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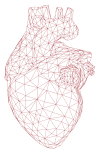
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Management of Asymptomatic Severe Degenerative Mitral Regurgitation

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ABSTRACT

The decision for surgery in the management of asymptomatic severe degenerative mitral regurgitation (MR) is about doing the right thing at the right time and place. European and American guidelines have provided us with guidance on surgical indications, albeit with different levels of recommendations. However, the timing for surgery especially in asymptomatic patients not meeting Class I indications for intervention, i.e. no evidence of left ventricular dysfunction is still avidly debated. In this review, we will present the literature on the indications and timing of surgical intervention in asymptomatic severe MR, covering guidelines from both societies. We will also touch on the emerging role of other imaging techniques, biomarkers and exercise stress testing. Finally, we will present arguments for and against both management strategies, i.e. early surgery and watchful waiting. To summarize, the management of patients with asymptomatic severe degenerative MR should be a joint decision between all members of the Heart Team and tailored according to the availability of surgical expertise, patient's surgical risk and patient's wishes.

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KEYWORDS Degenerative mitral regurgitation; guidelines; management; outcome; risk factors

Introduction

Degenerative mitral valve (MV) disease is the most common cause of mitral regurgitation (MR) in the developed world.¹ Often, patients with degenerative MR are asymptomatic, even if the regurgitation is severe. Studies on the natural history of severe MR have shown that even in patients without symptom, some may develop downstream hemodynamic consequences over time.^{2–4} These consequences often portend poor prognosis and surgery is indicated when they emerge. Thus, the key to the management of severe MR in asymptomatic patients is to identify these adverse hemodynamic consequences early with the hope that timely surgical intervention may reverse them before they become irreversible. With the improvement of surgical outcomes, surgery has cemented its status in the management of severe MR to be superior to medical therapy when a patient becomes symptomatic or develops downstream complications of severe MR. In this regard, there is little question about whether to carry out surgery or not when surgical expertise is available and the patient is a candidate for surgery. In recent years, the debate on the management of severe MR has been evolving around asymptomatic patients who have yet to meet Class I surgical criteria for MV surgery: should we advocate prophylactic surgery before complications of MR set in, i.e. early surgery?; or should we wait and watch the patient closely, seeking surgical attention at the very onset of

complication, i.e. watchful waiting? The 2017 ACC/AHA guidelines for the management of valvular heart disease provide a Class IIa recommendation for surgery in asymptomatic patients with chronic severe primary MR and preserved left ventricular (LV) function if the expected operative mortality rate is <1% and the probability of a successful and durable repair is >95%.⁵ This however, did not end the early surgery versus watchful waiting debate. In fact, the debate is still going strong and far from over, as we will reveal subsequently.

The present review will (1) cover the indications for surgery and evidence behind the guidelines; (2) touch on emerging imaging techniques and biomarkers that contribute to the risk stratification of MR; (3) discuss the debate on early surgery versus watchful waiting strategy.

Discussion

Triggers for surgery in asymptomatic patients

In asymptomatic patients, surgery should be considered if there is evidence of adverse downstream consequences of severe MR. There is, however, a lack of randomized controlled trials in the literature; thus, the highest evidence available is of Level B. The triggers for surgery include impaired LV function, increased systolic pulmonary artery pressure (sPAP), or development of atrial fibrillation (AF) (Table 1).

Table 1. Indications for surgery in severe primary MR.

	2012 ESC/ EACTA	2017 ACC/AHA
Symptom and LVEF >30%	I	I
Asymptomatic and LVEF 30–60%	I	I
Asymptomatic and LVESD ≥40 mm	–	I
Asymptomatic and LVESD ≥45 mm	I	
Asymptomatic with flail leaflet and LVESD ≥40 mm, with low surgical risk and high likelihood of repair	Ila	Ila
Asymptomatic and new onset AF or sPAP ≥50 mmHg	Ila	Ila
MV repair reasonable in asymptomatic patients with LVESD <40 mm and LVEF ≥60% when likelihood of successful and durable repair without residual MR is > 95% with an expected mortality rate <1% when performed at Heart Valve Center of Excellence	–	Ila
Asymptomatic with left atrial dilatation (≥60 ml/m ²) or exercise sPAP ≥60 mmHg when there is a low surgical risk and high likelihood of repair	Ilb	

Note. LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; AF, atrial fibrillation; sPAP, systolic pulmonary artery pressure.

