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STATE-OF-THE-ART PAPER

Chronic Mitral Regurgitation and Aortic Regurgitation

Have Indications for Surgery Changed?

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The timing of surgery in patients with mitral regurgitation (MR) and aortic regurgitation (AR) continues to elicit uncertainty and considerable controversy. Some patients will incur myocardial structural changes, pulmonary hypertension, or arrhythmias before they manifest symptoms, with the risk that these adverse endpoints will not be reversible after valve repair or replacement. Imaging to assess valve morphology, severity of regurgitation, and left ventricular (LV) volume and function is firmly established, and the guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology support this approach. However, with improvement in surgical technique and outcomes, there is momentum toward earlier intervention before patients reach class I indications of symptoms or LV systolic dysfunction, particularly in patients with degenerative MR who are candidates for mitral repair. In expert centers, mitral valve repair is achieved at low risk and with excellent long-term durability of repair, returning patients to a lifespan equivalent to that of the normal population. In AR, decision making is more complex because patients almost invariably require valve replacement. Prospective clinical trials are needed to provide the evidence base for more objective decisions regarding timing of surgery. Biomarkers and new methods to assess interstitial fibrosis and regional myocardial function have also evolved for clinical investigation and hold the promise of enhanced determination of those in whom early surgical intervention is warranted. (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

Major advances in the evaluation and management of patients with valvular heart disease during the past half century have improved the survival and quality of life for patients with mitral and aortic valve disease. Enhanced diagnosis, understanding of natural history, and striking improvements in surgical valve repair and replacement have completely transformed the approach to patients with mitral regurgitation (MR) and aortic regurgitation (AR). The surgical windows have expanded to encompass both older patients with severe comorbidities and younger patients earlier in the natural history of their disease, to include even those who are asymptomatic. Rather than waiting to operate until patients are severely symptomatic and have impaired left ventricular (LV) function, which was the paradigm 50 years ago, current clinical strategies now emphasize earlier intervention in many patients before the onset of symptoms, LV dysfunction, and other adverse endpoints such as pulmonary hypertension and atrial fibrillation. These latter trends are especially pertinent in patients who have MR and AR because the chronic LV volume overload may lead to irreversible LV dysfunction before the onset of symptoms.

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The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) practice guidelines for management of patients with valvular heart disease represent a major step toward improving and standardizing patients' quality of care (1,2). The ESC/EACTS guidelines were revised in 2012, and the ACC/AHA guidelines are currently undergoing revision. However, there are unique hurdles in developing and implementing guidelines in this field. There is a paucity of prospective clinical trials addressing management of valve disease, and the published literature primarily represents the retrospective experiences of single institutions in relatively small numbers of patients. Virtually all of the recommendations in both guidelines are based on expert consensus (level of evidence C). In the ACC/AHA valve guidelines, only 1 of 320 recommendations (0.3%) was based on level of evidence A data (3). It is thus remarkable that the ACC/AHA and ESC/EACTS guidelines are concordant in the majority of their recommendations.

Changes in clinical practice, with new imaging methods, greater surgical experience, and a trend toward earlier surgery in patients with regurgitant lesions, raise the question of whether the indications for surgical intervention have evolved beyond the current guidelines for some patients with valvular regurgitation. The answer clearly de-

Abbreviations and Acronyms

ACC = American College of Cardiology

AHA = American Heart Association

AR = aortic regurgitation

AVR = aortic valve replacement

CABG = coronary artery bypass graft

EACTS = European Association for Cardio-Thoracic Surgery

ESC = European Society of Cardiology

LV = left ventricular

MR = mitral regurgitation

MV = mitral valve

MVP = mitral valve prolapse

STS = Society of Thoracic Surgeons

pends on the experience of the referring cardiologist and the expertise of the surgical team. A "reasonable" Class IIa guideline recommendation has different interpretations and implications in various settings.

Degenerative MR

Class I recommendations for surgery in the ACC/AHA and ESC/EACTS guidelines (1,2) for patients with degenerative MR (predominantly mitral valve prolapse [MVP] from myxomatous disease and fibroelastic deficiency) include patients with symptoms and those with asymptomatic LV systolic dysfunction (Table 1). Because LV shortening may be enhanced in the setting of severe MR by the ability to unload into the low-impedance left atrium, LV dysfunction in severe MR is defined as an ejection fraction ≤60% or an elevated end-systolic dimension. Surgery is also reasonable (class IIa) for patients who have pulmonary hypertension at rest or new-onset atrial fibrillation if they are candidates for mitral valve (MV) repair. Exercise testing is helpful in many situations (4) for determining if a patient is truly asymptomatic and in identifying those who develop pulmonary hypertension with exercise (>60 mm Hg) (1,2).

