and by the surgeon bias all results. Patients may prefer a minimally invasive approach which is technically more demanding. There are probably innumerable examples of surgeon preferences in virtually every

decision may bias results. *Third*, long term studies incorporate evolving medical and surgical practice. This means that new surgical approaches, by definition, are introduced early in the study where the learning curve is steep. These same patients disproportionately weight long-term studies since the poorest outcomes may occur earliest. Furthermore, technologies in cardiopulmonay bypass, cardiac imaging, anesthetic techniques, etc., evolve continuously. *Finally*, strict follow up is essential in evaluating surgical outcomes but is typically absent. For example, a patient with good results at 1 year may be lost to follow-up because he is an assisted-care nursing facility with severe congestive heart failure three years after surgery, yet may be counted as a good outcome. An effort, supported by the NIH, is underway to address these issues (18).

There is no dispute that better trial design would be welcomed in the field. With available information, the European Society of Cardiology, the American Heart Association and the American College of Cardiology have provided recommendations for indications and timing for mitral valve surgery. These recommendations are summarized in Table 5 (6, 49). Generally the recommendations are consistent but the threshold for recommending surgery to an asymptomatic patient based on EVESD is lower in North America.

Table 5. Recommendations for Mitral Valve Surgery. This table is derived from two papers: Bonow et al. J Am Coll Cardiol. 2008; 52: 1-142; and Vahanian et al. Eur Heart J. 2007; 28: 230-68. Abbreviations: ESC, European Society of Cardiology; PAP, pulmonary artery pressure.

	ESC	ACC/AHA
Symptomatic patients	I	I
Asymptomatic patients with:		
Enlarged LV, ESD ≥ 40 mm		I
Enlarged LV, ESD ≥ 45 mm	I	
LV dysfunction (EF < 60%)	I	I
Pulmonary HTN (systolic PAP at rest > 50 mmHg)	IIa	IIa
Pulmonary HTN (systolic PAP during exercise		IIa
Atrial fibrillation	IIa	
New onset atrial fibrillation		IIa
Asymptomatic patients with preserved LV function		
Repair in an experienced center where likelihood of success > 90%		IIa
When there is high likelihood of durable repair and low risk for surgery	IIb	

Option #3: Minimally Invasive Mitral Valve Surgery

Surgical treatment of the mitral valve evolved dramatically in the 1900s. By the mid-1990s, new approaches *via* small incisions were explored and one of the successful developments was approach through a thoracotomy. Right thoracotomy mitral repair is challenging because of the increased distance from the chest wall to the valve rather than from the sternum to the valve. With advances in many technologies, primarily cardiopulmonary bypass, endoscopic visualization and surgical instruments, some surgeons now prefer this approach for many patients. The surgery is different in many respects compared to the classical median sternotomy. For example, cardiopulmonary bypass is usually established *via* the femoral vessels. Details vary depending on the precise technique, but surgical access is typically *via* a 5 - 7 cm right anterolateral thoracotomy, a videoscope is placed *via* another access, and the aortic cross-clamp is placed by a third thoracotomy.

This is, presumably, the same major operation through a right thoracotomy rather than a midline sternotomy. A number of questions can be raised. The first is rhetorical: "Is minimally invasive mitral valve repair really minimally invasive?" In many critical respects, the operation is not minimally invasive: the patient must be on cardiopulmonary bypass, the aorta must be cross-clamped, the heart must be arrested, etc. The risks of these procedures are unchanged (5). The only unequivocal benefit is cosmetic, but other benefits have been reported in database studies (Table 6).

Morbidity and mortality of less-invasive approaches compared to conventional sternotomy were reported recently (17); see Table 6. About 20% of isolated mitral valve procedures in the US are performed using these methods. After controlling for preoperative characteristics, patients having less invasive operations had a similar risk of operative mortality. The risk of blood or platelet transfusion was lower in the less invasive group, as was the risk of post-operative atrial fibrillation and the length of stay. The rates of re-operation for bleeding were higher in the less invasive group. The risk of permanent stroke was almost twofold higher in the less-invasive group.