LV function and size

LV ejection fraction

The LV dimensions and ejection fraction reflect the heart's ability to adapt to increased volume load. In the chronic compensated phase (the patient could be asymptomatic), the forward stroke volume is maintained through an increase in LV ejection fraction (EF) explained by the Frank–Starling mechanism. In the chronic decompensated phase (the patient could still be asymptomatic or may fail to recognize deterioration in clinical status), the forward stroke volume decreases and the left atrial (LA) pressure increases significantly (Figure 1). The LV contractility can thus decrease silently and irreversibly. However, the LVEF may still be in the low normal range despite the presence of significant muscle dysfunction. Not uncommonly the LVEF decreases after surgery. This is intuitive and at the same time, substantiated by evidence. Patients with a preoperative LVEF >60% have been shown to have better long-term post-operative survival compared to the EF 50–60% and EF <50% groups.⁶ This finding is in concordance with the Mitral Regurgitation International Database (MIDA) registry, which showed that LVEF ≤60% was associated with higher all-cause mortality.⁷ Of note, the lack of contractile reserve during exercise echocardiography (< 4% increase in EF) also predicts decrease in LVEF and symptoms at follow-up in medically managed patients; it also predicts post-operative LV systolic dysfunction in surgically treated patients.^{8,9} In the current guidelines, surgery is recommended (class I) in asymptomatic patients with severe degenerative MR when the LV ejection is ≤60%. No recommendation is specifically made in case of no contractile reserve.

LV end-systolic diameter

The end-systolic diameter (ESD) is determined by LV contractility, afterload and the degree of eccentric LV remodeling, but not by preload. It could, in some cases, be more appropriate to monitor global LV function. An ESD ≥ 45 mm (ESC/EACTA) or >40 mm or > 22 mm/m² (AHA/ACC) also indicates (class I) the need for mitral valve surgery in asymptomatic patients with severe degenerative MR. Both cut-offs predict post-operative LV dysfunction, though the 40 mm threshold has been only highlighted in patients with flail MV in the MIDA registry.^{10,11}

The most important caveat of LVESD is that it is a unidimensional measurement of LV size. When LV remodels as a consequence of severe MR, it often assumes a spherical shape, with enlargement of mid to apical cavity. This would have been missed if LVESD were used as the sole representation of LV dimension. LV end-systolic volume obtained either from 3D echocardiography or cardiac magnetic resonance imaging (MRI) can better estimate the extent of LV remodeling.^{12,13}

LV ejection index

The LV ejection index is an indexed product of LVESD/LV outflow tract velocity time integral. It reflects changes in LV cavity as a result of remodeling and LV systolic function. In severe MR, the LVESD increases as a result of volume overload, while the LV outflow tract velocity time integral decreases, following the decrease in LV contractility. Together, these changes give rise to a markedly increased LV ejection index. A LV ejection index >1.13 is associated with post-operative LV dysfunction and mortality, even in patients with a pre-operative LVEF >60%.¹⁴ Although not included in the guidelines as part of the surgical criteria, it is nevertheless a handy parameter that takes into account both the size and function of the LV.

Pulmonary hypertension

The excess regurgitant blood entering in the LA may induce acutely or in a chronic way a progressive rise in pulmonary pressure. Pulmonary hypertension (PHT) is usually defined in the literature as a resting sPAP >50 mmHg or an exercise sPAP >60 mmHg. The prevalence of resting PHT in asymptomatic patients with at least moderate MR ranges from 15 to 30%,^{15,16} while that of exercise PHT approximates 48%.¹⁵ In the MIDA Registry, which included patients with flail MR, PHT was shown to independently predict overall survival, post-operative survival and heart failure.¹⁷ This echoes resemblance to another study on severe organic MR, which also showed poorer post-operative survival compared to patients with sPAP >50 mmHg.¹⁸ The caveat in both these studies was that a considerable proportion of patients, 35–36%, were in NYHA III–IV, which raises the question of whether the data applies to asymptomatic patients in our context. The presence of exercise PHT predicts symptom onset and helps to identify patients that require close follow-ups. In terms of hard clinical endpoints, exercise PHT was associated with lower symptom-free survival and more post-operative adverse cardiac events, such as AF, stroke, cardiac-related hospitalization and death.^{15,19} The survival is worse when both exercise PHT and right ventricular dysfunction (tricuspid annular plane systolic excursion <19 mm) coexist.¹⁶ In the ESC/EACTA guidelines, exercise-induced PHT can also be considered as a trigger for intervention if the patient is of low risk and there is high probability of durable repair, albeit with a low recommendation class (Iib). Exercise PHT is, however, not covered in the ACC/AHA guidelines.

