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CLINICAL REVIEW
Clinical update

Timing of intervention in asymptomatic patients with valvular heart disease

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Current management of valvular heart disease (VHD) seeks to optimize long-term outcome by timely intervention. Recommendations for treatment of patients with symptoms due to severe valvular disease are based on a foundation of solid evidence. However, when to intervene in asymptomatic patients remains controversial and decision requires careful individual weighing of the potential benefits against the risk of intervention and its long-term consequences. The primary rationale for earlier intervention is prevention of irreversible left ventricular (LV) myocardial changes that might result in later clinical symptoms and adverse cardiac events. A number of outcome predictors have been identified that facilitate decision-making. This review summarizes current recommendations and discusses recently published data that challenge them suggesting even earlier intervention. In adults with asymptomatic aortic stenosis (AS), emerging risk markers include very severe valve obstruction, elevated serum natriuretic peptide levels, and imaging evidence of myocardial fibrosis or increased extracellular myocardial volume. Currently, transcatheter aortic valve implantation (TAVI) is not recommended for treatment of asymptomatic severe AS although this may change in the future. In patients with aortic regurgitation (AR), the potential benefit of early intervention in preventing LV dilation and dysfunction must be balanced against the long-term risk of a prosthetic valve, a particular concern because severe AR often occurs in younger patients with a congenital bicuspid valve. In patients with mitral stenosis, the option of transcatheter mitral balloon valvotomy tilts the balance towards earlier intervention to prevent atrial fibrillation, embolic events, and pulmonary hypertension. When chronic severe mitral regurgitation is due to mitral valve prolapse, anatomic features consistent with a high likelihood of a successful and durable valve repair favour early intervention. The optimal timing of intervention in adults with VHD is a constantly changing threshold that depends not only on the severity of valve disease but also on the safety, efficacy, and long-term durability of our treatment options.

Keywords Valvular heart disease • Early intervention • Predictors of outcome • Surgery • Transcatheter intervention

Rational for intervention in asymptomatic valvular heart disease and general aspects to consider for decision-making

Management of valvular heart disease (VHD) has dramatically changed over the last few decades. The primary goal has moved away from relieving symptoms once they occur to optimizing long-term morbidity and mortality, which requires timely intervention. Early symptoms (beginning decline in exercise capacity/exertional shortness of breath) are a clear trigger for intervention but even asymptomatic patients may be at risk when followed conservatively. This is highlighted in current guidelines[1–3] and the question 'whether any signs are present in asymptomatic VHD that indicate a worse outcome if intervention is delayed' is listed as one of the essential key questions in the evaluation of these patients.[1]

What is the rationale for intervening in an asymptomatic patient with severe VHD?

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- Patients may remain asymptomatic until a life-threating event occurs that then precludes intervention.
- Irreversible end-organ damage, particularly of the myocardium and pulmonary vasculature, may develop during the asymptomatic phase which results in increased mortality and morbidity even after successful intervention.
- Risk of intervention may be lower at an early, compared to a later, stage of the disease.
- In healthcare settings with limited resources a long waiting time for intervention may put patients at significant risk if symptoms develop during the waiting period.
- Suboptimal follow-up and patient compliance may delay intervention once symptoms or other indications for intervention occur in asymptomatic patients.
- Even with close follow-up, the insidious onset of subtle symptom may lead to delays in intervention.
- Symptoms may not represent a perfect marker of disease severity and stage and assessment of the symptomatic state may particularly be challenging when exercise testing cannot be performed.

These potential benefits must be weighed against the risks of intervention:

- Operative risk is highly variable and requires consideration of the type of intervention (surgery versus catheter techniques, type of surgery), patient characteristics (comorbidities, frailty, etc. and anatomic features relevant for the specific intervention), and operator and medical centre outcome data for a given intervention.
- Long-term risks are highly dependent on the type of intervention (biological or mechanical valve replacement, valve repair) and include thromboembolic events, bleeding, endocarditis, and acute or chronic prosthetic valve failure resulting in heart failure, potentially requiring re-intervention.

Thus, decision-making in asymptomatic patients remains complex and requires careful individual weighing of risk vs. benefit of intervention (*Figure 1*). Recommendations are further hindered by the fact that we mostly rely on observational data and sometimes controversial results of studies. Therefore, it remains often difficult to estimate the above-mentioned potential benefits.

This review summarizes current recommendations and discusses recently published data that challenge them suggesting even earlier intervention. It is restricted to isolated intervention in primary native valve disease and focuses—in consideration of available data—on aortic and mitral valve disease.