Table 6. Odds Ratios (OR) for Outcomes of Less-Invasive Mitral Operations vs. Conventional Sternotomy. Data are adjusted for participant correlations and other potential variables. The excess "major morbidity or mortality" was driven largely by the risk of permanent stroke. Data from Gammie et al. Ann Thorac Surg. 2010; 90: 1401-8.

	Adjusted OR	**P**
Operative mortality	1.13	0.419
Any reoperation	1.12	0.177
Reoperation for bleeding or tamponade	1.22	0.040
Reoperation for valve dysfunction	0.89	0.702
Any infection	1.10	0.612
Permanent stroke	1.96	< 0.001
Postoperative atrial fibrillation	0.79	< 0.001
Renal failure	1.09	0.483
Prolonged ventilation	1.09	0.273
Major morbidity or mortality	1.14	0.029
Postprocedure length of stay > 14 days	0.88	0.284
Perioperative red blood cell transfusion	0.86	0.014
Perioperative platelet transfusion	0.81	< 0.001

Does minimally invasive surgery degrade the quality of the repair? There is no answer to this question because there are no randomized comparisons of the two approaches, midline sternotomy vs. right thoracotomy. One of the most interesting reports (see Table 7) involved 1230 patients with isolated mitral regurgitation and a mean LVEF >60%. The planned surgery was minimally invasive mitral valve repair in this low-risk, well-evaluated population in a very high-volume experienced center (44). Among those patients with posterior leaflet pathology, 3.1% had mitral valve replacement, but among those patients with anterior leaflet or bileaflet pathology (total n = 558), 53 patients or nearly 10% had mitral valve replacement in spite of the fact that the intended operation was repair. This raises the question of whether at least some of these patients would have had successful repair *via* a sternotomy.

In summary, technology for mitral valve repair surgery has progressed rapidly in the past 15 years. There is no question that the safety and efficacy of minimally invasive mitral valve surgery is established for selected patients and that large series have been reported with very low operative mortality and morbidity. The use of blood products and the risk of atrial fibrillation appear lower with minimally invasive methods, and the risk of permanent stroke may be increased with this approach. There is no clear benefit other than cosmetic.

Table 7. Surgical techniques in patients with isolated anterior (AML), posterior (PML), or bileaflet (BL) mitral valve prolapse. Data from Seeburger et al. Eur J Cardiothorac Surg. 2009; 36: 532-8.

	PML (n = 672) [n]	%	AML (n = 156) [n]	%	BL (n = 402) [n]	%
Mitral valve repair	651	96.9	142	91	363	90.3
Mitral valve replacement	21	3.1	14	9	39	9.7
Edge-to-edge (Alfieri)	6	0.9	7	4.5	37	9.2
Ring annuloplasty	645	96	139	89.1	358	89.1

PERHAPS IN THE FUTURE, OPTION #4: SURGICAL CONCEPTS ADAPTED TO CATHETERS

Survival is reduced among patients with severe MR associated with symptoms or with left ventricular dysfunction or with pulmonary hypertension. Hence, surgery to repair or replace the valve is indicated among patients with symptoms or among patients with left ventricular dysfunction. Surgery is a class IIA indication among patients with normal left ventricular function if repair is likely. Intuitively, mitral valve repair is the optimal procedure. However, surgery has associated morbidity and mortality, and some patients referred for repair have valve replacement. Furthermore, there are no randomized trials of mitral valve repair vs. replacement or mitral valve repair vs. medical therapy. Surgery is associated with significant morbidity and mortality and some patients are not candidates for surgery because of comorbidities.

The motivation for percutaneous methods is to offer an alternative to surgery. This option may be particularly important for patients at high risk of surgery. The inspiration for a catheter-based device begins with Alfieri's paper in which he described an orifice-reduction surgery. This has evolved to an approach termed the MitraClip, a small v-shaped device that clamps together the middle scallops of the anterior and posterior leaflets. The procedure itself requires a team of an anesthesiologist, echocardiographer and the interventionalist. It is performed in the cardiac catheterization lab with both tranesophageal guidance and fluoroscopic imaging. The patient is under general anesthesia. The clip delivery system is mounted on a 24 French catheter and passed across the interatrial septum. The clip is advanced across the central scallops of the anterior and posterior mitral valve leaflets. It can be repositioned, and after adequate positioning, it is permanently deployed. This creates a double orifice mitral valve, similar to Figure 7, with reduced severity of MR.