Atrial fibrillation

AF is common in patients with degenerative MR. One study on MR due to flail leaflets reported an AF incidence of approximately 5% per year, amounting to 18% at 5-year and

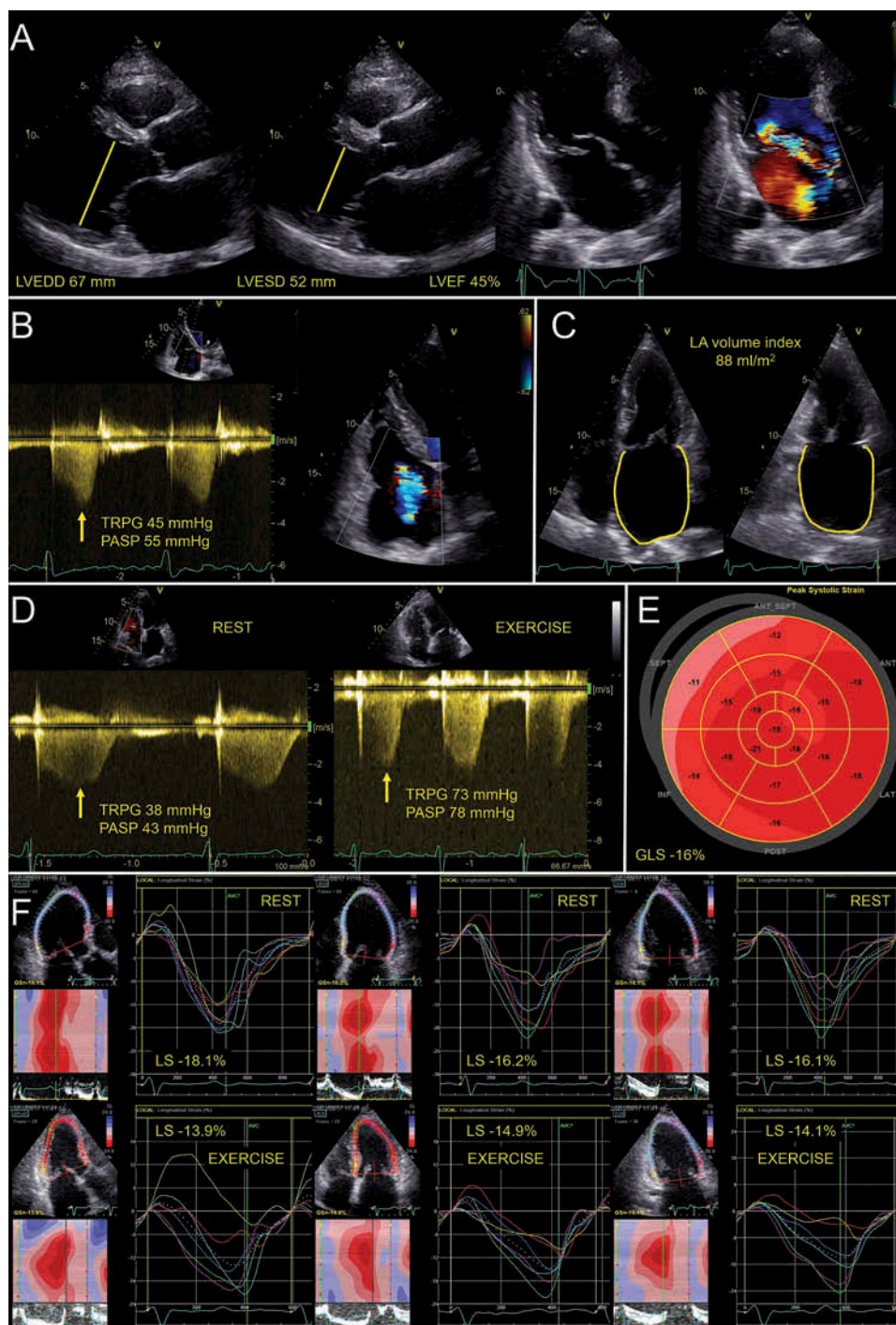


Figure 1. Examples of echocardiographic prognostic parameters in severe primary MR. (A) LVEF <60% or LV end systolic diameter ≥ 45 mm (2012 ESC/EACTA)/ ≥ 40 mm (2014 ACC/AHA), Class I. (B) Pulmonary artery systolic pressure ≥ 50 mmHg at rest, Class IIa. (C) Left atrial volume index ≥ 60 ml/m², Class IIb. (D) Exercise pulmonary artery systolic pressure ≥ 60 mmHg, Class IIb. (E) Impaired LV global longitudinal strain (LS) at rest (<-20%). (F) Impaired LV contractile reserve at exercise (<-2% increase in longitudinal strain, LS).

48% at 10-year follow up. AF is associated with a higher rate of cardiac death and heart failure when patients are managed conservatively.²⁰ In patients who did receive surgical intervention, 42% of the patients had already developed AF at the time of surgery. The presence of AF before surgery is associated with long-term mortality and post-operative LV dysfunction.^{21,22} As such, patients with new onset of AF are particularly well-suited for surgery as there is a chance that sinus rhythm may be restored following surgery, before AF

begets more AF and the LA dilates permanently. The presence of AF represents a class IIa indication for mitral valve surgery.

LA enlargement

The LA dilates in response to chronic volume and pressure overload. An excessive increase in the LA size to an indexed LA volume ≥ 60 ml/m² is associated with increased mortality and cardiac events in patients with primary MR.¹⁸ The

predictors of LA enlargement are in turn, higher mitral regurgitant volume, AF, older age, female gender, higher LV end-systolic volume and mass.²³ LA enlargement carries a class IIb recommendation for surgery in the ESC/EACTA guidelines if the surgery is low risk and there is high probability of durable repair. It is however, not covered in the ACC/AHA guidelines.