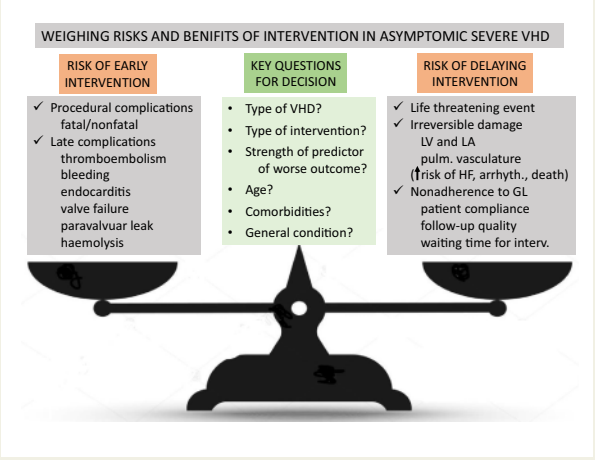

Figure 1 Weighing of risks and benefits of intervention in asymptomatic valvular heart disease. Aspects that need to be considered and key questions for decision-making. Arrhyth., arrhythmias; GL, guidelines; HF, heart failure; interv., intervention; LA, left atrium; LV, left ventricle; pulm., pulmonary; VHD, valvular heat disease.

Aortic stenosis

Established risk factors in asymptomatic severe aortic stenosis

A number of risk factors have become established in asymptomatic severe aortic stenosis (AS). While they could be demonstrated to be predictors of event-free survival it must be pointed out that in most studies the predominating event was development of symptoms requiring intervention. It remains to be shown whether in the presence of such risk factors patients benefit indeed from early surgery when they are still asymptomatic. Echocardiography, exercise testing, and biomarkers play currently the key role for risk stratification:

Echocardiography: valve calcification, peak aortic jet velocity,[4–7] left ventricular ejection fraction (LVEF),[8] rate of haemodynamic progression,[5] increase in gradient with exercise,[9,10] excessive left ventricular (LV) hypertrophy,[11] abnormal longitudinal LV function, in particular, global longitudinal strain (LVGLS),[8,12,13] and pulmonary hypertension[14–18] have been reported to predict outcome in asymptomatic patients.

Exercise testing: unmasking of symptoms during exercise testing in physically active patients, particularly those younger than 70 years, predicts a very high likelihood of patient-reported symptom development within 12 months. Abnormal blood pressure response and to an even greater degree ST-segment depression, however, have a lower positive predictive value than symptoms for prediction of poor outcome.[19]

Biomarkers: most data are available for natriuretic peptides demonstrating that elevated plasma levels are associated with worse outcome, precise cut-off values are, however, not very well defined.[12,20–23]

Current guidelines

Studies available for the most recent European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines[1–3] were felt not to provide convincing data to support a general recommendation of early intervention in patients with asymptomatic severe AS.[4–7,24–26] Although a large retrospective study of asymptomatic AS using propensity score matching suggested a substantial improvement of outcome with valve replacement compared to a conservative management,[26] these results were solely driven by the poor outcome of patients in the conservative group who developed symptoms during follow-up but did nevertheless not undergo aortic valve replacement. This and several other retrospective studies rather highlight the importance of

appropriate follow-up to make sure that patients receive treatment when they develop symptoms.

Current guidelines recommend careful weighing of the benefits against the risks. Early elective surgery is recommended in asymptomatic patients with reduced LV function, not due to other causes.[6] These patients are however very rare (<1% of AS patients) and the relatively poor outcome and observed questionable improvement with valve replacement raises the suspicion that these patients may frequently have other undiagnosed cardiac problems in addition to their AS.[27]

Early elective surgery is also indicated in asymptomatic patients with an abnormal exercise test, particularly with symptom development or a fall in blood pressure below baseline.[19,28,29]

An increase of mean pressure gradient with exercise by >20 mmHg[9,10] has also been reported to be a predictor of symptom development. The individual changes of gradient with exercise remain complex and are determined by AS severity and the ability to increase flow. In addition, the added value of exercise echo compared with the above-recommended criteria has been questioned by more recent studies.[30,31] Therefore, exercise echocardiography is no longer recommended for decision-making.

Table 1 summarizes current recommendations for asymptomatic AS in ESC and AHA/ACC guidelines. They differ only slightly. Both recommend to consider surgery when rapid progression or 'very severe AS' are present although with different thresholds for the latter. ESC guidelines include in addition pulmonary hypertension and elevation of neurohormone serum levels.

Current guidelines do not recommend transcatheter aortic valve implantation (TAVI) in any patients with asymptomatic AS.

