SECTION 35

Valvular heart disease

This section is supplementary data to the 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease published in the European Heart Journal.

The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Helmut Baumgartner (ESC Chairperson) (Germany), Volkmar Falk (EACTS Chairperson) (Germany), Jeroen J. Bax (The Netherlands), Michele De Bonis (Italy), Christian Hamm (Germany), Per Johan Holm (Sweden), Bernard Iung (France), Patrizio Lancellotti (Belgium), Emmanuel Lansac (France), Daniel Rodriguez Muñoz (Spain), Raphael Rosenhek (Austria), Johan Sjögren (Sweden), Pilar Tornos Mas (Spain), Alec Vahanian (France), Thomas Walther (Germany), Olaf Wendler (UK), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain)

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Chapter 35.1 Introduction and general comments

Valvular heart disease (VHD) accounts for a significant burden in the community and predominates in elderly patients, thereby raising particular problems for the evaluation of the risk:benefit ratio of interventions. Interventions for VHD are the only effective therapy for improving survival. Valvular interventions have been reoriented with the development of less invasive approaches, in particular transcatheter interventions.

This chapter will provide an updated review of the main aspects of each acquired valve disease in adults and include patients who have previously undergone valve surgery. It will also present principles of management with regards to diagnosis and treatment that are derived from the most recent guidelines.

Epidemiology

The age-adjusted prevalence of moderate or severe VHD has been estimated at 2.5% (95% confidence interval 2.2–2.7%) in a population-based series on 11,911 patients comprising systematic echocardiographic examination.[1] This prevalence was highly dependent on age and increased markedly after the age of 65 to reach 13% after 75. Age distribution of VHD in industrialized countries is related to the sharp decrease in the incidence of acute rheumatic fever and, therefore, of rheumatic heart disease.[2] This has been compensated for by an important increase in the prevalence of so-called degenerative VHD, a term encompassing heterogeneous pathophysiology and lesions but sharing an increased prevalence with age. Degenerative VHDs are mainly calcific aortic disease causing aortic stenosis (AS). They frequently involve the mitral annulus but most often without significant haemodynamic consequences. Degenerative lesions of the mitral valve and the aortic valve and root are the most frequent cause of primary mitral regurgitation (MR) and aortic regurgitation (AR).[3] Other aetiologies are infective endocarditis (IE), inflammatory, drug-induced, radiation-induced, and congenital VHD.

Calcific aortic disease occurs on normal or, more frequently, on bicuspid aortic valve disease. The early stage is aortic sclerosis, which progresses slowly to significant AS. Epidemiological studies reported consistent estimations of the prevalence of significant AS (Figure 35.1.1).[1, 4–8] The annual incidence of AS is estimated around 5 per 1000.[6] Due to population ageing and the absence of prevention, the number of elderly patients with AS is expected to be multiplied by two to three within the next 50 years.[9, 10]

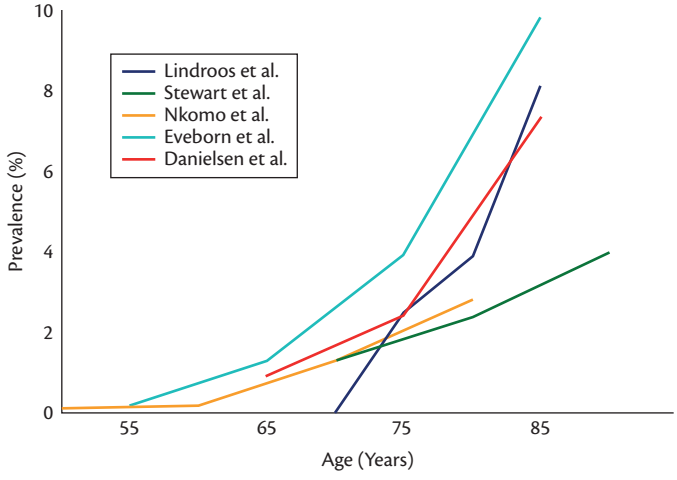

Figure 35.1.1 Prevalence of aortic stenosis according to age in population-based series from the United States or Europe: Lindroos et al. (Finland),[4] Stewart et al. (USA),[5] Nkomo et al. (USA),[1] Eveborn et al. (Norway),[6] and Danielsen et al. (Iceland)[7].
Lindman BR, Clavel MA, Mathieu P, Iung B, Lancellotti P, Otto CM, Pibarot P. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006.

Mitral valve prolapse is the most frequent cause of primary MR. Its prevalence is estimated at 2.4% but less than 5% of cases are associated with severe MR.[11] There are presently no reliable estimations of the prevalence of secondary MR, although it is likely to account for a high number of cases in the general population.[12]

The prevalence of moderate or severe AR is estimated at less than 1%.[2, 12] Degenerative AR may be due to abnormalities of the aortic valve or ascending aortic aneurysm, or both, on a tricuspid or bicuspid aortic valve.

Mitral stenosis (MS) is the only VHD which remains mainly of rheumatic origin, which explains its decline in industrialized countries, with a prevalence estimated at 0.1%.[1]

The annual incidence of IE is estimated between 15 and 80 cases per million from population-based studies in industrialized countries.[12] Over the last decades, IE has been characterized by an increase in patient age and in the percentage of cases due to staphylococci, which is now the most frequent responsible microorganism.[13, 14]

Rheumatic fever remains endemic in developing countries, where rheumatic heart disease is highly prevalent, with most estimations ranging between 5 and 10 cases per 1000 subjects according to clinical screening in school-aged children.[15] Prevalence rates are approximately tenfold higher when assessed using systematic echocardiographic screening.[16] The prevalence of rheumatic heart disease is largely associated with socioeconomic status. Consequently, the distribution between rheumatic and degenerative VHD follows an intermediate pattern in emerging countries, as illustrated by a Turkish survey in which 46% of cases of VHD were of rheumatic origin and 29% of degenerative origin.[17] Rheumatic heart disease remains, however, present in industrialized countries due to migrations.[3]

In the Euro Heart Survey, patients who had undergone previous valvular intervention accounted for as many as 28% of patients referred to hospital for VHD.[3] The percentage of valvular surgery has gradually increased in the decade 2000–2010 at the expense of coronary artery bypass grafting,[18] and this was associated with older age and increased frequency of co-morbidities.[19] Besides surgery, the number of transcatheter interventions is progressively increasing, mainly in AS, and is likely to continue to increase in the near future.

General principles of patient management

Patient evaluation

The aims of the evaluation of patients with VHD are to diagnose, quantify, and assess the mechanism of VHD as well as its consequences. The consistency between the results of diagnostic investigations and clinical findings should be checked at each step in the decision-making process. Decision-making should be made by a 'Heart Team' with a particular expertise in VHD, comprising cardiologists, cardiac surgeons, imaging specialists, anaesthesiologists, and, if needed, general practitioners, geriatricians, and heart failure (HF), electrophysiology, or intensive care specialists. The 'Heart Team' approach is particularly advisable in the management of high-risk patients and is also important for other subsets such as asymptomatic patients where the evaluation of valve reparability is a key component in decision-making.

Decision-making can be summarized according to the approach described in Box 35.1.1.

Finally, indications for intervention and which type of intervention should be chosen rely mainly on the comparative assessment of spontaneous prognosis and the results of intervention according to the characteristics of VHD and co-morbidities.

Box 35.1.1 Essential questions in the evaluation of a patient for valvular intervention

- How severe is VHD?
- What is the aetiology of VHD?
- Does the patient have symptoms?
- Are symptoms related to valvular disease?
- Are there any signs present in asymptomatic patients that indicate a worse outcome if the intervention is delayed?
- What are the patient's life expectancy* and expected quality of life?
- Do the expected benefits of intervention (vs spontaneous outcome) outweigh its risks?
- What is the optimal treatment modality?—Surgical valve replacement (mechanical or biological), surgical valve repair or catheter intervention?
- Are local resources (local experience and outcome data for a given intervention) optimal for the planned intervention?
- What are the patient's wishes?

* Life expectancy should be estimated according to age, gender, co-morbidities, and country-specific life expectancy.

Clinical evaluation

The aim of obtaining a case history is to assess symptoms and to evaluate for associated co-morbidity. The patient is questioned on his/her lifestyle to detect progressive changes in daily activity in order to limit the subjectivity of symptom analysis, particularly in the elderly. In chronic conditions, adaptation to symptoms occurs. Repeated clinical evaluations are useful in this setting. Symptom development is often a driving indication for intervention. Patients who currently deny symptoms, but have been treated for HF, should be classified as symptomatic after exclusion of other potential causes of HF unrelated to valve disease. The reason for functional limitation and its degree, together with its relation to the underlying valvular problem, should be documented in the records. In the presence of cardiac and extracardiac co-morbidities it is important to elucidate the true cause of the symptoms. In patients receiving chronic anticoagulant therapy, it is necessary to assess the compliance with treatment and look for evidence of thromboembolism or bleeding. It is also necessary to search for minor complications, such as transient ischaemic attack or minor bleeding, which are frequently overlooked by the patient.

Clinical examination, in particular auscultation, plays a major role in the detection of VHD in asymptomatic patients. It is the first step in the definitive diagnosis of VHD and the assessment of its severity, keeping in mind that a low-intensity murmur may coexist with severe VHD, particularly in the presence of HF. In patients with heart valve prostheses, it is necessary to be aware of any change in murmur or prosthetic valve sounds.[20] Clinical signs of HF are usually encountered at advanced stages of VHD.[21] Clinical examination also contributes to the search for co-morbidities.

Electrocardiogram and chest X-ray complete clinical evaluation. Analysis of pulmonary vascular distribution is useful in the interpretation of dyspnoea.

Echocardiography

Echocardiography is the key technique used to confirm the diagnosis of VHD as well as to assess its severity and prognosis. It should be performed and interpreted by properly trained personnel.[22] It is indicated in every patient with a murmur, unless no suspicion of valve disease is raised after the clinical evaluation.

The evaluation of the severity of stenotic VHD should combine the assessment of valve area with flow-dependent indices such as mean pressure gradient and maximal flow velocity.[23] Flow-dependent indices add further information and have a prognostic value.

The assessment of valvular regurgitation should combine different indices including quantitative measurements, such as the vena contracta and effective regurgitant orifice area (EROA), which are less dependent on flow conditions than colour Doppler jet size (Table 35.1.1).[24] However, all quantitative evaluations have limitations. In particular, they combine a number of measurements, are highly sensitive to errors of measurement, and are highly operator dependent; therefore, their use requires experience and integration of a number of measurements rather than reliance on a single parameter. It is necessary to be aware of potential errors of measurements. Detailed comments for specific parameters are provided in the chapters in the rest of Section 35.

Thus, when assessing the severity of VHD, it is necessary to check consistency between the different echocardiographic measurements as well as the anatomy and mechanisms of VHD. It is also necessary to check their consistency with the clinical assessment.

Echocardiography should include a comprehensive evaluation of all valves, looking for associated valve diseases and the aorta.

Indices of left ventricular (LV) enlargement and function are strong prognostic factors and play an important role in decision-making for interventions in regurgitant VHD. While diameters allow a less complete assessment of LV size than volumes, their prognostic value has been studied more extensively. LV dimensions should be indexed to body surface area. The use of indexed values is of particular interest in patients with a small body size, but should be avoided in patients with severe obesity (body mass index >40 kg/m^2). Indices derived from Doppler tissue imaging and strain assessments seem to be of potential interest for the detection of early impairment of LV function, but lack validation of their prognostic value for clinical endpoints.[25, 26]

Finally, the pulmonary pressures should be evaluated as well as right ventricular (RV) function.[27] There are several simple and reproducible methods of assessing RV systolic function such as fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and pulsed tissue Doppler S′. Combining more than one measure of RV function, such as S′ and RV index of myocardial performance may more reliably distinguish normal from abnormal function.

Three-dimensional echocardiography is useful for assessing anatomical features which may have an impact on the type of intervention chosen, particularly on the mitral valve.[28, 29]

Transoesophageal echocardiography (TOE) should be considered when transthoracic echocardiography (TTE) is of suboptimal quality or when thrombosis, prosthetic dysfunction, or endocarditis is suspected. Intraprocedural TOE is used to monitor the results of surgical valve repair or percutaneous procedures. High-quality intraoperative TOE is mandatory for all valve operations to document normal function of the implanted prosthesis, document the absence of paravalvular leaks, and assess the result of a repair procedure. Three-dimensional TOE offers a more detailed examination of valve anatomy than two-dimensional echocardiography and is useful for the assessment of complex valve problems as well as for the determination of feasibility of percutaneous intervention.

Other non-invasive investigations

Stress testing

Stress testing is considered here for the evaluation of VHD or its consequences (or both), but not for the diagnosis of associated coronary artery disease (CAD). Predictive values of functional tests used for the diagnosis of CAD may not apply in the presence

Table 35.1.1 Echocardiographic criteria for the definition of severe valve regurgitation: an integrative approach

	Aortic regurgitation	Mitral regurgitation		Tricuspid regurgitation
Qualitative				
Valve morphology	Abnormal/flail/large coaptation defect	Flail leaflet/ruptured papillary muscle/large coaptation defect		Abnormal/flail/large coaptation defect
Colour flow regurgitant jet	Large in central jets, variable in eccentric jets*	Very large central jet or eccentric jet adhering, swirling, and reaching the posterior wall of the left atrium		Very large central jet or eccentric wall impinging jet*
CW signal of regurgitant jet	Dense	Dense/triangular		Dense/triangular with early peaking (peak <2 m/s in massive TR)
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)	Large flow convergence zone*		–
Semiquantitative				
Vena contracta width (mm)	>6	≥7 (>8 for biplane)		≥7*
Upstream vein flow§	–	Systolic pulmonary vein flow reversal		Systolic hepatic vein flow reversal
Inflow	–	E-wave dominant ≥1.5 m/s¶		E-wave dominant ≥1 m/s**
Other	Pressure half-time <200 ms†	TVI mitral/TVI aortic >1.4		PISA radius >9 mm††
Quantitative		**Primary**	**Secondary**‡‡	
EROA (mm^2)	≥30	≥40	≥20	≥40
R vol (mL/beat)	≥60	≥60	≥30	≥45
+ enlargement of cardiac chambers/ vessels	LV	LV, LA		RV, RA, inferior vena cava

* At a Nyquist limit of 50–60 cm/s.
† Pressure half-time is shortened with increasing left ventricular diastolic pressure, vasodilator therapy, and in patients with a dilated compliant aorta, or lengthened in chronic aortic regurgitation.
‡ For average between apical four- and two-chamber views.
§ Unless other reasons for systolic blunting (atrial fibrillation, elevated atrial pressure).
¶ In the absence of other causes of elevated left atrial pressure and of mitral stenosis.
** In the absence of other causes of elevated right atrial pressure.
†† Baseline Nyquist limit shift of 28 cm/s.
‡‡ Different thresholds are used in secondary MR where an EROA >20 mm^2 and regurgitant volume >30 mL identify a subset of patients at increased risk of cardiac events.
CW, continuous wave; EDV, end-diastolic velocity; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricle; R vol, regurgitant volume; TR, tricuspid regurgitation; TVI, time–velocity integral.
Adapted from Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.

of VHD and are generally not used in this setting.[30] In addition, exercise testing is contraindicated in symptomatic AS.