Emerging biomarkers and imaging techniques in the risk stratification of MR (Table 2)

Brain natriuretic peptide

Increase in serum brain natriuretic peptide (BNP) level is associated with poor outcomes in patients with primary MR. In an earlier series of patients with various degrees of MR and some being symptomatic, a BNP value ≥ 31 pg/mL was associated with death and heart failure.²⁴ In asymptomatic patients with severe MR, a higher BNP cutoff value (≥ 105 pg/mL) has been shown to identify patients with higher risk of heart failure, LV dysfunction and death.²⁵ Our group has also shown that in asymptomatic degenerative MR patients, BNP release correlates with increased LA volume and decreased LV longitudinal function.²⁶ BNP also has added prognostic value in the face of a normal exercise LV systolic function. A rise in BNP predicts the development of exercise PHT and LA enlargement even when the exercise LVEF is normal.²⁷ It has also been suggested that BNP reflects primarily the hemodynamic consequences of MR such as an increase in LV end-systolic volume index rather than symptoms.²⁴

Detection of fibrosis using MRI

One of the strongest suits of cardiac MRI at stratifying MR patients lays on its ability to detect myocardial fibrosis. Cardiac MRI enables detection of discrete fibrosis using late gadolinium enhancement sequences and diffuse fibrosis using novel techniques such as T1 mapping and extracellular volume calculation. The presence of fibrosis, whether in the form of late gadolinium enhancement or extracellular volume expansion in primary MR, has been shown to predict adverse

LV remodeling and reduced LVEF. Studies have shown that patients with late gadolinium enhancement on cardiac MRI have higher LVESD.^{28,29} In addition, patients with higher extracellular volume have reduced exercise capacity, higher LVESD and lower LVEF.³⁰ On a different note, the presence of fibrosis in patients with MV prolapse and mild MR correlates with ventricular arrhythmias and sudden cardiac death.³¹