New data challenging current guidelines

Early surgery vs. watchful waiting

Data from the first randomized controlled trial (RCT) became just recently available. In this South Korean multicentre trial,[32] 145 asymptomatic patients (mean age 64 ± 9 years) with 'very' severe AS (defined by a valve area ≤ 0.75 cm^2 and peak velocity ≥ 4.5 m/s or mean gradient ≥50 mmHg), normal LVEF and low surgical risk (EuroSCORE II 0.9 ± 0.3) were randomly assigned to early surgery (within 2 months) or conservative care. During a median follow-up of 6 years (minimum 4 years), the primary endpoint—a composite of death during or within 30 days after surgery or death from cardiovascular causes during entire follow-up – occurred in 1% vs. 15% ($P = 0.003$). Although these data at first sight strongly support early surgery several caveats need to be pointed out. The majority of sudden cardiac deaths (SCDs)—the most frequent cause of cardiovascular deaths—occurred in patients who had developed symptoms but did not undergo valve replacement. This confirms once more that nonadherence to guidelines in this patient group is associated with increased mortality.[33] The rate of SCD in this study is also surprisingly high. A recent report from the Heart Valve Clinic International Database[34] confirms the low rate of SCD in asymptomatic AS with a rate of 0.25% per year. Finally, the operative mortality was zero in both groups which cannot be expected in a real-world scenario. Neurohormones and pulmonary artery pressure were not used for risk assessment and exercise testing was performed in only a few patients. This is critical as exercise testing has shown to reveal symptoms in approximately one-third of patients claiming to be asymptomatic.[35]

Nevertheless, the study supports that early surgery can be reasonable when appropriate follow-up and patient compliance cannot be expected, while interventional risk at the same time is low. However, it should be noted that 37% of the asymptomatic patients in the RCT[32] remained asymptomatic and did not require intervention during 4 years of follow-up. Similarly, one-third of patients in the Heart Valve Clinic International Database[34] were free of intervention at 4 years.

Further evidence on optimal timing of intervention in asymptomatic patients with AS is expected in the next few years based on results of the AVATAR (Aortic Valve replAcemenT vs. conservative treatment in Asymptomatic seveRe aortic stenosis; NCT02436655), EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; NCT03042104) and EASY-AS (Early Valve Replacement in Severe ASYmptomatic Aortic Stenosis Study; NCT04204915) trials. These randomized trials will assess whether surgical or transcatheter aortic valve replacement, respectively, is superior to conservative care in patients with severe AS and normal exercise testing.

In the meanwhile, a more selective approach with risk stratification for both, conservative outcome and intervention still appears preferable. Another ongoing RCT 'EVOLVED' (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS; NCT03094143) is evaluating such a strategy including patients with elevated high sensitive Troponin and LV midwall fibrosis.

Predictors of outcome

The negative impact of replacement fibrosis of LV myocardium[36,37] and more recently extracellular myocardial volume[38] on survival and morbidity has been well documented but mostly studied in symptomatic patients. A recent study including 61 asymptomatic patients studied myocardial fibrosis and its course prior to and after valve replacement by magnetic resonance imaging.[39] While diffuse fibrosis was reversible after intervention, midwall gadolinium enhancement which was present in 26% at baseline and rapidly accumulating during follow-up was not. These results suggest that assessment of myocardial fibrosis may gain importance for the risk stratification of asymptomatic patients.

Recent studies reported that a peak velocity >5 m/s[34,40] and LVEF <55%[41] or even <60%[34] are associated with an increased mortality suggesting that lowering the peak velocity cut-off and increasing the LVEF cut-off may be considered in future guidelines. Left ventricular global longitudinal strain has repeatedly been proposed as more sensitive technique to detect early LV damage but so far not been integrated into guideline recommendations because of vendor differences hindering standardization. A recent individual participant data meta-analysis[42] reports that in 1067 asymptomatic patients with LVEF >50% the risk of death for patients with LVGLS <15% was multiplied by >2.5.

A modified staging of cardiac damage including LV hypertrophy, LV diastolic and systolic function parameters, left atrial (LA) volume, mitral regurgitation (MR), atrial fibrillation, pulmonary pressure, tricuspid regurgitation, right ventricular systolic function, and stroke volume index has been reported to provide incremental prognostic

Table 1 ESC/EACTS and AHA/ACC Guideline recommendations for intervention in asymptomatic patients with valvular heart disease