- *Exercise ECG:* the primary purpose of exercise testing is to unmask the objective occurrence of symptoms in patients who claim to be asymptomatic or have doubtful symptoms. Exercise testing also has an additional value for risk stratification in AS.[31] Exercise testing will also determine the level of authorized physical activity, including participation in sports.
- *Exercise echocardiography:* exercise echocardiography may provide additional information in order to better identify the cardiac origin of dyspnoea, which is a rather unspecific symptom, by showing, for example, an increase in the degree of mitral regurgitation/aortic gradient and in systolic pulmonary pressures.[32] It has a diagnostic value in transient ischaemic MR which may be overlooked in investigations at rest. The prognostic impact of exercise echocardiography has been mainly shown for AS and MR.[33]
- *Other stress tests:* the search for flow reserve (also called contractile reserve) using low-dose dobutamine stress echocardiography is useful for assessing severity and operative risk stratification in AS with impaired LV function and low gradient as well as to assess the potential of reverse remodelling in patients with HF and functional MR after a mitral valve procedure.[34]

Cardiac magnetic resonance

In patients with inadequate echocardiographic quality or discrepant results, cardiovascular magnetic resonance (CMR) should be used to assess the severity of valvular lesions, particularly regurgitant lesions, and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis, as CMR assesses these parameters with higher reproducibility than echocardiography.[35] CMR is the reference method for the evaluation of RV volumes and function and is therefore useful to evaluate the consequences of tricuspid regurgitation (TR).[36]

Computed tomography

Multislice computed tomography (MSCT) may contribute to the evaluation of the severity of valve disease, particularly in AS, either indirectly by quantifying valvular calcification[37, 38] or directly through the measurement of valve planimetry.[39] CT is the most accurate technique to assess the extension, severity, and location of valvular calcification, providing essential information for pre-procedural planning. It is widely used to assess the dimensions and location of aneurysms of the ascending aorta and aortic arch.[40] Due to its high negative predictive value, MSCT may be useful to exclude CAD in patients who are at low risk of atherosclerosis.[39, 41]

MSCT plays an important role in the work-up of high-risk patients with AS considered for transcatheter aortic valve implantation (TAVI), and provides valuable information for pre-procedural planning before intervention.[42, 43] New applications of MSCT such as dual-energy CT and spectral CT may be of additional value for evaluation of cardiac function in VHD in the future, but at present the data is limited.[44] The risk of radiation exposure, and of renal failure due to contrast injection, should, however, be taken into consideration.

Both CMR and MSCT require the involvement of radiologists/cardiologists with special expertise in VHD imaging.[45]

Cinefluoroscopy

Cinefluoroscopy is more specific than echocardiography for assessing valvular or annular calcification. It is also useful for assessing the kinetics of the leaflets of a mechanical prosthesis.[46]

Biomarkers

B-type natriuretic peptide serum levels have been shown to be related to functional class and prognosis, particularly in AS and MR.[47] Natriuretic peptides may also be of additional value in risk stratification, particularly in asymptomatic patients.[48]

Invasive investigations

- *Coronary angiography:* coronary angiography is indicated for the detection of associated CAD when surgery is planned and determines if concomitant coronary revascularization is indicated (Table 35.1.2).[30] However, MSCT has become a valuable non-invasive diagnostic tool in patients who are at low risk or intermediate risk of atherosclerosis.[30]

Coronary angiography can be omitted in young patients with no atherosclerotic risk factors (men <40 years and premenopausal women) and in rare circumstances when its risk outweighs benefit (e.g. in acute aortic dissection, a large aortic vegetation in front of the coronary ostia, or occlusive prosthetic thrombosis in an unstable haemodynamic condition).

- *Cardiac catheterization:* the measurement of pressures and cardiac output or the assessment of ventricular performance and valvular regurgitation by ventricular angiography or aortography are restricted to the rare situations where non-invasive evaluation is inconclusive or discordant with clinical findings. Given its potential risks, cardiac catheterization to assess haemodynamics should not be performed routinely with coronary angiography. When elevated pulmonary pressure is the only criterion to support the indication for surgery, confirmation of echo data by invasive measurement is recommended.

Table 35.1.2 Management of coronary artery disease in patients with valvular heart disease

	Class[a]	Level[b]
Diagnosis of coronary artery disease		
Coronary angiography* is recommended before valve surgery in patients with severe valvular heart disease and any of the following: ◆ history of cardiovascular disease ◆ suspected myocardial ischaemia† ◆ left ventricular systolic dysfunction ◆ in men aged over 40 years and postmenopausal women ◆ one or more cardiovascular risk factors	I	C
Coronary angiography is recommended in the evaluation of moderate to severe secondary mitral regurgitation	I	C
CT angiography should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD, or in whom conventional coronary angiography is technically not feasible associated with a high risk.	IIa	C
Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥70%‡	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥50–70%	IIa	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments	IIa	C
PCI should be considered in patients with a primary indication to undergo transcatheter mitral valve interventions and coronary artery diameter stenosis >70% in proximal segments	IIa	C

[a] Class of recommendation. [b] Level of evidence.
* Multislice computed tomography may be used to exclude coronary artery disease in patients who are at low risk of atherosclerosis.
† Chest pain, abnormal non-invasive testing.
‡ ≥50% can be considered for left main stenosis.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.
Adapted from Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–2619.

Assessment of co-morbidity

The choice of specific examinations to assess co-morbidity is directed by the clinical evaluation. The most frequently encountered co-morbidities are peripheral atherosclerosis, renal and hepatic dysfunction, and chronic obstructive pulmonary disease. Specific validated scores enable the assessment of cognitive and functional capacities which have important prognostic implications in the elderly. The expertise of geriatricians is particularly helpful in this setting.

Table 35.1.3 Operative mortality after surgery for valvular heart disease in all comers

	STS (2014)[50]	UK (2012)[51]	Germany (2014)[52, 53]
Aortic valve replacement, no CABG (%)	2.4 (29,158)	1.7 (4561)	2.7 (11,881)
Aortic valve replacement + CABG (%)	3.9 (18,016)	4.0 (3263)	4.5 (3462)
Mitral valve repair, no CABG (%)	1.2 (8658)	2.0 (1456)	1.6 (3621)
Mitral valve repair + CABG (%)	5.1 (4205)	5.6 (588)	6.6 (1854)
Mitral valve replacement no CABG (%)	4.9 (6857)	4.2 (638)	8.4 (2001)
Mitral valve replacement + CABG (%)	9.9 (2582)	11.6 (232)	16.4 (786)

Reoperations are excluded in the STS and UK reports but not in the data from Germany.
() = number of patients.
CABG, coronary artery bypass grafting; STS, Society of Thoracic Surgeons (USA).
Mortality for STS includes first and redo interventions[50]; UK, United Kingdom.
Data from references.[50–53]

Risk stratification

The use of risk stratification scores is a useful tool in helping cardiologists and cardiac surgeons take decisions regarding valvular interventions, especially in patients at increased risk of perioperative morbidity and mortality.[49] The decision to intervene in a patient with VHD relies on an individual risk:benefit analysis, suggesting that improvement of prognosis as compared with natural history outweighs the risk of intervention (Table 35.1.3)[50–53] and its potential late consequences, particularly prosthesis-related complications.

Operative mortality can be estimated by various multivariable scoring systems using combinations of risk factors.[54] The formerly used EuroSCORE[55] (European System for Cardiac Operative Risk Evaluation, http://www.euroscore.org/ calc.html) has been shown to consistently overestimate operative mortality and its calibration of risk is poor.[56] Consequently, it should no longer be used to guide decision-making. The EuroSCORE II[57] and the STS[58, 59] (Society of Thoracic Surgeons) score (http://209.220.160.181/STSWebRiskCalc261/) have been shown to more accurately discriminate high- and low-risk patients as well as better calibration to predict individual postoperative outcome and they achieve comparable performance in valvular surgery.[60–65] The latter has the advantage of being specific to VHD. However, the calibration of the EuroSCORE II is less satisfying in high-risk patients.[66] Additionally, these scores have shown variable results in predicting the outcomes of intervention in TAVI.[67] New scores have been developed to estimate the risk of 30-day mortality in patients undergoing TAVI, with better accuracy and discrimination.[68, 69] It remains, however, essential not to rely on a single number to assess patient risk, nor to determine unconditionally the indication and type of intervention. The predictive performance of risk scores may be improved by repeated recalibration of scores over time, as is the case for STS and EuroSCORE with the EuroSCORE II, by the addition of variables, in particular indices aimed at assessing functional and cognitive capacities and frailty in the elderly,[70] or by the design of separate risk scores for particular subgroups, such as the elderly or patients undergoing combined valvular and coronary surgery.

The natural history of VHD should ideally be derived from contemporary series, but no scoring system is available in this setting. Certain validated scoring systems enable a patient's life expectancy to be estimated according to age, co-morbidities, and indices of cognitive and functional capacity.[71] Expected quality of life should also be considered. The futility of interventions in patients unlikely to benefit from the treatment has to be taken into consideration, particularly for TAVI and mitral edge-to-edge repair.

Local resources should also be taken into account, in particular the availability of valve repair, as well as outcomes after surgery and percutaneous intervention in the specified centre.[72] Depending on local expertise, patient transfer to a more specialized centre should be considered for procedures such as complex valve repair.[73]

Finally, a decision should be reached through the process of shared decision-making, first by a multidisciplinary heart team discussion, then by informing the patient thoroughly, and finally by deciding with the patient and family which treatment option is optimal.[74]

Special considerations in elderly patients

Older age and frequent co-morbidities increase the risk of interventions and have a negative impact on life expectancy, thereby making risk:benefit analysis of interventions more difficult than in younger patients. This is of particular importance for the choice between surgery, TAVI, and medical therapy in AS, which is the most prevalent VHD in the elderly. Chronic lung disease, renal insufficiency, liver disease, and vascular disease are the most frequent organ co-morbidities which have a negative impact on early and late results of surgery or TAVI[57–59, 68, 69, 75] and also impair life expectancy regardless of heart disease.[71, 76]

Chronic lung disease impairs immediate and late survival after valvular surgery and TAVI.[77–80] Poor mobility, as assessed by the 6-minute walk test, and oxygen dependency are the main factors associated with increased mortality after TAVI.[79, 80] Spirometric variables are associated with pulmonary complications but should be interpreted with other factors, in particular reflecting functional impairment.

There is a gradual relationship between the impairment of renal function and increased mortality after valvular surgery, TAVI, and transcatheter mitral edge-to-edge repair.[81–84] This relationship is particularly marked when glomerular filtration rate is less than 30 mL/min.[83]

Hepatic insufficiency is a rare condition in surgical databases and its impact is therefore difficult to assess.[49] Limited retrospective data have shown an association between the Model for End-stage Liver Disease (MELD) score and morbi-mortality after cardiac surgery.[85]

Coronary, cerebrovascular, and lower limb artery diseases have a negative impact on early and late survival after surgery and TAVI.[82, 86]

Besides specific organ co-morbidities, there is growing interest in the assessment of frailty, which corresponds to a syndrome of decreased reserve and resistance to stressors and is an overall marker of impairment of functional, cognitive, and nutritional status.[87] Frailty is associated with increased morbi-mortality after surgery and TAVI.[75, 88–91] This association is stronger in elderly patients undergoing TAVI than in younger patients undergoing cardiac surgery.[88] Frailty also predicts functional decline after TAVI.[92] The assessment of frailty should not rely on a subjective approach such as the 'eye ball test' but rather on the combination of different objective estimates. A number of tools are available for assessing frailty.[93] However, it is presently not possible to recommend a standardized and simple method for assessing frailty, in particular through the use of a limited subset of geriatric scales which could be selected according to their own prognostic value.