These indications for MV surgery are reasonable if a patient presents initially to the cardiologist with any of these findings. However, in the longitudinal management of asymptomatic patients with severe MR, would it be preferable for patients to undergo surgery before these endpoints develop, because LV dysfunction, pulmonary hypertension, or atrial fibrillation is not always reversible after surgery? This question frames the debate whether all asymptomatic patients with MVP and chronic severe MR should undergo elective MV repair. This dilemma can only be settled with a prospective randomized trial of elective MV repair versus a strategy of "watchful waiting."

Table 1 Guideline Recommendations for Surgery for Degenerative Mitral Regurgitation

Indication	ACC/AHA	ESC/EACTS
Symptomatic patients	Class I	Class I
Asymptomatic patients		
LV systolic dysfunction*	Class I	Class I
Pulmonary hypertension		
PASP >50 mm Hg at rest	Class IIa	Class IIa
PASP >60 mm Hg with exercise	Class IIa	Class IIb
Atrial fibrillation	Class IIa	Class IIa
Normal LV function, repair feasible	Class IIa	Class IIa†

This is a simplified table. See full guidelines (1,2) for complete recommendations.
*Defined as ejection fraction ≤60% or elevated end-systolic diameter (≥40 mm in ACC/AHA guidelines; >45 mm in ESC/EACTS guidelines). †Specifically for patients with flail leaflet and end-systolic dimension ≥40 mm; there is a separate class IIb recommendation for such patients with left atrial volume index ≥60 ml/m^2.

ACC/AHA = American College of Cardiology/American Heart Association; ESC/EACTS = European Society of Cardiology/European Association for Cardio-Thoracic Surgery; LV = left ventricular; PASP = pulmonary artery systolic pressure.

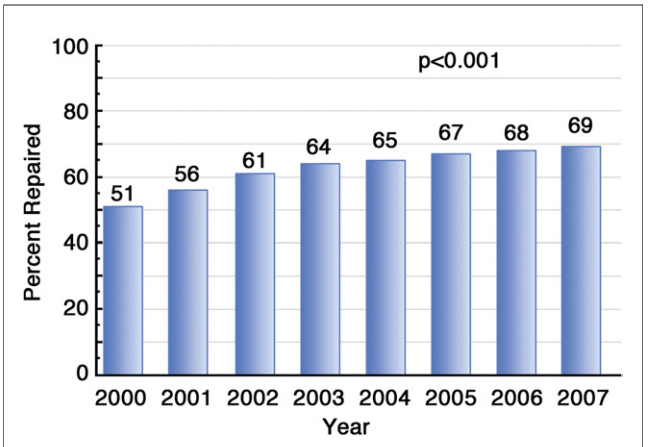

Figure 1 Mitral Valve Repair 2000 to 2007

Percentage of patients in the Society of Thoracic Surgeons Database undergoing mitral valve repair for primary mitral regurgitation from 2000 through 2007. Data include 47,126 patients at 910 hospitals. Patients with mitral stenosis, endocarditis, previous cardiac surgery, shock, emergency surgery, and concomitant coronary artery bypass graft or aortic valve surgery are excluded. Reprinted, with permission, from Gammie et al. (5).

One concern about a broad recommendation for MV surgery in all asymptomatic patients with MVP and severe MR in the United States is that many might be subject to the long-term risks of prosthetic valves when they are excellent candidates for MV repair. According to the database of the Society of Thoracic Surgeons (STS) (5), the frequency of MV repair for patients with MR in North America, after excluding patients with mitral stenosis endocarditis, emergency surgery, previous heart surgery, and concomitant coronary artery bypass graft (CABG) or aortic valve surgery, has increased during the last decade but has plateaued at just less than 70% (Fig. 1). Because the great majority of such operations are for MVP or functional MR, one would anticipate that a higher percentage of patients are candidates for MV repair.

The frequency of repair is just one aspect of the issue; there are no data regarding the actual success rates of MV repair in the United States in terms of elimination of MR. Residual MR at hospital discharge has adverse implications regarding the longevity of the repair and the likelihood that additional surgery may be necessary (6). In addition, despite excellent durability of a successful repair in most patients, there is the risk of recurrent MR over the long term (6–9).