Myocardial deformation and subclinical LV dysfunction

Myocardial deformation measured using 2D strain imaging is useful at detecting subclinical LV dysfunction. In particular, measurement of global longitudinal strain by speckle-tracking technique has been shown to predict post-surgery LV function and mortality. A global longitudinal strain below -18% to -20.5% is associated with LV systolic dysfunction after surgery,^{9,32-34} while a global longitudinal strain below -20% predicts poorer event-free survival.³⁵ Moreover, the absence of contractile reserve, weaker changes in global longitudinal strain ($< -2\%$) revealed by exercise stress echocardiography, also identifies patients with subclinical LV dysfunction at higher risk of events and of post-operative decrease in LVEF.³⁶

Early surgery versus watchful waiting in severe asymptomatic PMR

One of the most revolutionary changes in the recent ACC/AHA guidelines ought to be the new IIa recommendation for MV repair in severe asymptomatic patients who have no evidence of LV dysfunction, as long as curative surgery is likely, i.e. likelihood of a successful and durable repair without residual MR $>95\%$ with an expected mortality rate $<1\%$, performed at a Heart Valve Center of Excellence. Some wonder if this is the conclusion to the early intervention versus watchful waiting debate. For the proponents of watchful waiting, the answer is a resounding no. In fact, the debate is still far from over. Judging from the numbers of qualifiers that needs to be fulfilled, it is no mean feat and might only be applicable to a handful of bona fide "Centers of Excellence." Nevertheless, the recommendation is appropriate and timely, in view of the mounting evidence of excellent outcomes in dedicated MV centers. It represents an ideal that some centers have achieved and the rest should all strive towards.

Early surgery strategy

Early or prophylactic surgery refers to MV surgery before the onset of symptoms and the LV function is still preserved (EF $>60\%$ or LVESD <40 mm). The proponents of early surgery argue that surgery performed after LV dysfunction, AF or PHT develop should be considered rescue surgery and like all rescue operations, however noble the intention, not all can be saved in time. One of the studies that is invariably mentioned to justify early surgery is the landmark paper by the Mayo Clinic group, which showed that medically-managed asymptomatic patients with severe MR, as defined by an effective regurgitant orifice area (EROA) ≥ 40 mm² had poor long-term survival.³⁷ The proponents of early surgery use this to support intervention before it is too late, while the supporters of watchful waiting would beg to differ. In this elegant, albeit historical study, the authors further divided the 198

Table 2. Prognostic parameters in severe primary MR.

	With guideline recommendations	Without guideline recommendations
Symptom/Exercise capacity	> NYHA class II	Maximal oxygen consumption Predicted METs Heart rate recovery
Left ventricular structure/function	LV ejection fraction LV end-systolic diameter	LV deformation (GLS) LV contractile reserve (ejection fraction /GLS) LV ejection index
Left atrial structure/function	New onset AF Left atrial dilatation	Emptying fraction Reservoir function Pump function
Pulmonary circulation/Right ventricular function/size	Pulmonary hypertension at rest/exercise	Tricuspid annular plane systolic excursion Right ventricular strain Right ventricular dilatation
Biomarker		Serum brain natriuretic peptide

Note. LV, left ventricular; AF, atrial fibrillation; METs, metabolic equivalents; GLS, global longitudinal strain.



patients with severe MR into three strata according to EROA: $<20 \text{ mm}^2$, $20\text{--}39 \text{ mm}^2$ and $\geq 40 \text{ mm}^2$. The proponents of watchful waiting will be quick to point out that no doubt the group with EROA $\geq 40 \text{ mm}^2$ had poor outcome, but so did the ERO $20\text{--}39 \text{ mm}^2$ group, which had 34% mortality at 5-year follow-up (versus 42% for ERO $\geq 40\%$). The lesson from the study, in the words of the watchful waiters, is not to offer surgery to all patients with poor outcome, but rather, to find out why these patients had such poor outcome. Some of them already had AF, PHT, and LVEF $< 60\%$ at baseline. They would have been offered surgery by today's standard. Instead, they were treated medically. Also, these patients did not have dedicated regular follow-ups.