2014 and 2017 AHA/ACC Guidelines	2017 ESC/EACTS Guidelines
ASYMPTOMATIC SEVERE AORTIC STENOSIS	
LV systolic dysfunction with LVEF ≤50 % **(IB)**	LV systolic dysfunction with LVEF <50% not due to another cause **(IC)**
Decreased exercise tolerance or exercise fall in blood pressure **(IIaB)**	Abnormal exercise test showing • symptoms clearly related to AS **(IC)** • fall in blood pressure below baseline **(IIaC)**
Low surgical risk and • very severe AS (V_{max} ≥ 5.0 m/s) **(IIaB)**or • rapid disease progression (≥0.3 m/s/year) (**IIbC**)	Low surgical risk and one of the following **(IIaC)** • very severe AS (V_{max} ≥ 5.5 m/s) • severe calcification and rate of V_{max} progression ≥ 0.3 m/s/year • markedly elevated BNP (>three-fold age- and sex-corrected range) • severe pulmonary hypertension (PA systolic pressure > 60 mmHg confirmed by invasive measurement) without other explanation
ASYMPTOMATIC CHRONIC SEVERE AORTIC REGURITATION	
LV systolic dysfunction (LVEF < 50%) **(IB)**	LV systolic dysfunction (LVEF ≤ 50%) **(IB)**
Normal LV systolic function (LVEF ≥ 50%) but with severe LV dilation (LVESD > 50 mm) **(IIaB)**	Normal LV systolic function (LVEF > 50%) with severe LV dilatation: LVEDD > 70 mm or LVESD > 50 mm (or LVESDi > 25 mm/m^2 BSA in patients with small body size) **(IIaC)**
Normal LV systolic function (LVEF ≥ 50%) but with progressive severe LV dilation (LVEDD > 65 mm) if surgical risk is low **(IIbC)**	
Bicuspid aortic valve: indications for surgery on the ascending aorta	**Aortic root or tubular ascending aorta aneurysm[a] (irrespective of the severity of AR)**
Diameter of the aortic sinuses or ascending aorta >50 mm and risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥5 mm per year) **(IIaC)**	Patients with Marfan syndrome with maximal ascending aortic diameter ≥50 mm **(IC)**
Diameter of the aortic sinuses or ascending aorta >55 mm **(IB)**	Patients with aortic root disease and maximal ascending aortic diameter: **(IIaC)** • ≥45 mm in the presence of Marfan syndrome and additional risk factors,[b] or patients with TGFBR1 or TGFBR2 mutation (including Loeys–Dietz syndrome)[c] • ≥50 mm in the presence of a bicuspid valve with additional risk factors[b] or coarctation • ≥55 mm for all other patients.
Patients with aortic valve surgery because of severe AS or AR if the diameter of the ascending aorta is >45 mm **(IIaC)**	Patients with primary indication for the aortic valve with maximal ascending aortic diameter ≥45 mm, particularly in the presence of a bicuspid valve.[d] **(IIaC)**
ASYMPTOMATIC MITRAL STENOSIS	
PMC for very severe mitral stenosis (mitral valve area ≤1.0 cm^2) and favourable valve morphology in the absence of left atrial thrombus or moderate-to-severe mitral regurgitation **(IIaC)**	Valve area ≤1.5 cm^2, without unfavourable clinical and anatomical characteristics for PMC[e] and • high thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the left atrium, new onset, or paroxysmal atrial fibrillation) **(IIaC)**and/or • high risk of haemodynamic decompensation (systolic pulmonary pressure > 50 mmHg at rest, need for major non-cardiac surgery, desire for pregnancy) **(IIaC)**
PPMC for severe mitral stenosis (mitral valve area ≤1.5 cm^2) and favourable valve morphology in the absence of left atrial thrombus or moderate-to-severe mitral regurgitation, with new onset of atrial fibrillation **(IIbC)**	
ASYMPTOMATIC CHRONIC SEVERE PRIMARY MITRAL REGURGITATION	
LV systolic dysfunction (LVEF 30–60% and/or LVESD ≥ 40 mm) **(IB)**	LV systolic dysfunction (LVESD ≥ 45 mm or LVEF ≤ 60%) **(IB)**
Preserved LV function (LVEF >60% and LVESD <40 mm) and a high likelihood of a successful and durable repair with new onset of atrial fibrillation or PA systolic pressure at rest >50 mm Hg **(IIaB)**	Preserved LV function (LVEF >60% and LVESD <45 mm) and atrial fibrillation secondary to severe MR or PA systolic pressure at rest >50 mm Hg confirmed by invasive measurement **(IIaB)**
Preserved LV function (LVEF >60% and LVESD < 40 mm) if (all must be present): • likelihood of a successful durable repair is >95%,	Normal LV function (LVEF > 60% and LVESD 40–44 mm) and all of the following: • a durable repair is likely,

Continued

Table 1 *Continued*

2014 and 2017 AHA/ACC Guidelines	2017 ESC/EACTS Guidelines
• expected surgical mortality is <1%, • valve repair if performed at a Heart Valve Center of Excellence **(IIaB)**	• surgical risk is low, • valve repair if performed at a Heart Valve Center, and • a flail mitral leaflet or severe LA dilation (volume >60 mL/m^2 in sinus rhythm) is present **(IIaC)**
Preserved LV function (LVEF > 60% and LVESD < 40 mm) with a progressive increase in LV size or decrease in EF on serial imaging studies **(IIaC)**	

Adapted from Refs.[1–3]

ACC, American College of Cardiology; AHA, American Heart Association; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; BSA, body surface area; EACTS, European Association for CardioThoracic Surgery; ECG, electrocardiogram; ESC, European Society of Cardiology; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PA, pulmonary artery; PMC, percutaneous mitral commissurotomy; V_{max}, peak transvalvular velocity.