Assuming that a high-volume, high-quality surgical center can provide asymptomatic patients who have MVP and severe MR with successful repair more than 95% of the time

Table 2 Mortality of Asymptomatic Patients With Degenerative MR Without Surgery

First Author (Ref. £)	No. of Patients	Mortality Rate	Mean Age	Mean LVEDD
Enriquez-Sarano et al. (11)	Severe MR 198	8.4%/yr	61 yrs	61 mm
	Moderate MR 129	6.7%/yr	65 yrs	54 mm
Rosenhek et al. (12)	132	0%/yr*	55 yrs	56 mm
Grigioni et al. (13)	394	2.8%/yr	64 yrs	59 mm
Kang et al. (14)	286	0.7%/yr	50 yrs	57 mm

*Two deaths occurred in patients who fulfilled guideline criteria for surgery but refused the operation.

LVEDD = left ventricular end-diastolic dimension; MR = mitral regurgitation.

(10), the question then shifts from feasibility of MV repair to clinical outcomes of a strategy of early MV repair. Because MV repair will not improve symptoms in truly asymptomatic patients, the issue is whether it will improve long-term survival.

There are conflicting data regarding whether patients with asymptomatic severe degenerative MR are at risk of death before they develop the objective class I or IIa indications for surgery. Four studies that observed asymptomatic patients with severe degenerative MR have reported markedly divergent findings regarding the risk of death in those who are not referred for surgery (Table 2), with annual mortality rates ranging from 0% to 8% per year (11–14). It is noteworthy that the study reporting the highest mortality rate (11) was a retrospective analysis of patients enrolled between 1991 and 2000; these patients were managed by their referring physicians and not the study investigators, with many of them enrolled before the same investigators had published their seminal papers describing the predictors of outcome and before publication of the first ACC/AHA guidelines in 1998. In contrast, the study with the lowest mortality rate (12) followed patients prospectively and used guideline recommendations as the only indications for surgery. The 2 deaths related to MR in that study occured in patients who fulfilled the criteria for surgery but refused to undergo the operation. Although it is true that the 2 series reporting the higher mortality rates (11,13) studied patients who were older and had more severe LV dilation (as a marker of severity of MR), these differences in mortality among the 4 studies are not readily rationalized.

However, all 4 studies are consistent, and in keeping with the earlier data of Rosen et al. (15), in demonstrating that the rate at which patients with asymptomatic severe MR develop symptoms or other objective indications for MV surgery is relatively fast, with 30% to 40% of patients achieving an indication for surgery over a 5-year period (Fig. 2). Moreover, Enriquez-Sarano et al. (11) quantified severity of MR according to the current recommendations of the American Society of Echocardiography (16) and showed that in asymptomatic patients with severe MR (defined as an effective regurgitant orifice area >0.4 cm^2), the likelihood of remaining alive and asymptomatic without heart failure or atrial fibrillation was only 36% at 5 years. Thus, independent of whether asymptomatic patients with severe MR are at risk of dying, the majority will develop indications for surgery within only a few years.

Although the risk of death before surgery is debatable, a stronger argument for earlier surgery for severe MR can be made based on the survival results after MV surgery. Survival results after MV repair are significantly related to the presence and severity of preoperative symptoms. Postoperative survival is equivalent to that of age- and sex-matched normal subjects in patients who are categorized as New York Heart Association functional class I or II preoperatively, whereas survival is significantly lower than expected in patients who have developed New York Heart Association functional class III or IV symptoms before surgery (7,17). It follows that if surgery is delayed until patients exhibit significant symptoms, many will have developed LV dysfunction, pulmonary hypertension, and/or atrial fibrillation that may not be reversible and will affect survival adversely after otherwise successful MV repair. Thus, it is not unreasonable to consider elective MV repair as a treatment option, in patients who are candidates for repair, if it can be performed in a center with a high likelihood of success and at low risk.