A more recent study supporting early surgery comes from the MIDA registry, which showed that early surgery confers superior long-term survival compared to medical management in a propensity-matched cohort of patients.³⁸ In this study, limited to patients with flail MV, early surgery was defined by operation within 3 months of diagnosis and it was compared against an initial strategy of medical therapy. This study is not without some caveats. It was a retrospective registry and the reasons for or against surgery were unknown. In addition, patients from the early surgery group were younger and more often had PHT or other class II indications for surgery. In the medical management arm, 19% of the patients had class II indication for surgery (AF 10% and PHT 12%) but did not receive surgery. In other words, the early surgery group is not exactly the asymptomatic patients with no surgical triggers that we have been deliberating on. The same goes for the medical therapy group, which is a strategy of only masterly inactivity and not watchful waiting, which calls for surgical attention once surgical triggers are met. One also needs to be cognizant that this is a registry that spans decades and includes patients since the year 1980. The diagnosis of MR then was very different from what it is today. Doppler echocardiography for example, was not widely available until the end of the 1980s. It is therefore tricky to draw parallels between this study and the current debate of early surgery versus watchful waiting.

Another study that is invariably cited to support early surgery strategy is the series from south Korea, which showed excellent outcome in the early surgery group compared to conventional medical therapy.³⁹ This study, however, raised a few eyebrows among the opponents of early surgery. Firstly, there was no surgical mortality whatsoever. Also, all patients who were lost to follow-up were exclusively from the surgical group and it is well-known that patients lost to follow-up are usually associated with poor outcomes. The same group subsequently expanded the study cohort and published another study, also looking at early surgery versus conventional treatment in asymptomatic severe MR. This time, there was no difference in overall mortality. There was, however, a higher rate of AF and fatal stroke associated with early surgery. Again, there was no operative mortality in the surgical group, a triumph in the eyes of naysayers, rather improbable. In the subgroup analysis using an age cutoff of 50 years, the reduction in cardiac events was only demonstrated in the subgroup < 50 years and not in those > 50 years. The authors, therefore, concluded that watchful waiting is preferred in

patients below 50 years and surgery should be considered in selected patients above 50 years.⁴⁰

Watchful waiting strategy: what is in a name

Watchful waiting is in fact a proactive approach. It involves a structured surveillance system and readiness to intervene with surgery when triggers emerge. The Heart Valve Clinic (HVC) epitomizes this concept well. In the HVC, patients are being followed-up regularly with timely electrocardiogram and echocardiogram. They are also encouraged to report symptoms, if any. Once symptom develops or other surgical criteria are met, prompt attention, ideally in the form of a multidisciplinary Heart Team is sought.⁴¹ An important argument that supporters of early surgery often bring up is that early surgery could benefit patients that default follow-up and consequently surgical triggers were missed. It is true that prophylactic surgery may have a role in parts of the world where healthcare is not easily accessible and the attrition during follow-up is high. However, when healthcare accessibility is not an issue, the problem of lost to follow-up could be more aptly addressed by having a dedicated clinician/nurse checking on patients and reminding them to return for appointments at the HVC.

Watchful waiting strategy: critical considerations

There are a few additional considerations that one needs to bear in mind when it comes to the execution of the watchful waiting strategy (Table 3). First and foremost, one needs to have no doubt about the severity of MR. Second, the functional status of the patient, ideally obtained from stress testing should be used to follow-up the patient longitudinally. Third, one needs to recognize the degree to which other triggers are inevitable and predictable. Finally, one ought to carefully weigh the risk of surgery against the consequences of waiting and individualize the decision according to the patient's surgical risk and the availability of surgical expertise.

Confirming the severity of MR. Having this diagnostic certainty is especially important when severe MR is the only indication for surgery and other surgical triggers are not met. In the wise words of Hippocrates, we should first do no harm. The worst thing that could happen is sending a patient who otherwise doesn't need a surgery for one. However, the humbling fact is that MR severity assessment is complex. In practice, an integrated approach should be used

Table 3. Watchful waiting check list.