Two trials have been published or are underway. The first trial, Endovascular Valve Edge-to-Edge Repair Study (EVEREST I), enrolled symptomatic patients with grade 3 or grade 4 MR and a central MR jet, with the goal of evaluating safety and durability. Procedural success was defined as a predischarge MR grade ≤ 2 which was achieved in 74% of patients (13). The randomized clinical trial, EVEREST II, prospectively randomly assigned patients to percutaneous repair or surgery. The effectiveness endpoint requires a reduction in MR to ≤ 2 at 1 year. This is a seminal trial not only because it evaluates the MitraClip but it is also the first randomized trial comparing surgery to an alternative therapy. Currently the MitraClip is not available for sale in the United States.

SUMMARY

Mitral regurgitation is a very complex condition that may be due to degenerative disease of the valve, ischemic heart disease, or a cardiomyopathy. Although patients may initially be asymptomatic, severe MR is associated with a steady progression to left ventricular dysfunction, atrial fibrillation and right heart failure. Medical therapy is beneficial for patients with congestive heart failure, but there is little evidence that the course of mitral regurgitation is improved. Delaying surgery until symptoms or overt LV dysfunction is unattractive because post operative outcomes are worse. A watchful waiting strategy – careful monitoring by echo to detect asymptomatic dilation of the ventricle plus clinical surveillance – is recommended by some experts whereas others recommend early surgery. New diagnostic technologies are needed to identify patients who are likely to suffer from lack of immediate surgery.

REFERENCES

1. Adams DH, Anyanwu A. Pitfalls and limitations in measuring and interpreting the outcomes of mitral valve repair. J Thorac Cardiovasc Surg. 2006; 131: 523-9. PMID: 16515900

2. Adams DH, Anyanwu AC. Seeking a higher standard for degenerative mitral valve repair: begin with etiology. J Thorac Cardiovasc Surg. 2008; 136: 551-6. PMID: 18805250

3. Adams DH, Anyanwu AC. Valve Disease: Asymptomatic mitral regurgitation: does surgery save lives? Nat Rev Cardiol. 2009; 6: 330-2. PMID: 19377493

4. Anyanwu AC, Adams DH. Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. Semin Thorac Cardiovasc Surg. 2007; 19: 90-6. PMID: 17870001

5. Baumgartner FJ, Gheissari A, Panagiotides GP, Capouya ER, Yokoyama T. What is "minimally invasive"? Ann Thorac Surg. 1998; 66: 980-1. PMID: 9768980

6. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the 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). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008; 52: e1-142. PMID: 18848134

7. Daneshmand MA, Milano CA, Rankin JS, Honeycutt EF, Swaminathan M, Shaw LK, Smith PK, Glower DD. Mitral valve repair for degenerative disease: a 20-year experience. Ann Thorac Surg. 2009; 88: 1828-37. PMID: 19932244

8. David TE, Ivanov J, Armstrong S, Rakowski H. Late outcomes of mitral valve repair for floppy valves: Implications for asymptomatic patients. J Thorac Cardiovasc Surg. 2003; 125: 1143-52. PMID: 12771888

9. Dujardin KS, Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ. Effect of losartan on degree of mitral regurgitation quantified by echocardiography. Am J Cardiol. 2001; 87: 570-6. PMID: 11230841

10. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. 2005; 352: 875-83. PMID: 15745978

11. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994; 90: 830-7. PMID: 8044955

12. Fedak PW, McCarthy PM, Bonow RO. Evolving concepts and technologies in mitral valve repair. Circulation. 2008 Feb; 117: 963-74. PMID: 18285577

13. Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, Whitlow PL, Gray W, Low R, Herrmann HC, Lim S, Foster E, Glower D; EVEREST Investigators. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009; 54: 686-94. PMID: 19679246