On the basis of these considerations, the ACC/AHA guidelines (1) conclude that it is reasonable to consider (Class IIa) MV repair in asymptomatic patients with severe MR in whom the likelihood of successful repair without residual MR is >90%, although the ESC/EACTS guidelines (2) recommend repair only in patients with a flail leaflet and an LV end-systolic dimension ≥40 mm (class IIa) or those with left atrial dilation ≥60 ml/m^2 (class IIb). The stronger class I statement in both guidelines is that MV repair is preferrable to MV replacement in patients with MR who require surgery (1,2), and that patients should be referred to surgical centers experienced in MV repair (1). With the understanding that there are no prospective trials

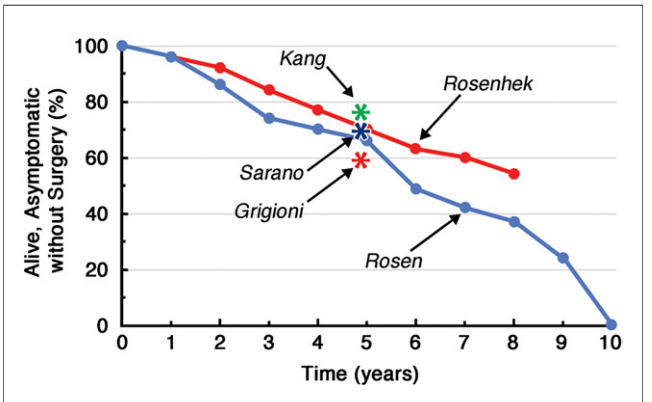

Figure 2 Natural History of Degenerative Mitral Regurgitation

Natural history of asymptomatic patients with degenerative mitral regurgitation and normal left ventricular systolic function. Data from Enriquez-Sarano et al. (11), Rosenhek et al. (12), Grigioni et al. (13), Kang et al. (14), Rosen et al. (15).

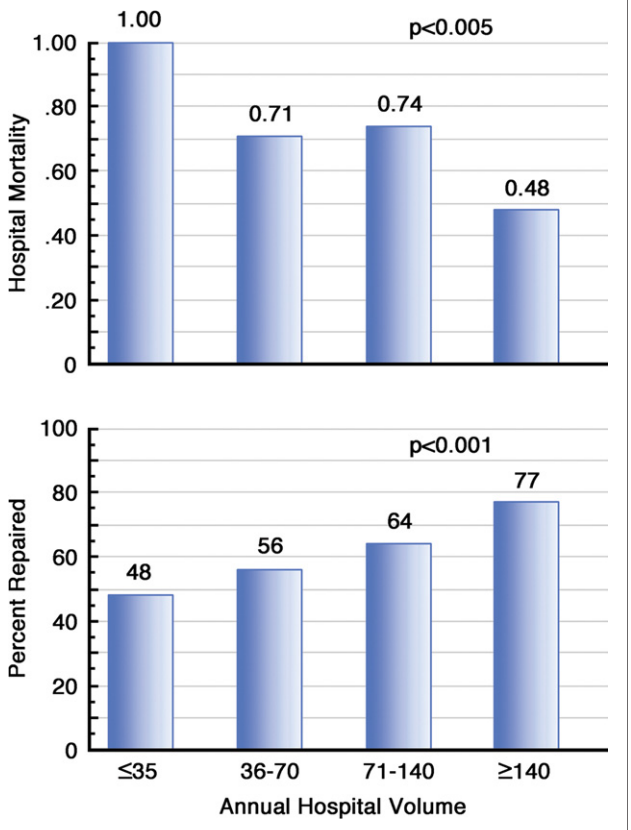

Figure 3 **Hospital Volume of Mitral Valve Surgery and Outcomes**

Data linking volume of mitral valve surgery to in-hospital mortality and the frequency of mitral valve repair. Data include 13,614 patients at 575 hospitals. Hospitals are divided into quartiles of mitral valve surgery volume, with mortality at the lowest-volume centers set at 1.0. Patients with mitral stenosis, previous cardiac surgery, shock, recent myocardial infarction, and concomitant surgery (other than tricuspid valve procedures) are excluded. Reprinted, with permission, from Gammie et al. (21).

comparing MV repair with replacement, the majority of comparative studies indicate a survival advantage with repair (8,18–20).