Multivariate risk scores are the only way to combine the respective prognostic weights of co-morbidities. However, the predictive performance of risk scores is decreased in elderly or high-risk patients.[49, 66, 94, 95] There is limited experience concerning the addition of variables reflecting frailty to co-morbidities in risk scores. The interpretation is difficult due to the absence of a standardized assessment. In addition, available predictive analyses of early or short-term morbi-mortality showed a modest improvement of discrimination when adding frailty estimates.[96, 97]

In current practice, the search for co-morbidities is oriented by clinical evaluation. Respiratory, renal, hepatic, and vascular co-morbidities should be systematically searched for and quantified in the elderly. The involvement of organ specialists is particularly needed to determine if a single co-morbidity contraindicates an intervention. The assessment of frailty by a geriatrician is particularly recommended when it has an important impact in decision-making. However, the most frequent situation is the conjunction of different co-morbidities, which individually do not firmly contraindicate intervention. In these cases, the only means to assess the overall impact of co-morbidities is the use of risk scores. The limitations of the predictive performance of risk scores in high-risk patients should be kept in mind and highlight the importance of a multidisciplinary assessment by the heart team, weighing the risk of intervention against the natural history of the VHD. It is particularly important in the elderly that the patient and relatives are involved through a shared decision-making process.[74]

Endocarditis prophylaxis

Patients with a prosthetic valve, including transcatheter valves, or in whom valve repair has been performed using prosthetic material, and those with previous IE are at higher risk of IE and present higher morbidity and mortality from IE.[98] Hence, current European Society of Cardiology guidelines indicate that antibiotic prophylaxis should be considered for high-risk procedures in these patients.[99] Recommendations regarding dental and cutaneous hygiene and strict aseptic measures during any invasive procedure are advised in this population. Additionally, antibiotic prophylaxis should be considered in dental procedures involving manipulation of the gingival or periapical region of the teeth or manipulation of the oral mucosa.[99]

Prophylaxis for rheumatic fever

Prevention of rheumatic heart disease should preferably be oriented to preventing the first attack of acute rheumatic fever. Improvements in hygiene, living conditions, and access to medical care significantly impact its incidence. Additionally, treatment of group A streptococci sore throat by oral or injectable penicillin is key in primary prevention.[15] In patients with rheumatic heart disease, secondary long-term prophylaxis against rheumatic fever is recommended to prevent recurrent episodes and consequent progression of the disease. Three- to four-weekly injections of intramuscular benzathine penicillin, preferred to oral regimens due to higher efficacy in prevention of relapse, is recommended for at least 10 years after the last episode of acute rheumatic fever or until 40 years of age, whichever is the longest. Lifelong prophylaxis should be considered in high-risk patients according to the severity of VHD and exposure to group A streptococci.[100, 101]

Concept of valve clinic, heart team, and centres of excellence

When patients with VHD are referred in a timely manner, an intervention carries a lower risk and is usually more successful in improving survival and reducing symptoms. The main advantage of a specialist clinic is to deliver better quality of care than in a general clinic as a result of greater volumes associated with specialization of training, continuing education, and clinical interest. In specialized clinics, guidelines are more consistently applied and the number of inappropriate examinations is reduced. Specialization will also result in timely referral of patients before irreversible adverse effects occur and techniques with a steep learning curve are more likely to be applied in hospital with more experience (e.g. mitral valve repair).

The mechanisms of how valve clinics can optimize care are multiple: adequate evaluation of the patient, monitoring of the disease at appropriate time intervals, determining the right time and type for valve intervention, referring to the right surgeon or interventional cardiologist, and assessing the results after the intervention.[102]

A centre of excellence should provide a multidisciplinary team (heart team) that meets on a regular basis, works with standard operating procedures, and implements current guidelines. Risk assessment should be performed by application of risk scores such as the STS score or EuroSCORE II and taking other conditions not captured by these risk scores into account. The collaborative approach between cardiologists, surgeons, specialists in imaging, and anaesthesiologists should also include the judgement of other specialist such as intensivists or geriatricians as required. Expert imaging including echocardiography, computed tomography, and magnetic resonance imaging is essential and exercise tests should be readily available if needed to assess valvular lesions under exercise conditions, assess potential for reverse remodelling, and

allow for precise pre-procedural planning of surgery or interventions.[103] Valve intervention should only be carried out in those hospitals where there is both a cardiology and a cardiac surgery department on site.

There is no formal European qualification process to establish competency in VHD and there is controversy with regard to adequate hospital volumes and individual surgical or interventional case load. For most valve interventions, there is both an effect of the number of cases performed per year and per surgeon or interventional cardiologist as well as per hospital.[104–108] For both aortic and mitral valve replacement, a trend over time for adjusted odds ratios of mortality in very low-volume hospitals to very high-volume hospitals from 2000 to 2008 favouring high-volume hospitals has been observed in the United States.[109] The precise numbers of procedures per individual surgeon/interventionalist or hospital required to provide high-quality care, however, remain controversial and more scientific data are required before solid recommendations can be provided. Experience in the full spectrum of surgical procedures including valve replacement; aortic root surgery; mitral, tricuspid, and aortic valve repair; repair of complicated valve endocarditis such as root abscess; and treatment of atrial fibrillation (AF), as well as surgical myocardial revascularization must be available. The spectrum of interventional procedures in addition to TAVI should include mitral valvuloplasty, mitral valve repair (edge-to-edge), closure of atrial septal defects, closure of paravalvular leaks, and left atrial appendage closure, as well as percutaneous coronary intervention. Expertise in interventional and surgical management of vascular diseases and complications must be available.

A Heart Valve Centre (Box 35.1.2) should encounter structured training programmes for physicians and staff. Standard operating procedures in line with current guidelines should be implemented and updated on a regular basis. Team members should be involved with research and teaching and membership of a specialized society. A database to monitor outcomes which is available for regular internal and external audit should be available. Participation in national and European registries should be mandatory.

Box 35.1.2 Recommended requirements of a Heart Valve Centre

1. *Multidisciplinary teams* with competencies in valve replacement, aortic root surgery, mitral, tricuspid, and aortic valve repair, as well as transcatheter aortic and mitral valve techniques, including re-operations and re-interventions. The heart teams must meet on a regular basis and work with standard operating procedures.
2. Imaging including three-dimensional and stress echocardiographic techniques, perioperative TOE, cardiac computed tomography, magnetic resonance imaging, and positron emission tomography.
3. Regular consultation with community, other hospitals, and extracardiac departments, and between non-invasive cardiologists and surgeons and interventional cardiologists.
4. *Back-up services* including other cardiologists, cardiac surgeons, intensive care, and other medical specialties.
5. *Data review:*
   - Robust internal audit processes including mortality and complications, repair rates, durability of repair and reoperation rate with a minimum of 1-year follow-up.
   - Results available for review internally and externally.
   - Participation in national or European quality databases.

Adapted from Chambers J, Prendergast B, Iung B, Rosenhek R, Zamorano JL, Pierard LA, Modine T, Falk V, Kappetein AP, Pibarot P, Sundt T, Bamgartner H, Bax JJ, Lancellotti P. Standards defining a "heart valve centre": ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery viewpoint. Eur Heart J 2017;38:2177–2182.

Management of associated conditions

Coronary artery disease

The use of stress tests to detect CAD associated with severe VHD is discouraged because of their low diagnostic value and potential risks.

A summary of the management of associated CAD is given in Table 35.1.2 and detailed in specific guidelines.[30] Significant coronary disease generally leads to combined coronary artery bypass grafting when valvular surgery is indicated. Hybrid approaches combining percutaneous coronary intervention and valvular surgery have been proposed but experience remains limited and the management for antithrombotic therapy is difficult in this setting.

Atrial fibrillation and anticoagulation

Oral anticoagulation with a target international normalized ratio of 2–3 is recommended in patients with native VHD and any type of AF, taking the bleeding risk into account.[110] A higher level of anticoagulation may be necessary in specific patients with valve prostheses (see section on Prosthetic Valves).

Non-vitamin K antagonist oral anticoagulants (NOACs) are approved only for non-valvular AF, but there is no uniform definition of this term.[111] Recent subgroups analyses of randomized trials on AF support the use of rivaroxaban, apixaban, dabigatran, and edoxaban in patients with AS, AR, or MR presenting with AF.[112–115] The use of NOACs is discouraged in patients who have AF associated with moderate to severe MS given the lack of data and the high thromboembolic risk.[116, 117] Despite the absence of data, NOACs may be used in patients who have AF associated with a bioprosthesis after the third postoperative month.[118] NOACs are strictly contraindicated in patients with mechanical prostheses (see 'Interruption of anticoagulant therapy for planned invasive procedures' in Chapter 35.9).[119]

Except in cases where AF causes haemodynamic compromise, cardioversion is not indicated before intervention in patients with severe VHD, as it does not restore a durable sinus rhythm. Cardioversion should be attempted soon after successful intervention, unless in long-standing chronic AF.

Surgical ablation of AF combined with mitral valve surgery is effective in reducing the incidence of AF, but at the expense of more frequent pacemaker implantation, and has no impact on

Table 35.1.4 Management of atrial fibrillation in patients with valvular heart disease

	Class[a]	Level[b]	Ref.[c]
Anticoagulation			
NOACs should be considered as an alternative to VKA in patients with aortic stenosis, aortic regurgitation and mitral regurgitation presenting with AF	IIa	B	112–115
NOACs should be considered as alternative to VKA after the third month of implantation in patients who have AF associated with a surgical or transcatheter aortic valve bioprosthesis	IIa	C	
The use of NOACs is not recommended in patients with atrial fibrillation and moderate to severe mitral stenosis	III	C	
NOACs are contraindicated in patients with AF and mitral stenosis or a mechanical valve	III	B	119
Surgical interventions			
Surgical ablation of AF should be considered in patients with symptomatic AF who undergo valve surgery	IIa	A	110
Surgical ablation of AF may be considered in patients with asymptomatic AF who undergo valve surgery if feasible with minimal risk	IIb	C	
Surgical excision or external clipping of the left atrial appendage may be considered in patients undergoing valve surgery	IIb	B	121

[a] Class of recommendation. [b] Level of evidence. [c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonists.
Data from references.[110, 111, 119, 121]

short-term survival.[120] Surgical ablation should be considered in patients with symptomatic AF and may be considered in patients with asymptomatic AF if feasible with minimal risk. The decision should be individualized according to clinical variables, such as age, the duration of AF, and left atrial size.

For patients with AF and risk factors for stroke, long-term oral anticoagulation is therefore currently recommended although surgical ablation of AF and/or surgical left atrial appendage excision or exclusion may have been performed.[110]

Recommendations for the management of AF are summarized in Table 35.1.4.

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Chapter 35.2 Aortic regurgitation

Introduction

Aortic regurgitation (AR) can be caused by primary disease of the aortic valve cusps and/or abnormalities of the aortic root and ascending aortic geometry. The analysis of the mechanism of AR influences patient management, particularly when valve repair is considered.

Aetiology

AR results from disease of either the aortic leaflets or the aortic root that distorts the leaflets and prevents their correct apposition. Common causes of leaflet abnormalities that result in AR include senile leaflet calcifications, bicuspid aortic valve, infective endocarditis, and rheumatic fever. Aortic causes of AR include annulo-aortic ectasia (idiopathic root dilatation), Marfan syndrome, aortic dissection, collagen vascular disease, and syphilis.[1]

Degenerative tricuspid and bicuspid AR are the most common aetiology in Western countries, accounting for approximately two-thirds of the cases of AR in the Euro Heart Survey on valvular heart disease.[2] It is characterized by dilation of the aortic annulus, sinuses, and/or sinotubular junction diameters preventing coaptation of pliable leaflets which may also be subjected to prolapse.[3] Depending on whether the sinuses of Valsalva or the tubular ascending aorta are dilated (or both), three phenotypes can be individualized: (1) aortic root aneurysms (sinuses of Valsalva >45 mm); (2) tubular ascending aortic aneurysm (sinuses of Valsalva <40–45 mm); and (3) isolated AR (all diameters <40 mm) (Figure 35.2.1). Prolapse may be due to an elongated free edge of myxoid leaflets or a ruptured congenital fenestration at commissural level, or both of these[4] (Figure 35.2.1).

Aortic root aneurysms are encountered in Marfan syndrome and in rare degenerative diseases, such as Loeys–Dietz syndrome, Turner syndrome, Ehlers–Danlos disease, osteogenesis imperfecta, or familial forms of thoracic aortic aneurysms.[5, 6] The dilation of the aortic root in these cases is a consequence of cystic degeneration of the medial layer, which is generally caused by mutations in the gene encoding principally for fibrillin and transforming growth factor beta.[6] The same aortic root phenotype can be encountered in patients who do not have generalized tissue disease and this is known as idiopathic annuloaortic ectasia.[7]

Bicuspid aortic valve accounted for 15% of the causes of AR in the Euro Heart Survey, but AR is a rarer complication of bicuspid aortic valve disease than AS (Figure 35.2.2). Its frequency may be underestimated by echocardiography since the bicuspid type accounted for 29% of explanted valves for AR.[8] The most frequent mechanism of regurgitation is a prolapse of the fused cusp, followed by a lack of valve coaptation secondary to the dilation of the ascending aorta, or superimposed infective endocarditis. The ascending aorta is frequently enlarged and this predominates most often above the sinuses of Valsalva. The dilatation pattern differs according to the valve morphology.[9] The dilatation of the ascending aorta associated with bicuspid aortic valves is related to dystrophic abnormalities of the aortic wall and is not a consequence of valve dysfunction alone.[10]

Rheumatic fever has become a rare cause of AR in Europe,[2] but remains common in developing countries. Central regurgitation is the consequence of thickening and retraction of aortic leaflets.

Endocarditis still represents approximately 10% of the aetiologies of AR.[2] Regurgitation is related to leaflet tearing or perforation and, in certain cases, to a perivalvular abscess communicating with the aorta and the left ventricle (LV).

Aortitis is a heterogeneous group representing less than 5% of the aetiologies of AR.[2] Aortitis may be encountered in inflammatory diseases, such as ankylosing spondylitis, Takayasu's arteritis, rheumatoid arthritis, lupus erythematosus, Behçet's disease, giant cell arteritis, relapsing polychondritis, or syphilis, nowadays a very unusual cause.

Dissection of the ascending aorta often extends into the aortic root sinuses, most frequently the non-coronary and right coronary ones. It compromises commissural support and causes acute AR by cusp prolapse, which can be well tolerated, while tamponade is the life-threatening complication.

Besides bicuspid aortic valves, AR can be associated with ventricular septal defects or subvalvular AS in which regurgitation is caused by jet lesions.

The other rare causes are traumatism, radiation therapy, and drug-induced AR.

Pathophysiology

Acute severe AR in a non-dilated LV causes an abrupt increase in end-diastolic pressure and consequently a decrease in cardiac output. In chronic AR, progressive LV enlargement maintains LV compliance within a respectable range and therefore limits the increase in LV end-diastolic pressure. The increased LV volume enables total stroke volume to increase, thereby compensating for the regurgitant volume and helping to preserve normal cardiac output. Increased afterload is compensated for by eccentric LV hypertrophy. This compensation of volume and pressure overload explains why some patients with chronic severe AR may remain asymptomatic for a long time.[11] In many cases, symptom onset is the consequence of systolic LV dysfunction. LV dysfunction is potentially reversible if related to afterload mismatch, but may persist after the correction of AR if related to structural myocardial injury.