[a]For clinical decision-making, dimensions of the aorta should be confirmed by ECG-gated CT measurement.

[b]Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe aortic regurgitation or mitral regurgitation, desire of pregnancy, systemic hypertension, and/or aortic size increase >3 mm/year (on repeated measurements using the same ECG-gated imaging technique, measured at the same level of the aorta with side-by-side comparison and confirmed by another technique).

[c]In females with low body surface area, presence of TGFBR2 mutation, or patients with severe extra-aortic features a lower threshold of 40 mm may be considered.

[d]Considering age, BSA, aetiology of valvular disease, presence of a bicuspid aortic valve, and intraoperative shape and thickness of the ascending aorta.

[e]Unfavourable characteristics for percutaneous mitral commissurotomy can be defined by the presence of several of the following characteristics: (i) clinical characteristics: old age, history of commissurotomy, NYHA Class IV, permanent atrial fibrillation, and severe pulmonary hypertension. (ii) Anatomical characteristics: echo score >8, Cormier score 3 (calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, and severe tricuspid regurgitation.

value in asymptomatic moderate to severe AS.[43] However, it has to be kept in mind that the components of each stage are not specific for AS and can reflect cardiac and noncardiac comorbid factors, such as coronary artery disease, hypertension, atrial fibrillation, and chronic lung disease.

There is an increasing interest in using biomarkers for risk stratification and the association of their increased blood levels particularly for natriuretic peptides has been confirmed in further studies.[44] It has, however, to be emphasized that simple dichotomous biomarker cut-points are unlikely to be helpful, as biomarker levels require accounting for age, sex, race/ethnicity, body size, renal function, and other factors.[45] In addition, using more than one biomarker may provide more accurate prognostic information.[45]

In summary, justification of surgery beyond the currently recommended indications requires supporting data of additional randomized trials. Thresholds for peak velocity and LVEF as well as inclusion of LV myocardial fibrosis assessment and LV strain measurements will require discussion when revising the guideline recommendations for intervention in asymptomatic AS.

Aortic regurgitation

Established risk factors in asymptomatic severe aortic regurgitation

The prognostic impact of LV enlargement and dysfunction has been recognized in prospective studies in the 1980's and still represent the most important basis of current guidelines. The annual rate of a composite endpoint of death, symptom onset, or LV dysfunction was 4.3% and was predicted by LV end-systolic diameter >50 mm and LVEF <50%.[46–48] Subsequent series led to consider LV diameters indexed to body surface area since the use of non-indexed diameters led to delayed indications for surgery and increased long-term mortality in patients with small stature, particularly women.[49,50]

Except when there are concerns on the absence of symptoms, exercise testing does not seem to improve risk stratification in asymptomatic aortic regurgitation (AR).

Baseline and serial brain natriuretic peptide serum levels have an incremental predictive value of event-free survival, in addition to measurements of AR severity and LV remodelling.[51]

A particularity of AR is the frequent association of an enlarged ascending aorta. An enlarged aorta has its own prognostic value due to the risk of aortic dissection, which is related to maximal aortic diameter.

Current guidelines

In patients with asymptomatic AR, 2017 ESC guidelines[1] consider ascending aortic diameter first, recommending surgery when maximal diameter is >45–55 mm according to the aetiology, regardless of AR severity (*Table 1*). Thresholds of aortic diameters are lower in syndromic diseases, such as Marfan syndrome. In asymptomatic patients with severe AR, surgery is recommended with a Class I when LVEF is <50% and with a Class IIa according to LV diameters (*Table 1*). American guidelines[2,3] are consistent but do not consider indexed diameters.