Although the criteria for an "experienced" surgical center were not defined, there are data supporting the concept that centers of excellence in MV surgery yield better patient outcomes. Findings from the STS Database (21) demonstrate that volume of MR surgery at the hospital level (excluding patients who have mitral stenosis, previous cardiac surgery, shock, or recent myocardial infarction and those undergoing concomitant surgery except procedures on the tricuspid valve) was significantly related to in-hospital mortality after MV surgery, which in turn is related to the likelihood that patients receive MV repair instead of replacement (Fig. 3). Although hospital volume is only a rough surrogate for quality, similar outcomes have been observed in Medicare data (22), with in-hospital mortality rates after MV surgery twice as high in centers in the lowest decile of surgical volume compared with that in centers in the highest volume decile (Fig. 4). These data at the hospital level do not provide insights into outcomes of the individual cardiac surgeon. However, Bolling et al. (23) have tied procedural volume of individual surgeons performing MV surgery to the likelihood of MV repair versus replacement. Among 1,008 surgeons performing 28,507 MV operations from 2007 to 2009 at 639 North American hospitals in the STS Database, those performing a higher volume of MV operations performed a higher percentage of MV repairs. A striking finding in these data was that only 3 surgeons peformed more than 100 MV operations per year and only 16 performed more than 50 per year. The median number of MV operations was only 5 per surgeon per year (range 1 to 166), and the mean rate of MV repair was only 41% (range 0% to 100%). Thus, at both the hospital and the provider level, there is strong evidence of variability in surgical treatment, with the majority of patients undergoing surgery by low-volume operators with a high likelihood of receiving MV replacement instead of repair. Whether there are volume thresholds or variations in care at the level of the individual surgeon that translate into disparate survival outcomes (as has been shown at the hospital level) will require further study.

Bridgewater et al. (24) addressed the concept of centers of excellence for MV surgery; recommended development of multidisciplinary teams of surgeons, cardiologists, anesthesiologists, and nurses; and proposed 19 best practices for MV repair. These criteria focus on surgical training, quality control, and patient volume at the hospital and surgeon level. Whether the volume thesholds they proposed (50 per year for the hospital and 25 per year for the surgeon) are possible in light of the data of Bolling et al. noted earlier (23) is questionable. More important than volume alone, auditing of surgical results was emphasized, with proposed targets of <1% operative mortality and <5% five-year

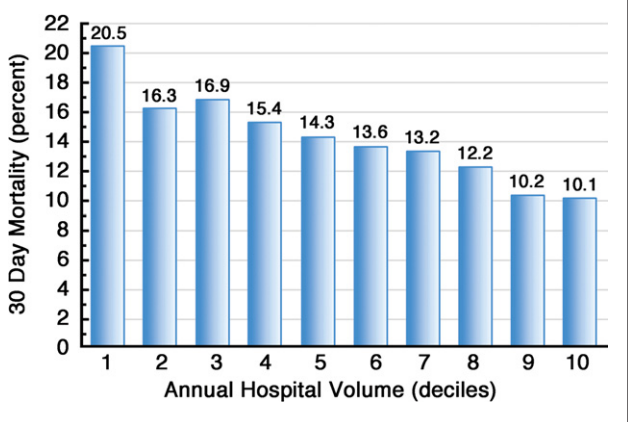

Figure 4 **Hospital Volume and Outcome of Mitral Valve Replacement**

Relationship between hospital volume and in-hospital mortality for mitral valve replacement in patients enrolled in Medicare, including 61,252 mitral valve operations in 684 U.S. hospitals. From Goodney et al. (22).

reoperation rates (24). This underscores the principal that a low-volume center can still be a high-quality center if there is attention to quality. Finally, quality control of cardiology practice, echocardiography, and intraoperative transesophogeal echocardiography was also emphasized.

With or without a mandate for centers of excellence for MV surgery, there is also evidence of variability in physician adherence to accepted recommendations for optimal patient management, including large numbers of patients with symptomatic MR who are not referred for surgery (25–27). At a time when there are strong currents toward earlier surgery in asymptomatic patients with MR, there needs to be renewed emphasis on the clear class I recommendations for surgery in symptomatic patients.

Functional MR

Functional MR stemming from LV dilation and remodeling occurs commonly in patients with ischemic or dilated cardiomyopathy and is the second leading cause of MR in the United States and developed countries of the world (28). Because this is a disease of the myocardium and not the valve itself, uncertainty exists regarding the indications for primary MV surgery.

Current evidence clearly indicates that the presence of functional MR identifies a higher risk group among patients with LV systolic dysfunction and that increasing severity of MR adds incrementally to this risk (29,30). Although mild MR in patients with primary degenerative MR is well tolerated for years, even mild functional MR in a patient with a low ejection fraction has important adverse prognostic implications. What is less clear is whether functional MR is merely a marker of severity of LV dysfunction or whether its attendant volume load contributes to progressive LV dysfunction and is thus a target for therapy.