Diagnosis

History

Acute AR rapidly leads to disabling dyspnoea or pulmonary oedema due to the rapid elevation of end-diastolic pressures in the non-dilated, non-compliant LV.

In chronic AR, there is a long latent period and exertional dyspnoea occurs at a late stage of the disease process due to elevated LV end-diastolic pressures. Even without atherosclerotic disease angina may occur due to decreased myocardial perfusion

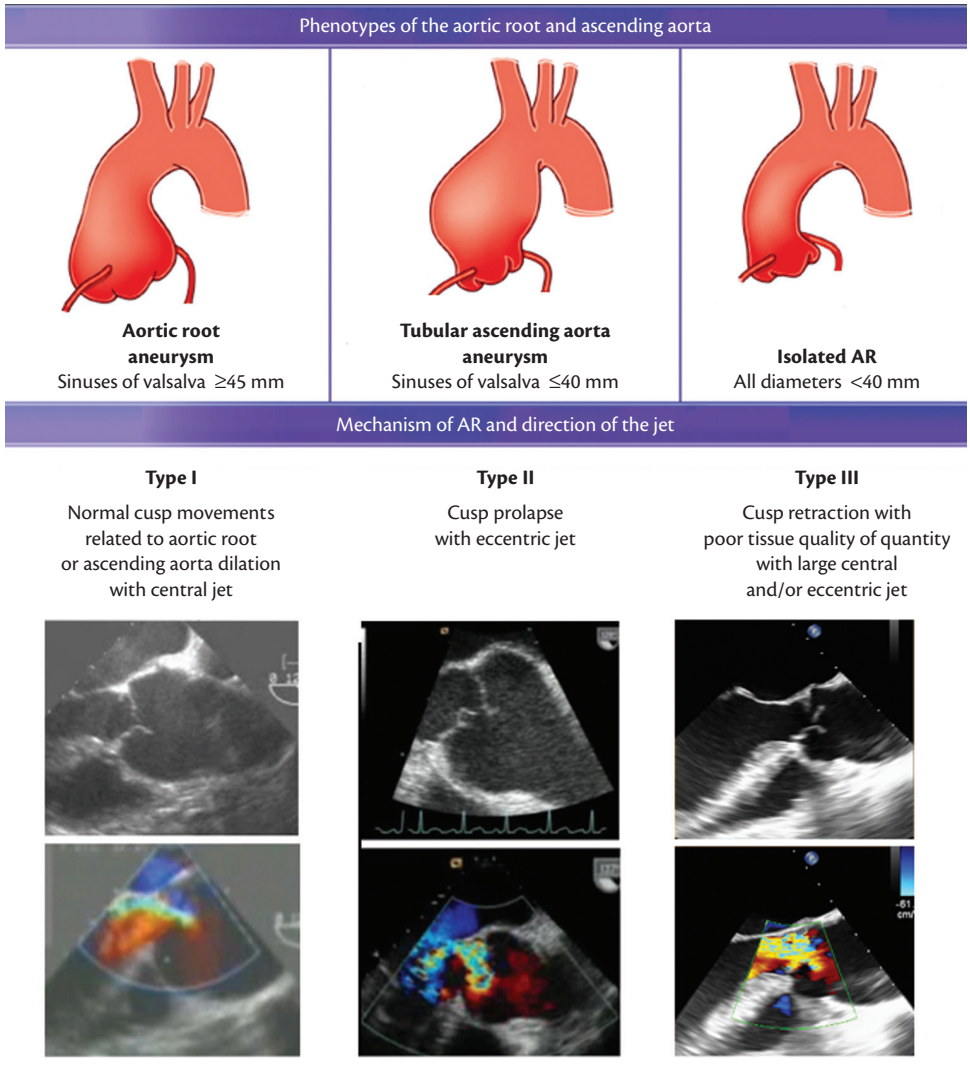

Figure 35.2.1 Definition of aortic root and ascending aortic phenotypes and mechanisms of aortic regurgitation (AR) (echocardiographic view) and direction of the regurgitant jet (Doppler view).

pressure (i.e. decreased aortic diastolic pressure) and increased oxygen demand. Sudden death is rare.

Physical examination

Exaggerated arterial pulsations are related to the increased forward stroke volume and diastolic flow reversal. Widened pulse pressure is the main clinical sign for quantifying chronic AR. The classic peripheral signs of severe AR are the Corrigan's pulse of the water hammer type with abrupt distension and quick collapse at the level of finger nails; Musset's sign with movements of the head (i.e. head bobbing) following exaggerated carotid pulsations; and Duroziez's sign with systolic and diastolic bruit heard at the level of femoral arteries. LV apical impulse is enlarged and displaced leftwards because of the LV dilatation. The holodiastolic murmur is at its maximum at the left sternal border, best heard in the sitting, forward-bended position. It is typically blowing, holodiastolic with an early peak and decrescendo. It is frequently associated with a mesosystolic murmur caused by the increased stroke volume. Other signs of severe AR are an apical diastolic low-pitched rumble (Austin Flint) due to a jet directed towards the anterior leaflet causing vibrations and a mesosystolic sound ('pistol shot') heard at the level of femoral arteries. The second aortic sound may be louder in the case of aortic root aneurysm. When LV decompensation occurs, the pulse pressure narrows and the third heart sound may be heard at the apex.

In acute AR, patients are tachycardic and could present with clinical signs of pulmonary oedema and cardiac shock. The diastolic murmur and peripheral signs are attenuated because the pulse pressure is narrow.

Electrocardiography and chest radiograph

LV hypertrophy is the main feature of AR.

Cardiomegaly is the main abnormality found on chest X-ray in chronic AR. Signs of left heart failure are frequent in acute AR and are observed at an advanced stage in chronic AR. Although specific, the chest X-ray is not a sensitive examination to detect ascending aortic aneurysm.

Echocardiography

Echocardiography (transthoracic echocardiography/transoesophageal echocardiography (TOE)) is the key examination to describe valve anatomy, quantify AR, evaluate regurgitation

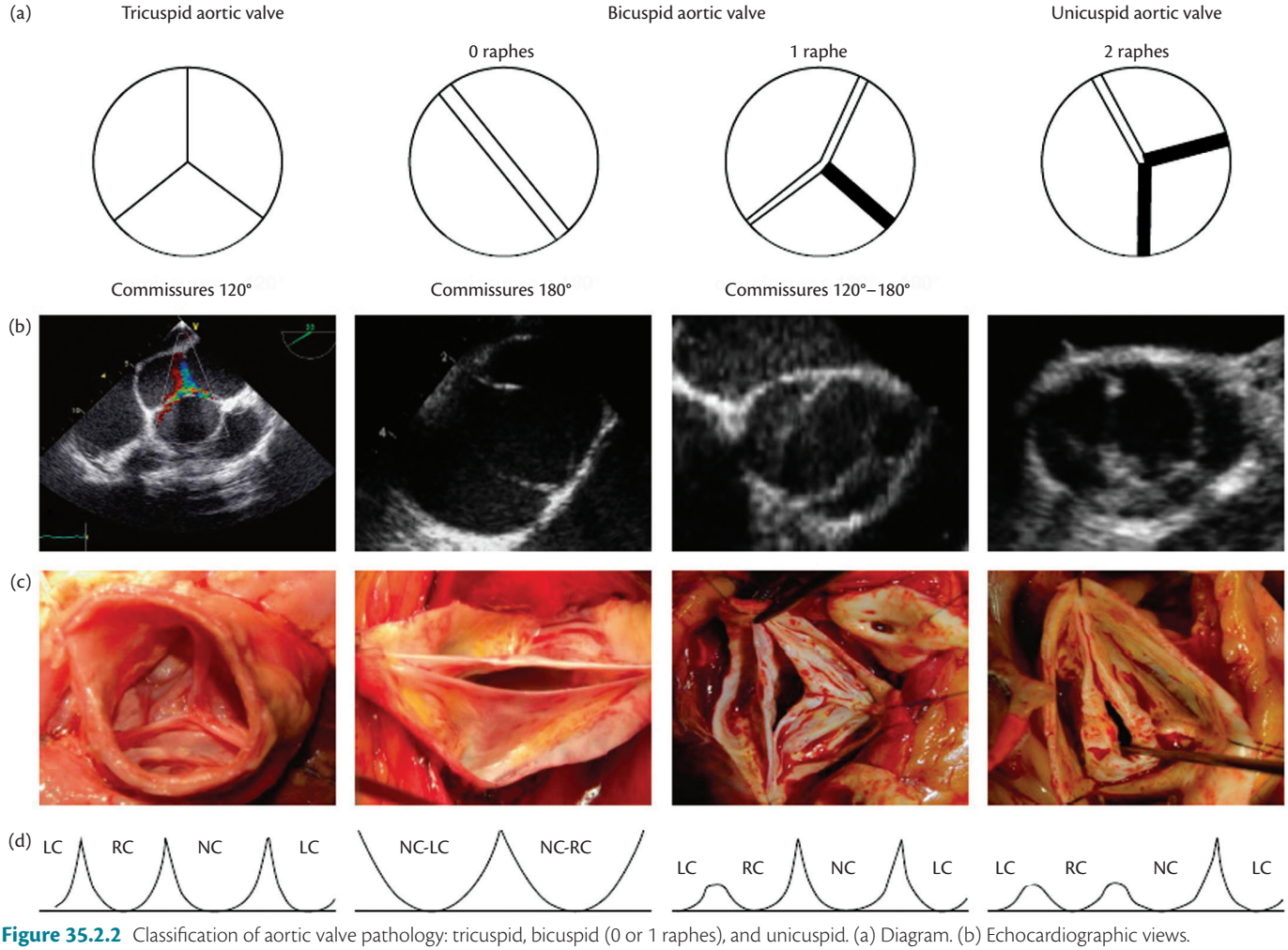

Figure 35.2.2 Classification of aortic valve pathology: tricuspid, bicuspid (0 or 1 raphes), and unicuspid. (a) Diagram. (b) Echocardiographic views. (c) Pathology specimens. (d) schematic illustration of the cusp insertion. LC, left coronary; NC, non-coronary; RC, right coronary.

mechanisms, define the morphology of the aorta, and determine the feasibility of valve repair.

The valve pathology should be precisely determined (ordered by its frequency): tricuspid, bicuspid (no or one raphe), unicuspid (two raphes), or quadricuspid. Bicuspid aortic valves should be named according to the fused cusp, for example, R–L for the most common type of right–left fusion and precise the commissural orientation from 120° to 180°. The presence of one or two raphes, even if incomplete, makes the valves anatomically bicuspid or unicuspid[9, 12] (Figure 35.2.2).

AR jet analyses should provide the direction of the jet in the long-axis view (central or eccentric) and its origin in the short-axis view (central or commissural). The mechanism of AR can be classified in three groups, according to the valve lesions, following the same principle as for mitral regurgitation: normal cusps movement related to ascending aortic dilation with central jet (type 1); cusp prolapse with eccentric jet (type 2); or retraction with poor cusp tissue quality and large central or eccentric jet (type 3)[13, 14] (Figure 35.2.1). If aortic valve repair or a valve-sparing intervention is considered, TOE may be performed preoperatively to define the anatomy of the cusps and assess the reparability of the valve. TOE in the operating room is mandatory in patients with aortic valve repair to assess the functional results and identify patients who are at risk of early recurrence of AR.[13]

AR quantification by echocardiography should follow an integrated approach considering all qualitative, semiquantitative, and quantitative parameters.[15] For details, see Chapter 35.1. If echo quantification is equivocal, magnetic resonance imaging (MRI) should be used to estimate regurgitant fraction by calculating forward and backward flow in the ascending aorta.

Determining LV function and dimensions is essential. Indexing LV diameter for body surface area (BSA) is recommended, especially in patients with small body size (BSA <1.68 m^2).[16] New parameters obtained by three-dimensional echocardiography, tissue Doppler, and strain rate imaging may be useful[17,18] mainly when the ejection fraction is less than 55% as subtle LV dysfunction can be obtained and can help in making the decision for surgery.

The aortic root and ascending aorta should be measured in two-dimensional mode at four levels: annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta. Measurements are taken on the parasternal long-axis view from leading edge to leading edge at end-diastole except for the aortic

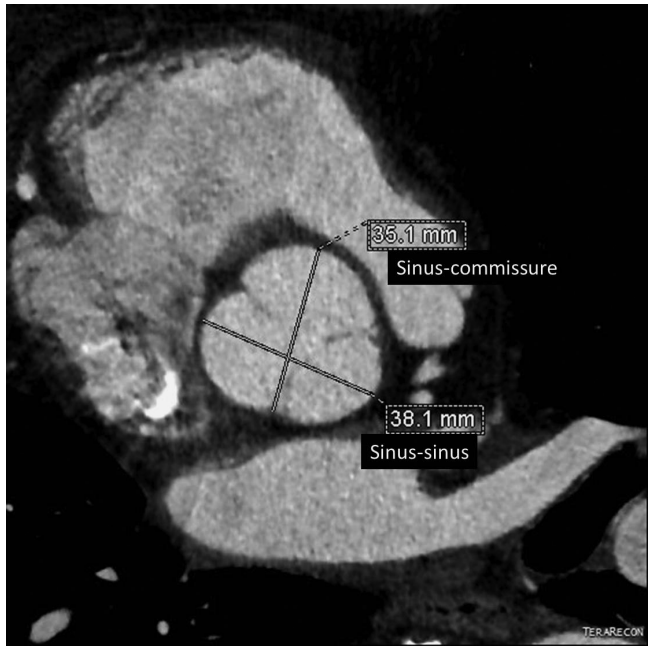

Figure 35.2.3 CT measurements of aortic root diameters: sinus-to-sinus measurement correlates more closely to long-axis leading edge-to-leading edge echocardiographic diameters.