New data challenging current guidelines

Indications for earlier surgery are supported by two studies reporting higher 5- to 10-year survival in asymptomatic patients who underwent surgery before reaching the thresholds of guidelines, i.e. an LV end-systolic diameter between 20 and 25 mm/m^2 or LVEF <55%.[52,53] This is consistent with a recent series in which 10-year survival and freedom from hospitalization for heart failure after surgery was better in patients operated before thresholds of Class II

recommendations (LV diameters) and, even more, with Class I recommendations (symptoms or LVEF < 50%). This series also supported indications for surgery in asymptomatic patients with LVEF <55% or LV end-systolic diameter >20 mm/m^2.[54] Data supporting earlier surgery than recommended in current guidelines should be balanced by a series showing the absence of benefit of earlier surgery, although valve-sparing surgery was performed in most of these patients, provided patients undergoing conservative management had close follow-up and were treated according to current guidelines.[55]

Left ventricular global longitudinal strain may also contribute to identify LV dysfunction at an early stage in asymptomatic AR. A series of 1063 asymptomatic patients with severe AR, LVEF >50% and LV end-systolic diameter <25 mm/m^2 reported a higher mortality in unoperated patients with LVGLS <-19.5%.[56,57]

In summary, thresholds for LV size and EF as well as inclusion of neurohormones and LV strain measurements will require discussion when revising the guideline recommendations for intervention in asymptomatic AR.

Mitral stenosis

Established risk factors in asymptomatic severe mitral stenosis

The evolution of mitral stenosis (MS) is slow. Asymptomatic patients have a 10-year survival over 80%.[58] However, approximately half of them become symptomatic after 10 years. Symptom onset is the most important prognostic factor and 10-year survival decreases to <40% in patients who are symptomatic in New York Heart Association (NYHA) Class III–IV.[58] A particularity of MS is the frequent occurrence of embolic events which are most often triggered by atrial fibrillation.[59] Due to low mortality, the aim of intervention in asymptomatic MS is mainly to decrease the incidence of complications, particularly embolic events, and to defer symptom onset.

Mitral gradient and pulmonary pressure increase during exercise but no thresholds have been validated for decision-making on intervention.

Current guidelines

In the 2017 ESC guidelines,[1] indications for intervention in asymptomatic patients with significant MS (valve area <1.5 cm^2) mainly refer to percutaneous mitral commissurotomy (PMC). In the absence of randomized trials, the level of evidence of recommendations for interventions is low. The largest comparative but non-randomized series reports better event-free survival up to 11 years in patients undergoing PMC in NYHA Class I–II vs. III–IV, with a marked benefit in patients at high risk for thromboembolism.[60] Current guidelines recommend PMC in asymptomatic MS with a Class IIa in selected patients at high risk for thromboembolic events or haemodynamic decompensation (*Table 1*).

New data challenging current guidelines

The use of PMC in asymptomatic MS may be restricted by the suitability to PMC in industrialized countries since patient became older with less favourable valve anatomy over the last decades.[61] Mitral stenosis may also be of degenerative origin, due to mitral annular calcification without commissural fusion and therefore not amenable to PMC.[62] Transcatheter mitral valve implantation has been recently proposed but indications have to be refined. Morbidity and mortality associated with this procedure make it unlikely to be considered in asymptomatic patients.[63]

The major challenge is to increase the availability of PMC in developing countries in which rheumatic fever remains endemic but PMC underused due to the cost of the device and the need for an environment of interventional cardiology.[64]

With regards to the prevention of embolic events, there are few specific data concerning medical and interventional antiarrhythmic therapies in MS.[59] Non-vitamin K antagonists anticoagulants (NOACs) are not recommended in MS since these patients were excluded from randomized trials.[1] A large observational series suggests a good safety and efficacy profile of NOACs as compared with vitamin K antagonists,[65] however, this should be evaluated by a randomized trial.

In summary, intervention in asymptomatic MS will remain restricted to patients with rheumatic aetiology suitable for PMC who are at high risk for thromboembolic events or haemodynamic decompensation.

Primary mitral regurgitation

Established risk factors in asymptomatic severe primary mitral regurgitation

Concerns that irreversible damage, particularly of LV myocardium, may occur already during the asymptomatic stage of disease and result in worse outcome when delaying intervention are greatest in severe primary MR.[1–3] LV size and function,[66] development of atrial fibrillation[67] or pulmonary hypertension,[68] flail leaflet as the underlying mechanism of MR,[69] and marked LA enlargement in the presence of sinus rhythm[68] have been identified as predictors of outcome. Elevation of natriuretic peptide levels has also been reported to identify asymptomatic patients at higher risk to develop LV dysfunction, heart failure, and death during long-term follow-up[70] and absence of neurohormone activation has a high negative predictive value.[71]

A high percentage of patients with degenerative MR can undergo successful and durable valve repair as long as performed in high volume centres and by experienced surgeons reducing the long-term risk of valve-related complications.[72–74]

Current guidelines

Current guidelines[1–3] recommend mitral valve surgery for asymptomatic patients with chronic severe primary MR when there is evidence of LV systolic dysfunction or when atrial fibrillation or pulmonary hypertension occur. Recommendations are summarized in *Table 1*. Valve repair is recommended in preference to replacement because long-term outcomes after repair are excellent, whereas prosthetic valves either require long-term anticoagulation (for mechanical valves) or are subject to valve deterioration (for bioprosthetic valves). Transcatheter approaches are not recommended for any asymptomatic patients with MR.