Therapies that produce beneficial reverse LV remodeling and reduction in LV volume, such as beta-adrenergic blockade or cardiac resynchronization therapy, reduce the severity of functional MR (31–33) and also improve outcomes in terms of survival and quality of life. It does not necessarily follow that interventions primarily targeted to reduce MR will have similar beneficial effects in addition to, or instead of, optimal medical therapy. To the best of my knowledge, there are no prospective studies demonstrating this effect. A retrospective study using propensity analyses failed to show a benefit of surgery compared with medical treatment of functional MR (34), and another study failed to show any benefit of CABG plus MV repair compared with CABG alone in patients with ischemic functional MR (35). Moreover, unlike repair of degenerative MR, in which successful repair has established durability for decades (7,8,36), functional MR commonly recurs after intially successful MV repair because of the progressive nature of the underlying ventricular disease (37). This situation creates the additional uncertainty of whether the more advantageous surgical approach to functional MR is MV replacement instead of MV repair.

Table 3 Guideline Recommendations for Surgery for Functional MR

Indication	ACC/AHA	ESC/EACTS
Severe MR, EF >30%, undergoing CABG		Class I
Moderate MR, undergoing CABG		Class IIa
Severe MR, EF <30%, option for CABG and evidence of viability		Class IIa
Severe MR, EF >30%, no option for CABG, symptoms desipte optimal medical therapy (including CRT), low comorbidity		Class IIb
Severe MR, EF <30%, NYHA FC III-IV symptoms desipte optimal medical therapy (including CRT)	Class IIb	

This is a simplified table. See full guidelines (1,2) for complete recommendations.
CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; EF = ejection fraction; MR = mitral regurgitation; NYHA FC = New York Heart Association functional class; other abbreviations as in Tables 1 and 2.

The National Heart, Lung, and Blood Institute's Cardiothoracic Surgical Trials Network is addressing several of these surgical issues through its 2 ongoing clinical trials of surgical treatment of functional MR (38). However, neither of these trials compares the surgical option versus medical management alone in patients with functional MR.

In the absence of data firmly supporting the role of surgery in functional MR, the ACC/AHA and ESC/EACTS guidelines [1,2] provide few specific recommendations for surgery (Table 3), and there is clear need for further investigation. There may also be a role for transcatheter MV repair in this condition (39), and future prospective trials could conceivably address this approach as well.

Aortic Regurgitation

As is the case in patients with MR, there is continuing uncertainty and considerable controversy regarding the timing of surgical intervention in patients with AR. Like those with MR, patients with AR often remain asymptomatic with normal LV systolic function for many years despite the substantial LV volume overload; however, by the time symptoms develop, a large number may have developed myocardial dysfunction, placing them at high risk for postoperative heart failure and death (40,41). Unlike the trend for early surgery in asymptomatic patients with severe degenerative MR, the majority of whom are candidates for MV repair, a higher threshold for surgery is set for patients with AR as they almost always face aortic valve replacement (AVR). Despite advances in aortic valve repair, especially in young patients with bicuspid aortic valves (42), the experience at a few specialized centers has not yet permeated into the expertise at the general community level, and durability of aortic valve repair remains a major concern.

AVR is clearly warranted in patients who have symptoms (40,41), and virtually every study that has examined the determinants of survival after AVR has also identified

LV ejection fraction and end-systolic dimension (or volume) as significant prognostic variables (1,40,41,43). Hence, the development of symptoms or a subnormal LV ejection fraction is a class I recommendation for AVR (Table 4) (1,2).