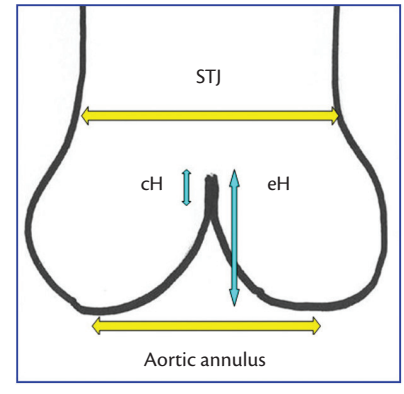

Figure 35.2.4 Definition of coaptation height (cH) and effective height (eH) of aortic valve cusps. STJ, sinotubular junction.

annulus, which is measured in end-systole.[15, 19] Since it will have surgical consequences, it is important to differentiate the three phenotypes (Figure 35.2.1) of (1) aortic root aneurysms (sinuses of Valsalva >45 mm); (2) tubular ascending aneurysm (sinuses of Valsalva <40–45 mm); and (3) isolated AR (all diameters <40 mm).[14] Root aneurysms need to have a total aortic root replacement, with or without preservation of the native aortic valve but definitely with coronary reimplantation, while tubular ascending aortic aneurysms require a supra-commissural tube graft replacement without coronary reimplantation. The ascending aorta does, of course, not need to be replaced in cases of isolated AR.

Other valves should be examined since mitral valve disease may be associated in particular with Marfan syndrome or rheumatic AR.

Computed tomography and magnetic resonance imaging

MRI can be used to quantify regurgitant fraction when echocardiographic measurements are equivocal.

In patients with aortic dilatation, gated multislice computed tomography (CT) is recommended to assess the maximum diameter. MRI can be used for follow-up but indications for surgery should preferably be based on CT measurements. On CT and MRI different methods of aortic measurements have been reported. They may result in diameter discrepancies of 2–3 mm and could influence therapeutic management.[20, 21] To improve reproducibility, it is recommended to measure diameters using the inner–inner edge technique at end-diastole on the strictly transverse plane by double-oblique reconstruction perpendicular to the axis of blood flow of the corresponding segment. One should precisely report on minimum and maximum diameter at annulus, sinus of Valsalva, sinotubular junction, tubular ascending aorta, and aortic arch level as well as comment on the presence or absence of coarctation, particularly in patients with bicuspid valves. Maximum root diameter should be taken from 'sinus to sinus' compared to 'sinus to commissure' diameter since it correlates more closely to long-axis leading edge to leading edge echo maximum diameters[22] (Figure 35.2.3).

Natural history

Patients with acute severe AR most frequently caused by infective endocarditis and aortic root dissection, have a poor prognosis without surgery due to their haemodynamic instability. Patients with chronic severe AR and symptoms also have a poor long-term prognosis. Once symptoms become apparent, mortality in patients without surgical treatment may be as high as 10–20% per year.[23]

In asymptomatic patients with severe chronic AR and normal LV function, the likelihood of adverse events is low. However, when the LV end-systolic diameter (LVESD) is 50 mm or larger, the probability of death, symptoms, or LV dysfunction is reported to be 19% per year.[23]

The natural history of ascending aortic and root aneurysms has been best defined for Marfan syndrome.[24] The strongest predictors of death or aortic complications are root diameter greater than 50 mm and in cases of family history of acute cardiovascular events (aortic dissection, sudden death) for diameters above 45 mm.[24, 25] Uncertainty exists as how to deal with patients who have other systemic syndromes with connective tissue disease associated with ascending aortic dilation, including familial forms. In these cases, it appears reasonable to assume a prognosis similar to patients with Marfan syndrome and treat them accordingly. When there is a mutation of the *TGFBR1*or *TGFBR2* gene, including in Loeys–Dietz syndrome, aneurysms grow even faster than marfanoid aneurysms, resulting in death at a mean age of 26 years.[26]

In general, patients with bicuspid aortic valves have been previously felt to be at increased risk of dissection. More recent evidence indicates that this hazard may be related to the high prevalence of aortic dilatation.[27] However, despite a higher aortic

diameter growth rate, it is currently less clear whether the likelihood of aortic complications is increased compared to patients with a tricuspid aortic valve of similar aortic size.[28, 29] In bicuspid aortic valves, tubular ascending aorta dilatation is the most common pattern and exhibits the fastest growing rate, irrespective of valve morphology and function. Sinuses growth rate is slower. Baseline aortic diameter does not proportionally predict the progression rate. Aortic dilatation progresses equally fast in patients with bicuspid aortic valves and Marfan syndrome, but a significantly higher patient proportion with a bicuspid aortic valve does not progress at all.[30]

Results of surgery

Treatment of isolated AR has traditionally been valve replacement. In the past 20 years, repair strategies for the regurgitant aortic valve have been developed for tricuspid aortic valves and congenital anomalies, particularly bicuspid valves.[31, 32, 34] When there is an associated aneurysm of the aortic root, and the native tricuspid or bicuspid valve can be preserved, valve-sparing aortic root replacement is increasingly employed. In experienced hands, it can be performed without excess operative mortality compared to conventional composite valve and graft replacement (Bentall operation) but in both procedures, coronary ostia need reimplantation.[35, 36] There is increased evidence that valve-sparing root replacement provides good long-term results with low rates of valve-related events as well as better quality of life.[37–40] It can be performed with similar results either through a reimplantation of the aortic valve into a Dacron graft or remodelling of the aortic root with a scallop graft replacing the sinuses of Valsalva.[41] However, if the aortic annulus during these operations is found to be dilated (>25–28 mm), it is recommended to favour a valve-sparing technique which also provides an aortic annuloplasty either through the proximal suture of the anchored tube in the reimplantation technique or through a separate circumferential annuloplasty when using the remodelling technique.[42–46] The reimplantation of the aortic valve into a Dacron tube should favour grafts designed with sinus functionality.[47] Intraoperative effective height assessment of the cusp reduces residual prolapse and reoperation (Figure 35.2.4).[48, 49]

In cases of isolated tubular ascending aneurysm, a supracommissural ascending aortic replacement can be performed with valve repair or replacement when root size is preserved (mid sinuses of Valsalva and sinotubular junction <40–45 mm) and coronary ostia are below the sinotubular junction.[50] Obviously, in this situation coronary reimplantation can be avoided.

In experienced hands, isolated aortic valve repair can be performed with satisfactory results in bicuspid and tricuspid valves. A combination of valve repair and annuloplasty improves the results.[44, 46, 51, 52]

In current practice, valve replacement is still the current standard but in the presence of AR or aneurysm of the ascending aorta (or both), a preoperative multidisciplinary heart team discussion is recommended to evaluate repairability of the aortic valve and the indication for valve repair or valve-sparing surgery in contrast to valve replacement. The choice of either therapy should be balanced by feasibility of the repair, age and life expectancy of the patient, as well as experience of the heart team. Operative mortality is low (1–4%) in isolated aortic valve surgery, both for replacement and repair.[53, 54] Mortality increases with advanced age, impaired LV function, and the need for concomitant coronary artery bypass grafting (CABG), where it ranges from 3% to 7%. The strongest predictors of operative mortality or heart failure after surgery are older age, higher preoperative functional class, LV ejection fraction less than 50%, and LVESD greater than 50 mm.[55] Criteria for immediate and long-term results after valve-sparing procedures (Figure 35.2.4) are residual AR less than or equal to 1, coaptation height of 4 mm or greater, and effective height of 9 mm or greater.[52, 56] Aortic root surgery with reimplantation of coronary arteries has a slightly higher mortality than isolated valve surgery. Nevertheless, multicentre evaluation of valve-sparing root replacement versus composite valve and graft showed similar operative mortality.[36] Mortality increases in emergency procedures for acute dissection. All biological and mechanical prostheses but also aortic valve repair and valve-sparing aortic root surgery are associated with the long-term risk of valve-related complications (Chapter 35.9).

Indications for surgery

In symptomatic acute severe AR, urgent/emergent surgical intervention is indicated.

In chronic severe AR, the goals of treatment are to prevent death, to relieve symptoms, to prevent the development of heart failure, and to avoid aortic complications in patients with aortic aneurysms

On the basis of robust observational evidence, recommended surgical indications are as follows (Table 35.2.1 and Figure 35.2.5).

Symptom onset is an indication for surgery in patients with severe AR. Surgery should also be performed in patients with LV dysfunction or marked LV dilation after careful exclusion of other possible causes. Although in these patients postoperative outcome is worse than in those operated on at an earlier stage, improvement of symptoms and acceptable long-term survival can be achieved.[54, 56–59]

Surgery is indicated in asymptomatic patients with severe AR and impaired LV function (ejection fraction <50%) and should be considered if LV end-diastolic diameter (LVEDD) is 70 mm or greater, or if LVESD is 50 mm or greater.[55] These cut-offs for LV dimensions should only be applied to adults of average size but may be too large for patients with a small body size. In this case, LVESD should be related to BSA and a cut-off of 25 mm/m^2 BSA appears to be more appropriate.[16] Indexed LVESD should not be used in the other patients, particularly not when they are obese.

Earlier intervention in asymptomatic patients does not result in better outcomes as long as individuals who do not undergo surgery are followed-up very closely.[60] In this context, exercise testing in asymptomatic patients should be performed to identify borderline symptomatic patients and to reduce the risk of missing these patients who would benefit from surgery. In truly

Table 35.2.1 Indications for surgery in severe aortic regurgitation and aortic root disease (irrespective of the severity of aortic regurgitation)

Indications for surgery	Class[a]	Level[b]
Severe aortic regurgitation		
Surgery is indicated in symptomatic patients[55, 58, 59, 77]	I	B
Surgery is indicated in asymptomatic patients with resting LVEF ≤50%[55, 59]	I	B
Surgery is indicated in patients undergoing CABG or surgery of the ascending aorta, or of another valve	I	C
Heart team discussion is recommended in selected patients[c] in whom aortic valve repair may be a feasible alternative to valve replacement	I	C
Surgery should be considered in asymptomatic patients with resting ejection fraction >50% with severe LV dilatation: LVEDD >70 mm, or LVESD >50 mm (or LVESD >25 mm/m^2 BSA in patients with small body size)[55, 57]	IIa	B
Aortic root or tubular ascending aorta aneurysm[d] (irrespective of the severity of aortic regurgitation)		
Aortic valve repair, using the reimplantation or remodelling with aortic annuloplasty technique, is recommended in young patients with aortic root dilation and tricuspid aortic valves, when performed by experienced surgeons	I	C
Surgery is indicated in patients with Marfan syndrome, who have aortic root disease with a maximal ascending aortic diameter ≥50 mm	I	C
Surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter:	IIa	C
◆ ≥45 mm in the presence of Marfan syndrome and additional risk factors,[e] or patients with a *TGFBR1* or *TGFBR2* gene mutation (including Loeys–Dietz syndrome)[f]		
◆ ≥50 mm in the presence of a bicuspid valve with additional risk factors[e] or coarctation		
◆ ≥55 mm for all other patients		
When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥45 mm, particularly in the presence of a bicuspid valve[g]	IIa	C

BSA, body surface area; CABG, coronary artery bypass grafting; CT, computed tomography; ECG, electrocardiogram; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter.

[a] Class of recommendation.

[b] Level of evidence.

[c] Patients with pliable non-calcified tricuspid or bicuspid valves who have a type I (enlargement of the aortic root with normal cusp motion) or type II (cusp prolapse) mechanism of aortic regurgitation.

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

[e] 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).

[f] A lower threshold of 40 mm may be considered in women with low BSA, in patients with a *TGFBR2* gene mutation, or in patients with severe extra-aortic features.[62]

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

asymptomatic patients, regular excellent imaging quality and confirmation of normal LV function as well as assessment of physical condition are crucial to identify the right time for surgery. A rapid worsening of ventricular parameters on serial testing are reasons to consider surgery.

Medical evidence does not differentiate between the risk of aortic root and ascending aortic aneurysm and this represents a limitation of current guidelines. In patients with a dilated aorta, the rationale for surgery has been best defined in patients with Marfan syndrome and root dilation. In patients with aortic diameters borderline for aortic surgery, the individual family history, the patient's age, and the anticipated risk of the procedure should be taken into consideration. In patients with Marfan syndrome, *TGFBR1* or *TGFBR2* gene mutations, including Loeys–Dietz syndrome, or connective tissue disease, surgery should be performed with a dilation of 50 mm or greater. A more aggressive approach is not justified by clinical evidence in all patients. However, in the presence of risk factors (family history of dissection, personal history of spontaneous vascular dissection, increase in size ≥3 mm/year in repeated examinations using the same electrocardiogram-gated technique and confirmed by another technique,[61] severe AR, systemic hypertension, or desire to become pregnant), surgery should be considered for a root diameter of already 45 mm or greater[24] In patients with a *TGFBR1* or *TGFBR2* mutation (including Loeys–Dietz syndrome), surgery should be considered at a maximal aortic diameter of at least 45 mm. In the latter group, females with a low BSA, presence of a *TGFBR2* mutation, or patients with severe extra-aortic features appear to be at particularly high risk and surgery may be considered already at a lower threshold of 40 mm.[62] Patients with marfanoid manifestations due to connective tissue disease, without complete Marfan criteria, should be treated as Marfan patients.

In individuals with a bicuspid aortic valve and no significant valve regurgitation, surgery should be considered with aortic diameters of at least 55 mm or at least 50 mm in the presence of additional risk factors (family history, systemic hypertension, severe AR, coarctation of the aorta or increase in aortic diameter >3 mm/year in repeated examinations, using the same technique and confirmed by another technique, desire to become pregnant). Aortic diameters should be indexed for individuals of small body size particularly in the presence of Turner syndrome where the aorta is considered as aneurysmal when 25 mm/m^2

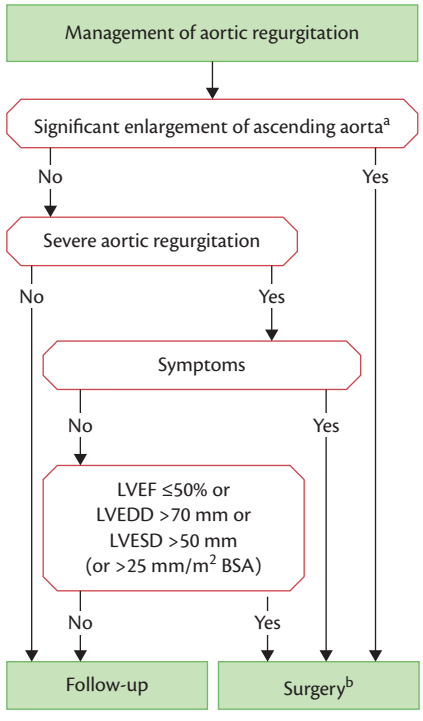

Figure 35.2.5 Management of aortic regurgitation. AR, aortic regurgitation; BSA, body surface area; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter.
[a] See Table 35.2.1 of recommendations on indications for surgery in severe aortic regurgitation and aortic root disease for definition.
[b] Surgery should also be considered if significant changes in LV or aortic size occur during follow-up (see Table 35.2.1 of recommendations on indications for surgery in severe aortic regurgitation and aortic root disease).

or larger. Threshold diameter for intervention is 27 mm/m^2 but a decision should be taken case by case after multidisciplinary discussion.