14. Gaasch WH, Meyer TE. Left ventricular response to mitral regurgitation: implications for management. Circulation. 2008; 118: 2298-303. PMID: 19029478

15. 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: 881-7. PMID: 17283266

16. Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien SM, Brown JM. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg. 2009; 87: 1431-7; discussion 1437-9.PMID: 19379881

17. Gammie JS, Zhao Y, Peterson ED, O'Brien SM, Rankin JS, Griffith BP. J. Maxwell Chamberlain Memorial Paper for adult cardiac surgery. Less-invasive mitral valve operations: trends and outcomes from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg. 2010; 90: 1401-8. PMID: 20971230

18. Gardner TJ, O'Gara PT. The Cardiothoracic Surgery Network: randomized clinical trials in the operating room. J Thorac Cardiovasc Surg. 2010; 139: 830-4. PMID: 20304133

19. Gillinov AM, Mihaljevic T, Blackstone EH, George K, Svensson LG, Nowicki ER, Sabik JF 3rd, Houghtaling PL, Griffin B. Should patients with severe degenerative mitral regurgitation delay surgery until symptoms develop? Ann Thorac Surg. 2010; 90: 481-8. PMID: 20667334

20. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol. 2002; 40: 84-92. PMID: 12103260

21. Grigioni F, Tribouilloy C, Avierinos JF, Barbieri A, Ferlito M, Trojette F, Tafanelli L, Branzi A, Szymanski C, Habib G, Modena MG, Enriquez-Sarano M; MIDA Investigators. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. JACC Cardiovasc Imaging. 2008; 1: 133-41. PMID: 19356418

22. Gupta DK, Kapoor A, Garg N, Tewari S, Sinha N. Beneficial effects of nicorandil versus enalapril in chronic rheumatic severe mitral regurgitation: six months follow up echocardiographic study. J Heart Valve Dis. 2001; 10: 158-65. PMID: 11297201

23. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. Am J Cardiol. 1991; 67: 259-63. PMID: 1990789

24. Harris KM, Aeppli DM, Carey CF. Effects of angiotensin-converting enzyme inhibition on mitral regurgitation severity, left ventricular size, and functional capacity. Am Heart J. 2005; 150: 1106. PMID: 16291006

25. Høst U, Kelbaek H, Hildebrandt P, Skagen K, Aldershvile J. Effect of ramipril on mitral regurgitation secondary to mitral valve prolapse. Am J Cardiol. 1997; 80: 655-8. PMID: 9295005

26. 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. PMID: 19188506

27. Le Tourneau T, Messika-Zeitoun D, Russo A, Detaint D, Topilsky Y, Mahoney DW, Suri R, Enriquez-Sarano M. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. J Am Coll Cardiol. 2010; 56: 570-8. PMID: 20688212

28. Le Tourneau T, Richardson M, Juthier F, Modine T, Fayad G, Polge AS, Ennezat PV, Bauters C, Vincentelli A, Deklunder G. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. Heart. 2010; 96: 1311-7.PMID: 20659951

29. Levine AB, Muller C, Levine TB. Effects of high-dose lisinopril-isosorbide dinitrate on severe mitral regurgitation and heart failure remodeling. Am J Cardiol. 1998; 82: 1299-301. PMID: 9832115

30. Levine HJ, Gaasch WH. Vasoactive drugs in chronic regurgitant lesions of the mitral and aortic valves. J Am Coll Cardiol. 1996; 28: 1083-91. PMID: 8890799

31. Mack MJ. Percutaneous mitral valve repair: a fertile field of innovative treatment strategies. Circulation. 2006; 113: 2269-71. PMID: 16702486

32. Magne J, Lancellotti P, Piérard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. Circulation. 2010; 122: 33-41. PMID: 20566950

33. Magne J, Sénéchal M, Dumesnil JG, Pibarot P. Ischemic mitral regurgitation: a complex multifaceted disease. Cardiology. 2009; 112: 244-59. PMID: 18758181

34. Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. J Thorac Cardiovasc Surg. 2003; 126: 1987-97.PMID: 14688717