A strategy to intervene before symptoms and/or LV systolic dysfunction develop might also be considered, but data supporting pre-emptive surgery in patients with severe AR are less compelling than in patients with severe MR. Unlike the decision for MV repair, the decision for replacing the aortic valve, and then selecting a mechanical prosthesis versus a bioprosthesis, can be an agonizing decision when dealing with an asymptomatic patient. In addition, the time course toward symptom onset or LV systolic dysfunction in asymptomatic AR is more gradual and protracted than in MR, especially in younger patients (1,44–46), with an average event rate of only 4% per year. The 3 largest natural history studies (44–46) provide similar data regarding the rate at which clinical events (death, symptoms, or LV systolic dysfunction) develop in asymptomatic patients (Fig. 5). Because the majority of such events represent the onset of symptoms leading to timely and successful AVR, these endpoints are usually not irretrievable. Hence, a detailed history probing for symptoms remains the most important test in the initial and serial evaluation of patients with AR. However, it is also apparent that death or asymptomatic LV dysfunction represents more than 33% of the clinical events, and thus more objective testing beyond a careful history is required as part of the ongoing evaluation of asymptomatic patients. The series which provide longitudinal data indicate that patients likely to develop symptoms or LV systolic dysfunction can be identified, both at initial evaluation and during serial studies, on the basis of the magnitude of LV dilation and the LV ejection fraction response to exercise (1,44–46). The guidelines make the point that severity of the volume load is an important variable to observe (Table 4) (1,2). These guideline recommendations have not been tested prospectively, but a long-term postoperative study (47) has demonstrated improved survival when patients undergo early AVR after onset of mild symptoms, mild LV dysfunction (ejection fraction 45% to 50%) or end-systolic dimension 50 to 55 mm rather than waiting for more severe symptoms or more severe LV dysfunction to develop (Fig. 6). Whether LV systolic and diastolic dimensions should be indexed to body size is uncertain, as the most appropriate index (such as body surface area or body mass index) has not been determined and there are limited data regarding the thresholds with which to recommend AVR (41). Guidelines notwithstanding, it would be acceptable to recommend AVR in a patient with severe AR when there are steady and progressive increases in LV volume or decreases in ejection fraction on serial studies. Optimal timing of AVR is often more of an art than a science. More objective markers of impending myocardial dysfunction are needed, but these remain elusive.

Table 4 Guideline Recommendations for Surgery in Patients With Aortic Regurgitation

Indication	ACC/AHA	ESC/EACTS
Symptomatic patients	Class I	Class I
Undergoing CABG or surgery on aorta or another valve	Class I	Class I
Asymptomatic patients		
LV systolic dysfunction (EF ≤50%)	Class I	Class I
Severe LV dilation (LVEDD >75 mm or ESD >55 mm)	Class IIa	—
Progressive LV dilation (LVEDD >70 mm or ESD >50 mm)	Class IIb	Class IIa

This is a simplified table. See full guidelines (1,2) for complete recommendations. ESD = end-systolic dimension; other abbreviations as in Tables 1, 2, and 3.

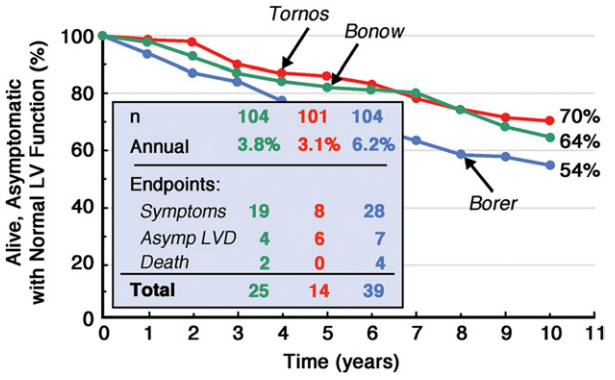

Figure 5 Natural History of Asymptomatic Aortic Regurgitation

Natural history of asymptomatic patients with aortic regurgitation and normal left ventricular systolic function. Data from Bonow et al. (44), Tornos et al. (45), and Borer et al. (46). Asymp LVD = asymptomatic left ventricular dysfunction (ejection fraction <50%); LV = left ventricular.

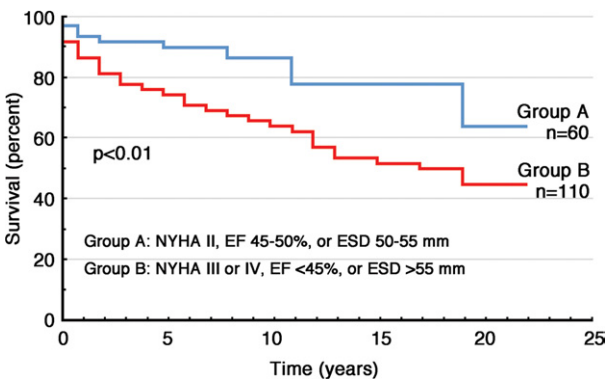

Figure 6 Survival After Aortic Valve Replacement for Aortic Regurgitation

Long-term survival after valve replacement for aortic regurgitation demonstrating improved outcome with early surgery. Reprinted, with permission, from Tornos et al. (47). EF = ejection fraction; ESD = end-systolic dimension; NYHA = New York Heart Association.