In aortic root dilatation of 55 mm or greater, surgery should be performed irrespective of the degree of AR and type of valve pathology.[63] Patients with an aneurysm and a tricuspid valve with severe uncontrolled hypertension (under triple therapy) may be considered for surgery with an aortic diameter of 50 mm or more.

For patients who have an indication for aortic valve surgery, lower thresholds can be used for concomitant aortic root or tubular ascending aorta replacement (45 mm) depending on age, BSA, aetiology of valvular disease, presence of a bicuspid aortic valve, and intraoperative shape and thickness of the ascending aorta.

The choice of the surgical procedure should be adapted to the experience of the team, the presence of an aortic root aneurysm, characteristics of the cusps, life expectancy, and desired anticoagulation status. Patients, in whom the heart team has identified the aortic valve to be repairable, should be referred to appropriate surgical teams for the procedure.

In elderly patients who face high risk for aortic valve surgery and in whom the AR is not a result of endocarditis or aortic root dilation, preliminary data exist on transcatheter aortic valve implantation.

Medical therapy

Vasodilators and inotropic agents may help for short-term symptomatic improvement in patients with severe heart failure before proceeding with urgent aortic valve surgery. In individuals with chronic severe AR who develop symptoms, medical therapy is not the final therapy but can provide symptomatic improvement while patients await surgical treatment. In patients who undergo surgery and suffered from preoperative severe heart failure and hypertension, vasodilators (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs) or carvedilol) are useful if hypertension or LV dysfunction persists postoperatively.[64, 65] A positive effect of these agents or dihydropyridine calcium channel blockers in asymptomatic patients without hypertension in order to delay the need for surgery or improve prognosis is unproven.[66]

In patients with Marfan syndrome, beta blockers or losartan, or both, may slow aortic root dilatation and reduce the risk of aortic complications, and should be considered before and after surgery.[24] By analogy, while there are no studies that provide evidence that medical treatment of a dilated aorta has any effect on the enlargement of the ascending aorta or aortic root in bicuspid aortic valves, it is common clinical practice to also advise beta blocker or losartan therapy, or both, in these patients if the aortic root and/or ascending aorta are dilated.

Although animal studies suggested that selective ARBs have an intrinsic effect on the aortic wall by preserving elastin fibres and preventing aortic dilation, three recent trials comparing losartan versus beta blockers have shown that the use of losartan compared with atenolol did not result in significant differences in the progression of aortic root dilation.[67–69]

Women with Marfan syndrome and an aortic diameter larger than 45 mm are strongly discouraged from becoming pregnant without prior repair because of the high risk of dissection. Although an aortic diameter smaller than 40 mm is rarely associated with dissection, a completely safe diameter does not exist. With an aorta between 40 and 45 mm, previous aortic growth and family history are important for advising pregnancy with or without repair. Although the actual risk of dissection is not well documented in the setting of bicuspid valves, counselling against pregnancy is recommended in the setting of aortic diameters exceeding 50 mm.[70–72]

Physical and sport activity in the presence of a dilated aorta remains a clinical situation where evidence is low but guidelines are very restrictive in order to avoid a catastrophic event.[73] This attitude is clearly justified in the presence of Marfan syndrome or marfanoid manifestations due to connective tissue disease or family risk factors, patients should be restricted from activities involving collision and heavy contact, avoid isometric exercise, and only participate in activities with low intensity, low dynamic, and low static components.

Given the family risk of thoracic aortic aneurysms, screening and referral for genetic testing of the patient's first-degree relatives with appropriate imaging studies is indicated in Marfan patients. For patients with bicuspid valves it is appropriate to have

an echocardiographic screening of first-degree relatives and, in case of inconclusive outcomes, MRI scanning.

Serial testing

Patients with mild to moderate AR can be reviewed on a yearly basis and echocardiography performed every 2 years. All asymptomatic patients with severe AR and normal LV function should be seen for follow-up at 6 months after their initial echocardiographic examination. If LV diameter or ejection fraction, or both, show significant changes, or come close to the threshold for surgery, follow-up should be continued at 6-month intervals. The clinical status should also be carefully assessed at each clinical examination and exercise testing performed to elicit symptoms. In inconclusive cases, brain natriuretic peptide (BNP) can also be used for follow-up: elevation of BNP during follow-up has been related to earlier signs of LV dysfunction.[74] Patients with stable clinical and echocardiographic parameters should be followed annually.

If the ascending aorta is dilated (>40 mm), it is recommended to perform a gated CT or cardiovascular magnetic resonance scan with injection as a reference of aortic root diameter. It allows precise measurement as well as concomitant coronary evaluation.

Follow-up of aortic diameters prior to an operation can be performed either by echo on a yearly basis or gated MRI avoiding radiation. Any increase in diameter by 3 mm or more should be validated by a gated CT compared to the CT of reference if available.

Special patient populations

If AR requiring surgery is associated with severe mitral regurgitation, both should be addressed during the same operation.

In patients with moderate AR who undergo CABG or mitral valve surgery, the decision to treat the aortic valve is controversial[75] as data show that progression of moderate AR is very slow in patients without aortic dilatation. The heart team should decide based on the aetiology of AR, other clinical factors, life expectancy of the patients, and operative risk preoperatively, according to life expectancy of the patients and operative risk.

More detailed information about patients with Marfan syndrome can be found in the ESC Guidelines on grown-up congenital heart disease.[76]

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Chapter 35.3 Aortic stenosis

Introduction

Aortic stenosis (AS) is now the most common valve disease requiring intervention in Europe and North America[1, 2] and it is increasing in prevalence due to the ageing population. The frequency of aortic valve sclerosis is approximately 25% at 65 years of age, rising to 48% after 75 years, while the frequency of AS is 4–5% in those aged over 65.[3, 4] AS has become the most common indication for valve surgery as well as catheter intervention for structural heart disease.

Aetiology

AS is most often due to calcification of a normal tricuspid valve or a congenitally bicuspid valve. In surgical series, bicuspid valves account for approximately 50%, tricuspid valves 30–40%, and rare unicuspid valves less than 10%.[5] However, it has to be emphasized that this distribution is highly dependent on the age of the study population. The frequency of AS observed on bicuspid valves is higher in patients aged less than 60, and then the trend is inverted afterwards. Calcification begins at the base of the cusps and progresses towards the edges, while the commissures remain open (Figure 35.3.1). The 'degenerative' aetiology accounts for 80% of cases in Western countries followed by rheumatic disease, which is characterized by commissural fusion and fibrosis, with retraction and stiffening of the cusps.[1] Other rare causes are familial hypercholesterolaemia, hyperuricaemia, hyperparathyroidism, Paget disease, ochronosis, Fabry disease, lupus erythematosus, and drug-induced diseases. In young adults, congenital aortic stenosis predominates.

Pathophysiology

Calcific 'degenerative' AS has long been considered as a passive and degenerative process ('wear and tear phenomenon') but recent data has challenged this concept—in fact, AS is an active, complex, and highly regulated pathobiological process including chronic inflammation, lipoprotein deposition, renin–angiotensin system activation, osteoblastic transformation of valvular interstitial cells, and active calcification[6–10] (Figure 35.3.2). The association with traditional atherogenic cardiovascular risk factors such as hypertension, current smoking, diabetes, cholesterol levels, and histopathological parallels have led to the hypothesis that AS is primarily an atherosclerotic-like process.[3, 4, 7–9] However, there are also important dissimilarities suggesting a more complicated picture. Several specific cell-signalling pathways regulating valvular calcification such as BMP2/RANK/runx2/Cbfa1 seem to be involved. Identification of familial clusters and recent findings implicating genetic polymorphisms of the vitamin D receptor and mutations such as in the *NOTCH1* gene[11, 12] in bicuspid aortic valves suggest that genetic factors may also influence valve pathogenesis.[13] These findings indicate that 'degenerative' may not be the most accurate term for this process, although it remains in common usage.

In addition, in patients with bicuspid valves, tissue abnormality is not only localized to aortic cusps but also to the wall of the ascending aorta leading to the development of aortic root and ascending aortic aneurysms.

Coronary artery disease (CAD) is present in 30% of patients with mild to moderate AS and 50% with critical AS, and of course again is age dependent.

Normal aortic valve area is 3–4 cm^2.[14] A gradient at rest between the left ventricle (LV) and aorta begins to appear once the valve area is less than 1.5 cm^2. AS is considered severe when the area is less than 1 cm^2 or, more accurately, 0.6 cm^2/m^2 body

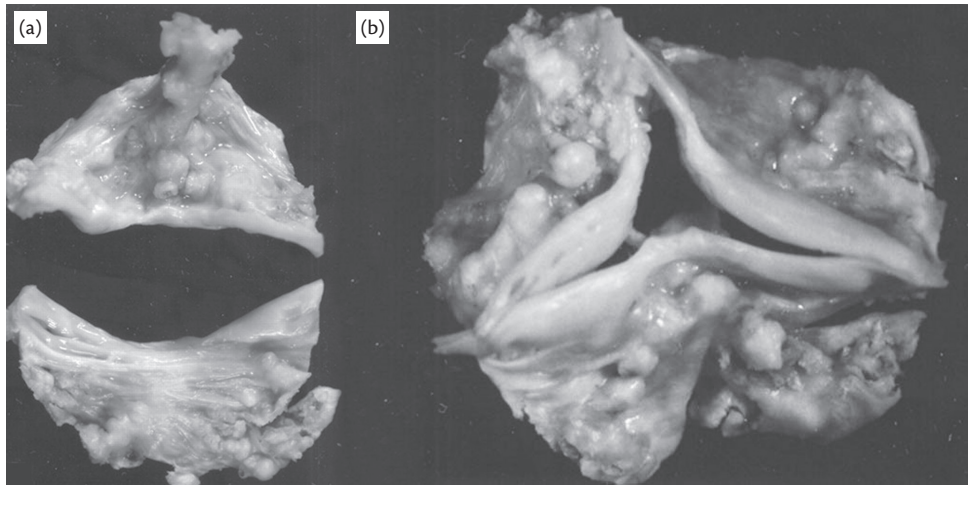

Figure 35.3.1 Aortic valves explanted during aortic valve replacement.
(a) Congenitally bicuspid valve;
(b) tricuspid valve.
Reproduced with permission from Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 2005;111:920–5.