Decision-making is more difficult in the asymptomatic patient in sinus rhythm with normal LV systolic function and lower pulmonary artery pressures in whom a durable repair is likely with a low

estimated surgical risk when surgery is performed at a Heart Valve Center. AHA/ACC guidelines[2,3] indicate that valve repair may be considered for all these patients which make valve repairability the primary criterion for consideration of surgical intervention. In contrast, current ESC guidelines[1] suggest intervention is reasonable only if there is a flail mitral leaflet or severe LA dilation in the presence of sinus rhythm and LV end-systolic diameter is 40 mm or larger (see *Table 1*). Although a recent study[75] supports the safety of watchful waiting until such guideline recommended criteria occur good long-term outcome with this strategy can only be expected when patients are carefully followed in expert hands.

Current guidelines, particularly the definition of severe MR and thresholds for LV size and function, primarily are based on physiological considerations and small observational studies of patients with imaging studies before and after surgical intervention. There are no randomized controlled clinical trials for timing of intervention and little data on risk stratification in patients with asymptomatic severe MR and preserved LV function, no pulmonary hypertension, and no atrial arrhythmias.

New data challenging current guidelines

Mitral regurgitation severity

Severity of MR is determined by echocardiography in most clinical settings. Both ESC and AHA/ACC guidelines[1–3] recommend an integrative approach to determine MR severity based on valve morphology, Doppler colour flow imaging, pulsed and continuous wave Doppler, estimated pulmonary systolic pressure, LA enlargement, and LV size and systolic function.[76] In asymptomatic patients with MR, it is particularly critical that we confirm that MR is indeed severe to avoid overtreatment. LV dilation and systolic dysfunction cannot be attributed to MR when regurgitant flow is only mild to moderate in severity. The diagnosis of severe MR is most secure when multiple measures are concordant and there is evidence of LV volume overload, rather than relying on any single parameter, such as regurgitant orifice area or regurgitant volume.

The major limitation of this approach is that accurate measurement of MR severity depends on meticulous imaging and measurements by an experienced echocardiographer, often requiring transoesophageal echocardiography for adequate visualization of valve morphology and regurgitation. Even with experienced echocardiographers, there is marked interobserver and physiological variability in quantitation of MR severity. More accurate, precise, and reproducible measures of MR severity are needed. A more objective definition based on prediction of clinical outcomes is desired.

Cardiac magnetic resonance imaging is useful for quantitation of MR severity when echocardiography is uncertain and provides ambiguous measurements of LV volumes and LVEF.[77] Cardiac magnetic resonance imaging is especially helpful when considering surgery in asymptomatic patients with an LV end-systolic diameter <40 mm^2 to confirm the presence of indeed severe MR.

Symptom status

As with any slowly progressive disease, the patient may adapt to the physiological changes due to chronic MR and fail to report symptoms promptly. Standard exercise or cardiopulmonary exercise testing can be helpful for objective determination of exercise capacity and symptom status.[78] Measurement of serum natriuretic peptide levels also may be helpful in identifying patients with subtle symptoms and, possibly, help justify early intervention.[79] Their inclusion should be considered in future guidelines.

Left ventricular response to chronic volume overload

The major concern in asymptomatic patients with chronic severe MR is that a gradual increase in LV size over several years may lead to irreversible systolic dysfunction if intervention is delayed too long. However, standard measures of LV systolic function are misleading because altered loading conditions often mask a reduction in LV contractility. Specifically, LVEF may remain normal despite significant myocardial dysfunction.

Clinical echocardiographers now routinely report two-dimensional and three-dimensional LV volumes, yet guidelines continue to use a linear LV diameter in defining timing of intervention. Unfortunately, the studies used to define the LV size and LVEF thresholds that indicate early systolic dysfunction in patients with chronic MR were performed many decades ago and only report dimensions, not volumes. Despite the wide availability of LV volume data on echocardiographic and cardiac magnetic resonance studies, there is no robust data to support using volume data in clinical decision-making.[80] Hopefully, this knowledge gap will be remedied by data from large registries in future clinical studies.