Moreover, basing decisions for surgical intervention on LV ejection fraction and internal dimensions alone may not be sufficient in all patients. In addition to the inherent variability of these measurements, ejection fraction notoriously fluctuates depending on blood pressure and other loading conditions, and LV short-axis diameters fail to adequately reflect the great individual variation in the 3-dimensional geometries of volume-loaded left ventricles. There is a paucity of new emerging evidence to guide management decisions and change the current recommendations for AVR. The guideline recommendations are grounded on the methods that were available more than 2 decades ago when the long-term natural history and postoperative outcome studies providing the bulk of the existing evidence base were performed. Rather than relying on 1-dimensional LV diameters, there is a great need for rigorous prospective assessments of LV geometry, volume, and regional and global systolic performance that are now possible with our current advanced imaging capabilities (48). Only recently have standardized criteria for LV volume measurements by using echocardiography been established (49), and these have not been subjected to extensive long-term studies in sufficiently large numbers of patients.

In the single paper thus far investigating LV volume measurements as a predictor of outcome in asymptomatic patients with AR and normal LV ejection fraction, Detaint et al. (50) demonstrated that volumetric measures are superior to LV linear diameters in identifying patients who are at risk of death, atrial fibrillation, or heart failure. This study also showed that quantitative measures of regurgitant volume and regurgitant fraction are more powerful than the current guideline indicators. These findings illustrate the potential for more advanced measures to provide better discrimination than the standard measures currently in routine use.

It is notable that the patients studied by Detaint et al. (50) also had a much higher rate of events than reported in the previous natural history studies referenced in the guidelines (1), including a 10-fold higher risk of death (2.2% per year) compared with the average mortality rate in the previous studies (0.2% per year). The higher rate of fatal and nonfatal events reported by Detaint et al. (50) may be explained by important age differences: 60 years in patients in that report compared with an average of 39 years in the natural history series cited in the guidelines (1). Older patients with asymptomatic AR may have a higher clinical event rate than younger patients because of concomitant coronary artery disease. Alternatively, a significant volume load may be less well tolerated in older individuals who have reduced vascular compliance and increased myocardial stiffness. This underscores the need for additional novel measures of cardiovascular structure and performance beyond the current standards of LV dimensions, volumes, and ejection fraction.

Newer methods to assess systolic and diastolic myocardial function by using tissue Doppler imaging and speckle tracking are now available, and cardiac magnetic resonance has the potential to identify and quantify interstitial fibrosis developing as part of the chronic hypertrophic process. Such findings may hold a key for earlier intervention. Although these have been evaluated more extensively in patients with aortic stenosis (51–53), work is forthcoming in those with AR (54,55). There is also the need to identify serum biomarkers that herald impending myocardial dysfunction. These will require careful prospective investigation to determine their potential role in clinical decision making regarding the indications for AVR (56). The prediction of surrogate measures, such as changes in LV volume and function after surgery, is no longer adequate. To move the needle toward earlier surgical indications will require demonstration that new measures predict improved survival. The poor outcome of patients with severe preoperative LV dysfunction and persistent dysfunction after AVR reported in previous decades may no longer be pertinent in the current era of better surgical techniques, aggressive medical therapy for heart failure, and availability of biventricular pacemakers and implantable cardioverter defibrillators (57).

Conclusions

In patients with valvular regurgitation, the goal is to operate late enough in the natural history of the disease to justify the risks of intervention but early enough to prevent irreversible LV dysfunction, pulmonary hypertension, and/or chronic arrhythmias. The balance between natural history versus the short- and long-term risks of surgery clearly favors intervention in symptomatic patients and those with LV dysfunction. As the balance shifts toward earlier intervention in asymptomatic patients, it is essential that patients be referred to surgical centers with established excellence in MV repair and AVR. It is equally important that patients be evaluated by cardiologists who have sufficient expertise and clinical judgment in determining the optimal time for making the referral for surgery. The management of patients with valvular heart disease has been hampered by the lack of definitive prospective clinical trials. Clinical trials to determine whether surgery or conservative management is the most appropriate strategy for patients with severe asymptomatic MR or AR, and to determine the most effective methods for risk stratification, are needed to guide the future management of these prevalent conditions.

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