→ Symptoms and functional capacity	→ Detailed anamnesis, Exercise stress test
→ Severity of MR	→ Imaging: TTE, TOE, MRI
→ Hemodynamic effects of MR	→ LVEF, ESD, AF, LA dilatation, pulmonary hypertension, GLS, BNP, etc.
→ Feasibility of MV repair	→ Valve morphology, Surgeon's skill
→ Operative risk	→ EuroSCORE II, Society of Thoracic Surgeons score

Note. MV, mitral valve; TTE, transthoracic echocardiography; TOE, transesophageal echocardiography; MRI, magnetic resonance imaging; LVEF, left ventricular ejection fraction; ESD, end systolic diameter; AF, atrial fibrillation; LA, left atrium; GLS, Global longitudinal strain; BNP, brain natriuretic peptide.



and quantitative assessment should be performed.⁴² Meticulous attention should be given to the potential pitfalls of each method of MR assessment. For example, in the context of severe degenerative MR with MV prolapse, the regurgitant jet may only be tele- or meso-systolic. As such, the EROA method may overestimate the severity of MR. Also, when the echocardiographic window is limited or the integrated approach yields conflicting information, cardiac MRI could be considered as a complementary tool.⁴³ However, even in the hands of experienced readers, there could still be substantial variations in MR severity grading. A recent study comparing echocardiography and cardiac MRI assessment of MR has shown that by echocardiographic criteria, 56% of the patients had severe MR, while by MRI flow assessment, the number of severe MR goes down to only 15%.⁴⁴ MRI was also shown to track ventricular response post-mitral surgery better than echocardiography. Although it is hard to determine which is the gold standard, this paper highlights the fact that MR quantification is an evolving field in the current era of multimodality imaging.

Functional and symptomatic status. Surgery is indicated once a patient becomes symptomatic.⁴⁵ Then, identifying patients who are truly asymptomatic is fundamental. Exercise stress testing is an objective way of confirming the absence of symptoms and to define one's true functional capacity, compared against age-gender predicted standards. Not infrequently, patients adapt their daily activities in order to avoid symptoms. Studies have shown that up to 20% of asymptomatic MR patients have reduced functional capacity as represented by markedly reduced peak oxygen consumption.^{23,46} Those patients are at higher risk of cardiovascular events, while delaying MV surgery by ≥ 1 year in those with preserved exercise capacity did not adversely affect outcomes.⁴⁷ For those patients who achieved an age-gender predicted METs of $\geq 85\%$, whether they underwent surgery or were treated medically was inconsequential as there was no difference between the two groups in terms of long-term death, myocardial infarction, stroke, and heart failure.⁴⁸

Are surgical triggers inevitable? In the study by Rosenhek and colleagues which followed asymptomatic severe MR patients, 45% of patients developed surgical triggers, namely LV dysfunction, LV dilatation, PHT or AF at 8-year. Proponents of surgery may use this to argue that surgical triggers are inevitable and to justify surgery before the onset of triggers. The supporters of watchful waiting will, however, focus on the other half, which is the 55% who are free of any triggers at 8-year follow-up.⁴⁹ The same analogy applies to the MIDA study, which looked at long-term outcome of MR due to flail leaflets on medical therapy. Heart failure developed in 50% and AF developed in 30% of the patients.⁵⁰ Depending on which camp one is from, one could either take the numbers at face value and arrive at the conclusion that complications are inevitable, hence arguing for early surgery, or look at the other half, which is the 50% who did not have heart failure and 70% who did not have AF, arguing against the fatalistic viewpoint.

There a risk of sudden cardiac death if we defer surgery? In the MIDA registry, the annual sudden cardiac death risk in no or minimally symptomatic patients and EF $>60\%$ was $<1\%$,⁵⁰ a figure comparable to that of the normal population. This is in line with another study, which showed that the risk of sudden cardiac death in patients who did not reach surgical triggers was $<0.5\%$ per year.⁴⁰ Adding to the watchful waiting argument is again the study by Rosenhek and colleagues, which showed that watchful waiting conveyed no surgical disadvantage and surgical outcomes in carefully followed-up watchful waiters were excellent.⁴⁹ In addition, there is no data that suggest a difference in surgical or post-op outcomes in terms of repair rates, LVEF and mortality between patients who undergo early surgery and those who receive surgery only when surgical criteria are met.

Are there potential risks associated mitral valve surgery?