Left ventricular global longitudinal strain is more sensitive for detection of myocardial dysfunction than LVEF. In a study of 506 patients with severe primary MR who underwent mitral valve surgery, multivariate predictors of cardiac events were age [hazard ratio (HR): 1.429, 95% confidence interval (CI): 1.116–1.831; $P = 0.005$], LA dimension (HR: 1.034, 95% CI: 1.006–1.063; $P = 0.019$), and GLS (HR: 1.229, 95% CI: 1.135–1.331; $P < 0.001$) but not ejection fraction.[81] In another study of 520 patients undergoing mitral valve surgery with normal LV systolic function, an abnormal pre-operative LVGLS measurement was a predictor of post-operative LV dysfunction.[82] These data are further supported by a study of 593 patients undergoing surgery for severe primary MR in whom pre-operative GLS was independently associated with all-cause mortality (HR: 1.13; 95% CI: 1.06–1.21; $P < 0.001$).[83] However, these studies were not restricted to asymptomatic patients and it remains unclear whether GLS provides additive value to standard clinical and imaging parameters used in clinical decision-making. In clinical practice, LVGLS measurements can vary with different instrumentation and are subject to considerable measurement variability even with the same recording method.

Valve repairability

Ultimately the primary factor driving timing of intervention in asymptomatic patients with severe degenerative MR is the ease, safety, efficacy, and durability of the procedure to eliminate MR. Obviously, patients would have better lifetime outcomes without severe MR. We do not intervene immediately in all patients because we do not have a perfect treatment. A successful mitral valve repair offers excellent long-term outcomes, but either is not or cannot be performed in all patients. Advanced imaging, particularly three-dimensional echocardiography, has improved our ability to visualize valve anatomy, determine whether the valve might be repairable and plan the surgical approach. However, whether the valve is successfully repaired depends on surgical skill and

programme experience, not just the patient's valve structure. Numerous studies have demonstrated higher rates of valve repair by surgeons and centre with higher operator volumes suggesting that a systems-based approach to improving outcomes may be beneficial.[84–87] The AHA/ACC now has defined performance criteria for centres operating on patients with primary degenerative MR in absence of annular or leaflet calcification as follows:

- overall surgical repair rate >75%,
- 30-day operative mortality <1%, and
- annual case volume of 25 per surgeon or 50 per programme.

This document also defines primary and comprehensive valve centres and recommends that surgery for MR due to isolated involvement of the central scallop of the posterior leaflet can be done at a primary valve centre but that more complex cases should be referred to a comprehensive valve centre.[87] Additional system-based approaches to improving outcomes in all patients undergoing mitral valve surgery are needed.

In summary, intervention in asymptomatic MR beyond currently recommended indications should ideally be supported by data of randomized trials. Valve repairability and securing of settings that can provide optimal treatment results remain critical for early intervention. Assessment of MR severity and LV response to volume overload require refinement. Inclusion of neurohormones and LV strain measurements will require discussion when revising the guideline recommendations for intervention in asymptomatic MR.

Conclusions and future perspectives

Timing of intervention in asymptomatic patients with VHD remains challenging. The decision requires careful individual weighing of the risk of procedural and late complications with intervention vs. the risks of delaying this intervention. Potential adverse effects of delay include life-threatening events, irreversible damage of LV, LA, or pulmonary vasculature resulting in increased long-term risk of heart failure, arrhythmias, and death. In addition, non-adherence to current guidelines with delay of timely intervention during follow-up because of poor patient compliance or inappropriate follow-up quality or prolonged waiting times for intervention all contribute to poor patient outcomes. The balance of risk and benefit of intervention highly depends on the type of valve disease, the type of intervention that can be offered, the strength of outcome predictors, the patient's age, comorbidities and general condition, and the local healthcare system (*Figure 1*). Although current guidelines already recommend early intervention either when symptoms first occur or when signs are present in asymptomatic patients that predict worse outcomes if intervention is delayed, recent studies suggest the threshold might be decreased even further. Randomized controlled trials are required to clarify when even earlier intervention is beneficial, particularly in non-selected patients. In addition, research is needed to better quantitate VHD severity and define signs that should prompt intervention in asymptomatic patients. Further improvement of treatment options with fewer procedural complications and less adverse long-term consequences of intervention also will influence future decision-making. Our efforts should focus not only on the discussion of when to intervene but also on optimal early diagnosis and guideline adherence for asymptomatic patients with VHD. With respect to these issues, the recently published results of the EURObservational Research Programme Valvular Heart Disease II Survey raise major concerns.[88] Based on this survey, almost half of interventions for VHD are still performed too late in the disease process, only after patients present with significant heart failure symptoms. Exercise testing for evaluation of patients with apparently asymptomatic severe VHD still is performed in only a small percentage. These deficiencies in current practice highlight that major efforts are required for effective guideline implementation.

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