35. Marcotte F, Honos GN, Walling AD, Beauvais D, Blais MJ, Daoust C, Lisbona A, McCans JL. Effect of angiotensin-converting enzyme inhibitor therapy in mitral regurgitation with normal left ventricular function. Can J Cardiol. 1997; 13: 479-85.PMID: 9179087

36. Mehra MR, Reyes P, Benitez RM, Zimrin D, Gammie JS. Surgery for severe mitral regurgitation and left ventricular failure: what do we really know? J Card Fail. 2008; 14: 145-50. PMID: 18325462

37. Mehta RH, Eagle KA, Coombs LP, Peterson ED, Edwards FH, Pagani FD, Deeb GM, Bolling SF, Prager RL; Society of Thoracic Surgeons National Cardiac Registry. Influence of age on outcomes in patients undergoing mitral valve replacement. Ann Thorac Surg. 2002; 74: 1459-67.

38. Mihaljevic T, Jarrett CM, Gillinov AM, Williams SJ, DeVilliers PA, Stewart WJ, Svensson LG, Sabik JF 3rd, Blackstone EH. Robotic repair of posterior mitral valve prolapse versus conventional approaches: potential realized. J Thorac Cardiovasc Surg. 2011; 141: 72-80. PMID: 21093881

39. Modi P, Rodriguez E, Hargrove WC 3rd, Hassan A, Szeto WY, Chitwood WR Jr. Minimally invasive video-assisted mitral valve surgery: a 12-year, 2-center experience in 1178 patients. J Thorac Cardiovasc Surg. 2009; 137: 1481-7. PMID: 19464468

40. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. J Am Coll Cardiol. 2009; 54: 1099-106.

41. Rosen SE, Borer JS, Hochreiter C, Supino P, Roman MJ, Devereux RB, Kligfield P, Bucek J. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. Am J Cardiol. 1994; 74: 374-80. PMID: 8059701

42. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, Schemper M, Maurer G, Baumgartner H. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation. 2006; 113: 2238-44. PMID: 16651470

43. Schön HR. Hemodynamic and morphologic changes after long-term angiotensin converting enzyme inhibition in patients with chronic valvular regurgitation. J Hypertens Suppl. 1994; 12: S95-104. PMID: 7965280

44. Seeburger J, Borger MA, Doll N, Walther T, Passage J, Falk V, Mohr FW. Comparison of outcomes of minimally invasive mitral valve surgery for posterior, anterior and bileaflet prolapse. Eur J Cardiothorac Surg. 2009; 36: 532-8. PMID: 19464911

45. Seeburger J, Borger MA, Falk V, Kuntze T, Czesla M, Walther T, Doll N, Mohr FW. Minimal invasive mitral valve repair for mitral regurgitation: results of 1339 consecutive patients. Eur J Cardiothorac Surg. 2008; 34: 760-5. PMID: 18586512

46. Tischler MD, Rowan M, LeWinter MM. Effect of enalapril therapy on left ventricular mass and volumes in asymptomatic chronic, severe mitral regurgitation secondary to mitral valve prolapse. Am J Cardiol. 1998; 82: 242-5. PMID: 9678300

47. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, Ferlito M, Tafanelli L, Bursi F, Trojette F, Branzi A, Habib G, Modena MG, Enriquez-Sarano M; 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: 1961-8. PMID: 19909877

48. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ, Frye RL. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation. 1999; 99: 400-5. PMID: 9918527

49. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A; Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007; 28: 230-68. PMID: 17259184

50. Varadarajan P, Joshi N, Appel D, Duvvuri L, Pai RG. Effect of Beta-blocker therapy on survival in patients with severe mitral regurgitation and normal left ventricular ejection fraction. Am J Cardiol. 2008; 102: 611-5.

51. Westaby S. Surgery for heart failure: now something for everyone? Heart Fail Clin. 2007; 3: 139-57. PMID: 17643919

52. Wisenbaugh T, Sinovich V, Dullabh A, Sareli P. Six month pilot study of captopril for mildly symptomatic, severe isolated mitral and isolated aortic regurgitation. J Heart Valve Dis. 1994; 3: 197-204. PMID: 8012639