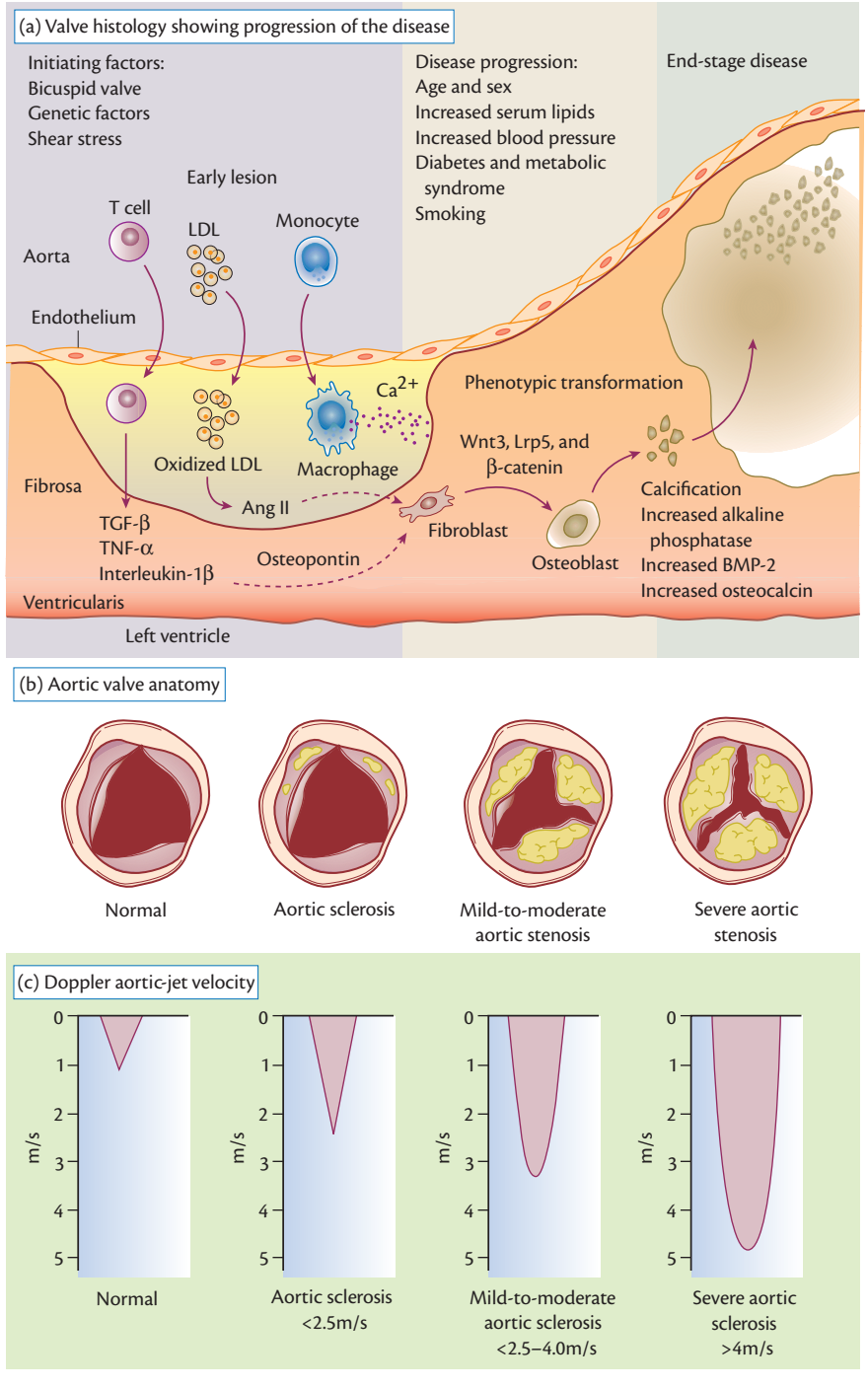

Figure 35.3.2 Disease progression in calcific AS, illustrating changes in aortic valve histological features, leaflet opening in systole, and Doppler velocities. In (a), the histology of the early lesion is characterized by a subendothelial accumulation of oxidized low-density lipoprotein (LDL), production of angiotensin (Ang) II, and inflammation with T lymphocytes and macrophages. Disease progression occurs by several mechanisms, including local production of proteins, such as osteopontin, osteocalcin, and bone morphogenetic protein 2 (BMP-2), which mediate tissue calcification; activation of inflammatory signalling pathways, including tumour necrosis factor alpha (TNF α), tumour growth factor beta (TGF-β), the complement system, C-reactive protein, and interleukin-1β; and changes in tissue matrix, including the accumulation of tenascin C, and up-regulation of matrix metalloproteinase 2 and alkaline phosphatase activity. In addition, leaflet fibroblasts undergo phenotypic transformation into osteoblasts, regulated by the Wnt3–Lrp5–β-catenin signalling pathway. Microscopic accumulations of extracellular calcification (Ca^{2+}) are present early in the disease process, with progressive calcification as the disease progresses and areas of frank bone formation in end-stage disease. The corresponding changes in aortic valve anatomy are viewed from the aortic side with the valve open in systole (b) and in Doppler aortic-jet velocity (c).
Adapted with permission from Otto CM. Calcific aortic stenosis—time to look more closely at the valve. N Engl J Med 2008;359:1395–8.

surface area (BSA) (see 'Evaluation'). The obstruction develops gradually. Bicuspid valves are less efficient than tricuspid valves at distributing mechanical stress, leading to the more rapid development of stenosis. The obstruction of the valve imposes a pressure overload on the LV, which subsequently causes the development of concentric hypertrophy at rates that vary individually. Ventricular hypertrophy is a key adaptive mechanism to counter pressure overload as it normalizes wall stress. However, it also has adverse consequences: an increase in the total collagen volume of the myocardium; a reduction of LV compliance leading to a limited preload reserve; and myocardial ischaemia with symptoms of angina, which may be present even when coronary disease is not, and is caused by the combination of increased myocardial oxygen demand and limited coronary flow.[15] LV systolic performance may be impaired (even if contractility is normal) due to afterload mismatch, leftwards shift of the ventricular preload on the Starling curve, or asynchrony of the temporal sequence of contraction. In addition, reduced systemic arterial compliance is a frequent occurrence in elderly patients with AS and independently contributes to increased afterload and decreased LV function. Late in the course of the disease, cardiac output, and therefore the transvalvular gradient, declines, whereas the pressures in the left atrium and

pulmonary artery rise. In advanced stages of disease, secondary pulmonary hypertension may result in right heart failure.

Evaluation

History

Frequently, the diagnosis is made when a systolic murmur is detected during a routine physical examination or on an echocardiographic examination for another reason. AS is gradually progressive and symptoms usually appear between the second and fourth decade in rheumatic AS, the fifth and sixth decade in patients with bicuspid valves, and the seventh or eighth decade in degenerative aetiology.

The most common initial symptom is exertional dyspnoea or fatigue. Exertional dyspnoea is mostly related to the increased LV end-diastolic pressure due to LV hypertrophy or systolic dysfunction, or both. Angina on exertion is due to an increased oxygen demand by the hypertrophic myocardium, exacerbated by the decrease of flow in the presence of coronary stenoses. It is a poor indicator of coronary disease, as coronary disease may be present in 25% of patients without angina and in 40–80% of those with angina.[16] Syncope, or light-headedness, also occurs on exertion when elevated LV pressures stimulate baroreceptors located in the LV, inducing arterial hypotension, decreased venous return, and bradycardia. Later, dyspnoea progresses to overt heart failure. In advanced stages, secondary pulmonary hypertension may result in right heart failure. In practice, AS may be discovered during attempted diagnosis of unexplained congestive heart failure.

Besides progressive deterioration, acute decompensation may be due to precipitating factors, such as atrial fibrillation, suppressing the atrial systole, which is of utmost importance for the filling of the hypertrophic ventricle. Other factors include fever, anaemia, and endocarditis leading to acute aortic regurgitation (AR) which is poorly tolerated in a small hypertrophic ventricle.

Careful questioning in order to check for the presence of symptoms is critical for proper patient management and must take into account the possibility that patients deny symptoms as they subconsciously reduce their activity. In the elderly, a clear description of symptoms and their onset may be difficult to obtain. These patients may present with atypical symptoms, with fatigue being most common. Breathlessness on exercise may be difficult to interpret in patients with only low physical activity. Finally, symptoms are rather non-specific and may be due to associated disease.

Physical examination

In severe AS, typically the prolonged LV ejection through the narrowed valve orifice yields a slow rising carotid pulse and the reduced stroke volume results in a weak and small amplitude pulse. However, this sign is frequently absent in patients with increased arterial stiffness such as the elderly and is therefore not helpful in the majority of patients seen in current practice. The murmur is related to the pressure gradient and jet velocity. It is crescendo–decrescendo and mid-systolic, with a late peaking sound in severe AS since the maximum gradient occurs later in systole when stenosis becomes severe. It is harsh and rasping at the base and is transmitted to the carotids. It often radiates towards the apex as a high-pitched murmur mimicking mitral regurgitation (MR). The differential diagnosis with MR may be performed on the timing of the murmur which has no early systolic components in AS. The intensity of the murmur is specific to the severity of obstruction but it has a poor sensitivity, since it may be soft if cardiac output is low, as in obese patients, or in patients with lung disease. When the murmur is of high intensity, a thrill may be palpated. In severe AS, the second heart sound may be paradoxically split, or more often single due to the inaudibility of the aortic component related to the rigidity of the thickened cusps. The disappearance of the second aortic sound is specific to severe AS although it is not a sensitive sign. An ejection click may be heard after the first sound at the base in patients with mobile valves, and, unlike the pulmonary clicks, it does not vary with respiration. Finally, a fourth sound is frequent at the apex, related to forceful atrial contraction.

The physical examination may be misleading in patients with low output since there is no slowly rising pulse; the murmur may become softer or even disappear and auscultation could be limited to a soft murmur of functional MR and the third heart sound at the apex.

It has to be emphasized that high blood pressure does not exclude severe AS. As a matter of fact, additional hypertension is frequent in elderly populations with AS.

Chest radiograph

Overall cardiac silhouette and pulmonary vascular distribution are normal unless cardiac decompensation is present. Dilatation of the ascending aorta is frequent in particular in patients with bicuspid aortic valves. Calcification of the valve is found in almost all adults with severe AS but may require fluoroscopy to be detected.

Electrocardiogram

LV hypertrophy, with or without repolarization abnormalities, is seen in approximately 80% of patients with severe AS. Other non-specific signs include left atrial enlargement, left axis deviation, and left bundle branch block. Atrial fibrillation can be seen at a late stage and may otherwise suggest coexisting mitral valve disease or coronary disease.

Echocardiography

Echocardiography is the key diagnostic tool. It confirms the presence of AS, assesses the degree of valve calcification, LV function, and wall thickness; detects the presence of other associated valve disease or aortic pathology; and provides prognostic information.

Doppler echocardiography is the preferred technique for assessing AS severity[14] (Figure 35.3.3).

Assessment of aortic stenosis severity

Figure 35.3.4 and Table 35.3.1 provide a practical stepwise approach for the assessment of AS severity and the definition of severe AS that may require intervention. Transvalvular velocities/gradients and aortic valve area are key parameters for the quantification of AS. In case of additional pathology it has to be

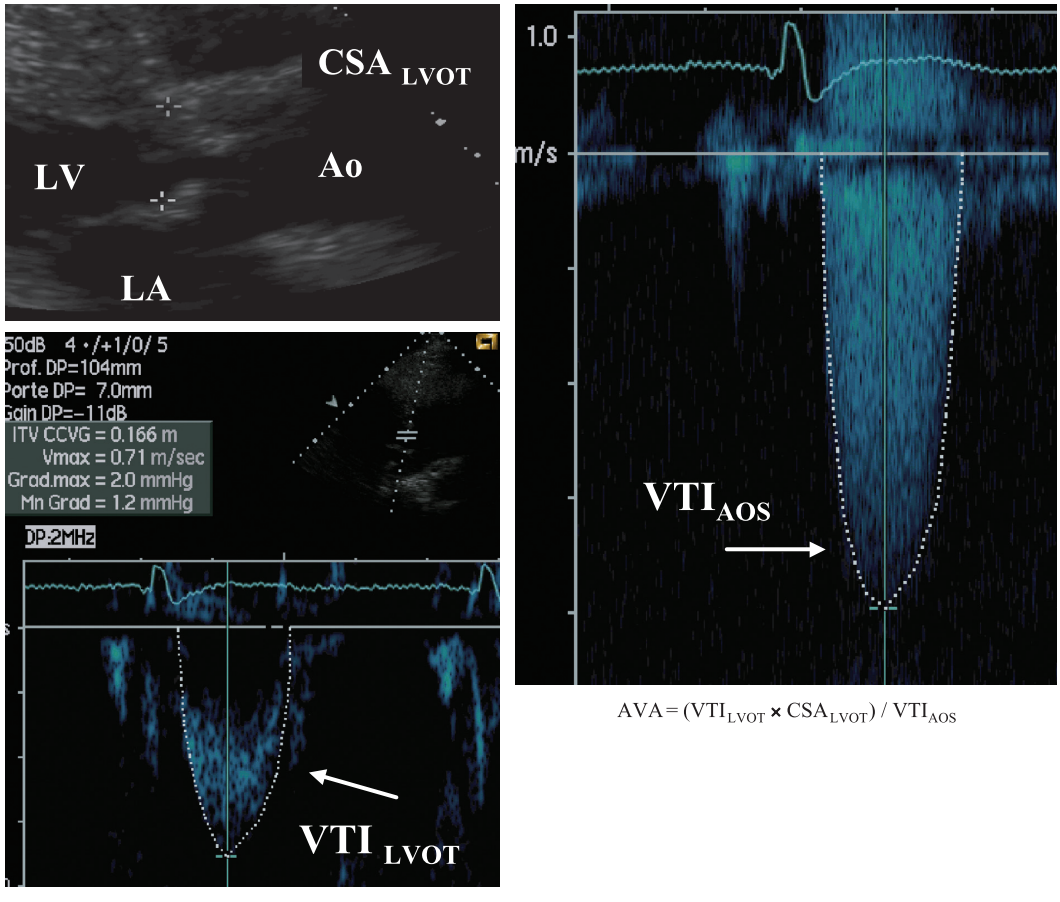

Figure 35.3.3 Calculation of the aortic valve area using the continuity equation. The continuity equation is based on the conservation of energy. Flow through an orifice is equal to the area of this orifice × velocity time integral. Ao, aorta; AOS, aortic stenosis; AVA, aortic valve area; CSA, cross-sectional area; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; VTI velocity time integral.
Courtesy of Dr E. Brochet.

made sure that velocity/gradient occurs at valve level and not subvalvular (subaortic stenosis or hypertrophic cardiomyopathy) or supravalvular. A combination of obstruction at both levels—outflow tract and valve—complicates severity assessment by these parameters.

Transvalvular pressure gradients are flow dependent and measurement of valve area represents, from a theoretical point of view, the ideal way to quantify AS. Nevertheless, valve area measurements are operator dependent and are less robust than gradient estimates in clinical practice. Thus, valve area alone with absolute cut-off points cannot be relied upon for clinical decision-making and should be considered in combination with flow rate, pressure gradients, ventricular function, size and wall thickness, degree of valve calcification and blood pressure, as well as functional status. Although AS with a valve area less than 1.0 cm^2 is considered severe, critical AS is most likely with a valve area less than 0.8 cm^2.[17] Indexing to BSA, with a cut-off value of less than 0.6 cm^2/m^2 BSA may be helpful, particularly in patients with an unusually small BSA.