Death, stroke and other morbidities. Surgery, as we know it, is not without risks. In high-volume valve centers, the guideline target mortality $<1\%$ may be achievable. However, registry data from the Society of Thoracic Surgeons, which reflects the collective experience from a variety of centers showed higher 30-day mortality rates, 1.2% for MV repair and 3.8% if the MV is replaced. The incidence of ischemic or fatal stroke after surgery for MR approximates 2%, which is not negligible considering it is an elective surgery.⁵¹ For some patients, the idea of a debilitating stroke may be tantamount to, or sometimes, worse than sudden cardiac death. In terms of overall major peri-operative events, which include operative mortality, renal failure, prolonged ventilation, stroke and reoperation, the number amounts to 10% even in the high-volume centers.⁵² A recent New York State-wide multicenter study has shown that individual surgeons' mitral valve case volume has a significant impact on early- and long-term patients' outcomes after mitral valve surgery.⁵³

Failure in mitral valve repair. Surgeons capable of successful and durable MV repair are not universally available.^{53,54} On average, a surgeon needs to perform at least 100 isolated mitral cases per year in order to have a repair rate of 83%. A total annual surgeon volume of <25 operations has been reported to be associated not only with lower mitral valve repair rates, but also with increased 1-year mortality and mitral valve reoperation rates.⁵³ The inconvenient truth is that the median number of MV surgeries is five per surgeon per year in the United States, which is associated with a repair rate of 55%.⁵⁵ In the Society of Thoracic Surgeons registry, although the repair rate has improved steadily over the years, the replacement rate for isolated primary MR is still over 30%⁵⁶ and we are well aware that prosthesis at the mitral position is associated with suboptimal outcomes. Also, there is a risk of anticoagulation or infection at 1–2% per year. Looking beyond the US, a study from the other side of the ocean strikes a similar chord. The United Kingdom Adult Cardiac Surgical Database Report sums it up well by comparing the variability of MV repair rates in different hospitals to that of the lottery system, in view of the wide range of repair rates, from 20 to 90%.⁵⁷ Last but not least, repair may not be a permanent solution even in the best of hands. Take the

surgical arm of EVEREST II trial for example. There is still a possibility of 4+ MR at 2-year at surgical sites with high-volume, skilled MV surgeons.⁵⁸ In other studies, the risk of recurrent MR was 2–3% per year,^{59,60} while the risk of re-do operation was 1% per year even after a successful surgery.²¹

Take-home message

To recapitulate, early surgery and watchful waiting are both viable options, substantiated by a plethora of evidence. The key is to really carry out the spirit of what each strategy embodies. As we have seen earlier, the majority of criticisms on either strategy arise when there is deviation from this principle. For instance, studies advocating early surgery in asymptomatic patients might have inadvertently included patients who are not truly asymptomatic due to a multitude of reasons, one being the historical nature of these studies and differences in the standard of care at the time of the study. Another example of problems arising from not staying true to the spirit is in studies comparing medical therapy to early surgery. Many a time, the medical therapy arm only practices inactivity and not watchful waiting, which requires vigilance and action readiness. We therefore cannot stress enough the importance of clinical judgment at interpreting these studies. Early surgery is not a sweeping pass that is to be plastered across the board, a shield that inferior outcomes can hide behind. It actually represents a privilege that only those with the capability can exercise. For those who advocate watchful waiting, it is not a security blanket, which permits comfortable inaction. When the surgical indications are met, it should be performed in a timely manner. With regards to the future of risk stratification in MR, our group believes that exercise stress testing has a promising role.⁶¹ It has the ability to elicit symptoms, enables objective assessment of functional capacity against age-gender matched subjects, and provides a dynamic evaluation of myocardial structure and function. At the end of the day, studies present numbers and figures that apply to a population and not to an individual. As the treating physicians, we should individualize care according to local practice settings, i.e. whether surgical and imaging expertise are available, patient's surgical risk profile and most importantly, patient's preference. Time taken to understand patient's wishes and how they perceive risks will be proven worthwhile. After all, it is the patient who is at the center of the Heart Team and surgery should always be a joint decision.

Conclusion

In conclusion, the indications and timing of surgery in asymptomatic severe MR patients is both a science and an art. The debate of early surgery versus watchful waiting in the literature is analogous to Newton's Third Law, in the sense that with every argument, there is an equal and opposite counter-argument. This debate seems unlikely to resolve at least in the near future. In the words of Pliny the Elder, in these matters the only certainty is

that nothing is certain. It is a matter that calls for sound clinical judgement, humility of wisdom, and further research.

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