Severe AS is unlikely if cardiac output (more precisely, transvalvular flow) is normal and there is a mean pressure gradient of less than 40 mmHg—i.e. 'normal-flow, low-gradient AS'.[18–20] In the presence of low flow, however, lower pressure gradients may be encountered in patients with severe AS (low-flow, low-gradient AS), although the majority will still present with 'high' gradients. This has for a long time been recognized in patients with poor systolic LV function. When the mean gradient is less than 40 mmHg, a small valve area does however not definitely confirm severe AS, since mild to moderately diseased valves may not open fully at low-flow states, resulting in a 'functionally small valve area' (pseudo-severe AS).[21] Low-dose dobutamine echocardiography may be helpful in this setting to distinguish truly severe AS from pseudo-severe AS and is therefore recommended in this setting. Truly severe AS shows only small changes in valve area (increase <0.2 cm^2 and remaining <1 cm^2) with increasing flow rate, but a significant increase in gradients (mean gradient >40 mmHg), whereas pseudo-severe AS shows a marked increase in valve area, but only minor changes in gradients.[22] In addition, this test may detect the presence of flow reserve (also termed contractile reserve) (increase >20% of stroke volume), which has prognostic implications because it is associated with a better outcome.[22, 23]

Over recent years, the possible presence of severe AS in patients with valve area less than 1.0 cm^2 and mean gradient less than 40 mmHg, despite preserved LV ejection fraction (LVEF), has become accepted as long as transvalvular flow is reduced (stroke volume index <35 mL/m^2).[17–19, 24, 25] This appears to be typically encountered in the elderly and is associated with small ventricular size, marked LV hypertrophy, and a history of hypertension.[19, 24, 25] This subset of AS patients remains challenging in terms of making the right diagnosis. It has also been

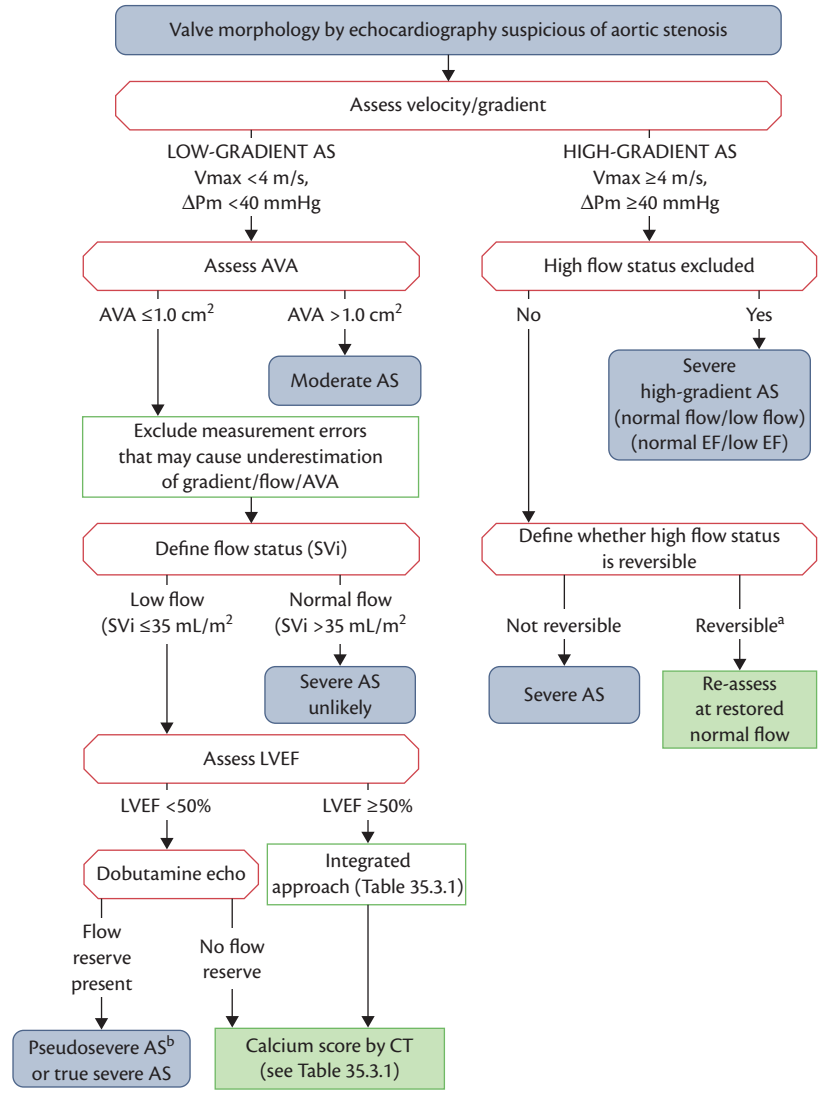

Figure 35.3.4 Stepwise integrated approach for the assessment of aortic stenosis severity. a) High flow may be reversible in settings such as anaemia, hyperthyroidism, and arteriovenous shunts. b) Pseudo-severe AS is defined by an increase to an AVA >1.0 cm^2 with flow normalization. ΔPm, mean transvalvular pressure gradient; AS, aortic stenosis; AVA, aortic valve area; CT, computed tomography; EF, ejection fraction; LVEF, left ventricular ejection fraction; SVi, stroke volume index; V_{max}, peak transvalvular velocity.
Modified from Baumgartner H, Hung J, Bermejo J, et al. Focus update on the echocardiographic assessment of aortic valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2016;18:254–75.

Table 35.3.1 Criteria that increase the likelihood of severe aortic stenosis in patients with aortic valve area (AVA) less than 1.0 cm^2 and mean gradient less than 40 mmHg in the presence of preserved ejection fraction

Criteria	
Clinical criteria	Typical symptoms without other explanation
	Elderly patient (>70 years)
Qualitative imaging data	LV hypertrophy (additional history of hypertension to considered)
	Reduced LV longitudinal function without other explanation
Quantitative imaging data	Mean gradient 30–40 mmHg[a]
	AVA ≤0.8 cm^2
	Low flow (SVi <35 mL/m^2) confirmed by techniques other than standard Doppler technique (LVOT measurement by 3D TOE or MSCT; CMR, invasive data)
	Calcium score by MSCT[b] ◆ Severe aortic stenosis very likely: men ≥3000; women ≥1600 ◆ Severe aortic stenosis likely: men ≥2000; women ≥1200 ◆ Severe aortic stenosis unlikely: men <1600; women <800

3D, three-dimensional; CMR, cardiovascular magnetic resonance; LVOT, left ventricular outflow tract; MSCT, multislice computed tomography; SVi, stroke volume index; TOE, transoesophageal echocardiography.
[a] Haemodynamics measured when the patient is normotensive.
[b] Values are given in arbitrary units using Agatston method for quantification of valve calcification.
Modified from Baumgartner et al. Focus update on the echocardiographic assessment of aortic valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2016;18:254–75.

demonstrated that patients presenting with small valve area, but low gradients despite normal LVEF, may frequently indeed have only moderate AS.[18–20, 26, 27] It must be recognized that there may frequently be reasons other than an underlying severe AS for this combination of measurements: (1) Doppler measurements tend to underestimate flow resulting in eventual underestimation of valve area and erroneous assumption of 'low-flow conditions'[14]; (2) small body size may be present[14]; (3) the cut-offs for gradients are not entirely consistent. It has been demonstrated that to generate a mean gradient of 40 mmHg the aortic valve area has to be closer to 0.8 cm^2 than 1.0 cm^2.[17] Thus, diagnosis of severe AS in this setting requires careful exclusion of these other reasons for such echo findings, before making the decision to intervene. Since such patients are typically elderly with hypertension and other co-morbidities, the evaluation remains challenging even after confirmation of haemodynamic data. LV hypertrophy and fibrosis as well as symptoms or elevation of neurohormones may partially be due to hypertensive heart disease and do not help to identify severe AS patients. Furthermore, it remains unclear how to exclude pseudo-severe AS in this setting although a small study has at least demonstrated a significant portion of patients may indeed have pseudo-severe AS when using dobutamine echo testing.[28] Evaluation of the degree of calcification by multislice computed tomography (MSCT) has gained increasing importance in this setting.[27, 29, 30] It has not only been demonstrated to be related to AS severity in this context but also to outcome.[29] When hypertension is present, the severity should be reassessed when the patient is normotensive.[14]

Additional diagnostic aspects including assessment of prognostic parameters

Exercise stress echocardiography may provide prognostic information in asymptomatic severe AS by assessing the increase in mean pressure gradient and change in LV function during exercise.[31–33] The clinical relevance of this finding has, however, been questioned by more recent data.[34]

Transoesophageal echocardiography (TOE) is less helpful for the quantification of AS, as valve area planimetry becomes difficult in calcified valves[14] but provides additional evaluation of concomitant mitral valve abnormalities. It has gained importance in assessing annulus size—particularly when using three-dimensional echocardiography—and anatomy of LV outflow tract and aortic root before transcatheter aortic valve implantation (TAVI) and in guiding both interventional and surgical procedures.[35–37]

Exercise testing is contraindicated in symptomatic patients with AS. Exercise testing is safe in asymptomatic patients, provided it is performed under the supervision of an experienced physician while monitoring for the presence of symptoms, changes in blood pressure, or ECG changes, or a combination of these.[31, 38] It is recommended in physically active patients for unmasking symptoms and for risk stratification of asymptomatic patients with severe AS.[31, 38] Breathlessness on exercise, however, may be difficult to interpret and is non-specific in patients with low physical activity levels, particularly the elderly.

MSCT and cardiovascular magnetic resonance (CMR) provide additional information on the assessment of the aortic root and ascending aorta including dimensions and extent of calcification. MSCT may be useful in quantifying the valve area and coronary calcification. Computed tomography (CT) has become particularly important for the quantification of valve calcification when assessing AS severity. Both techniques have gained importance for the pre-procedural assessment (primarily before TAVI but also surgery).

CMR may be useful for the detection and quantification of myocardial fibrosis, providing additional prognostic information in symptomatic patients regardless of the presence of CAD.[39]

Natriuretic peptides have been shown to predict symptom-free survival and outcome in normal and low-flow severe AS,[40–44] and may be useful in asymptomatic patients to determine optimal timing of intervention.

Retrograde LV catheterization to assess the severity of AS is nowadays not routinely performed. It may be useful to complement the aortic valve assessment in case of inconclusive non-invasive investigations. Accurate assessment of haemodynamics requires then simultaneous pressure measurement in the left ventricle and the aorta.

Diagnostic work-up prior to TAVI

When TAVI is considered, important additional information to plan the procedure itself is required.

In this context, MSCT is particularly helpful as it not only provides the anatomy and dimensions of the aortic root, size and shape of the aortic valve annulus, its distance to the coronary ostia, the distribution of calcifications, and the number of aortic valve cusps,[35, 36] but also allows within the same examination the in-detail assessment of the access route (dimensions, calcification, thombi, vessel tortuosity for transfemoral TAVI, as well as accessibility of the apex and quality of the ascending aorta and aortic arch for transapical and transaortic TAVI).

CMR—as an alternative technique—is in this context inferior to MSCT with regard to assessment of inner vessel dimensions and calcifications.

Three-dimensional TOE has been demonstrated to provide aortic annulus dimensions but remains more operator and image quality dependent than MSCT.[45] In addition, TOE does not allow the entire comprehensive evaluation including access route. It is, however, an important tool for monitoring the procedure.

Natural history

Calcific AS is a chronic progressive disease. During a long latent period, patients remain asymptomatic.[46–49] The duration of the asymptomatic phase varies widely between individuals. Sudden cardiac death is a frequent cause of death in symptomatic patients, but appears to be rare in the truly asymptomatic (<1% per year),[46–49] even in very severe AS.[52] In asymptomatic patients with severe AS, reported average event-free survival at 2 years ranged from 20% to more than 50%.[46–49] The lower estimates of event-free survival

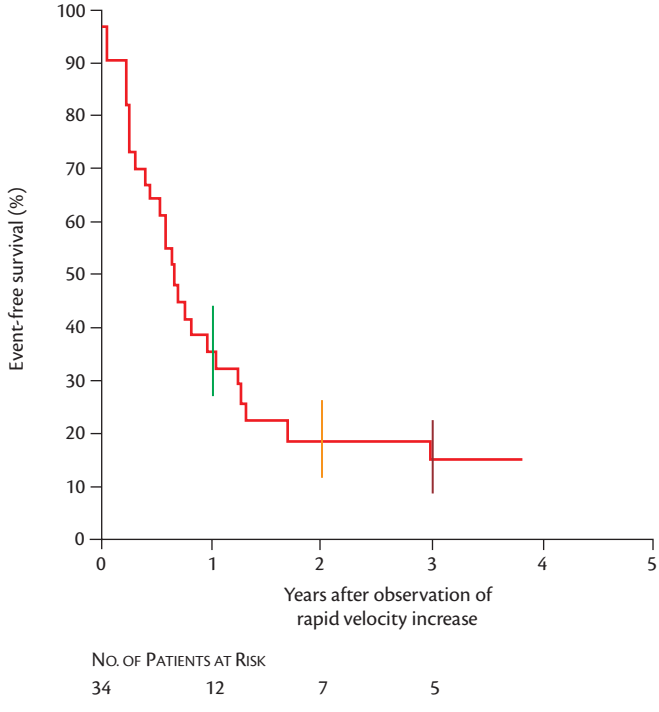

Figure 35.3.5 Outcome of asymptomatic patients with severe AS. Kaplan–Meier analysis of event-free survival among patients with moderate or severe calcification of the aortic valve and a rapid progression in aortic-jet velocity (at least 0.3 m/s within 1 year). The vertical bars indicate the standard errors. Reproduced with permission from Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe asymptomatic aortic stenosis. N Engl J Med 2000;343:611–17.

must, however, be viewed with caution since some patients in these studies underwent surgery without symptoms.

A number of risk factors have been reported in asymptomatic severe AS. However, it has to be emphasized that these factors have, in general, been demonstrated to be predictors of event-free survival, which was driven by development of symptoms requiring intervention in the majority of cases. It remains uncertain whether patients benefit from early surgery before symptom onset in the presence of these risk factors. Predictors of symptom development and adverse outcomes in asymptomatic patients are as follows:

- Clinical: older age, presence of atherosclerotic risk factors.
- Echocardiography: valve calcification, peak aortic jet velocity,[46–49] LVEF,[51] rate of haemodynamic progression[47] (Figure 35.3.5), increase in gradient with exercise,[32, 33] excessive LV hypertrophy,[50] and abnormal longitudinal LV function (in particular global longitudinal strain),[42, 51, 52] pulmonary hypertension.[53–57]
- Exercise testing: unmasking of symptoms during exercise testing in physically active patients, particularly those younger than 70 years, predicts a very high likelihood of symptom development within 12 months. Abnormal blood pressure response and, to an even greater degree, ST-segment depression have a lower positive predictive value than symptoms for prediction of poor outcome.[58]
- Biomarkers: elevated plasma levels of natriuretic peptides, although the precise values are not well defined.[40–44]

As soon as symptoms occur, the prognosis of severe AS is dismal with survival rates of only 15–50% at 5 years.[59]

The data on the spontaneous outcome of patients with low-gradient AS and normal EF remains still controversial. While some studies report outcome to be poor and similar to high-gradient AS,[24, 25] others found better outcomes compared to high-gradient, but worse than in mild and moderate AS[60, 61] or even similar outcomes to moderate AS.[20, 26] The most likely explanation for these discrepancies is the diagnostic dilemma in the patient group with an estimated aortic valve area less than 1.0 cm^2 but a mean gradient less than 40 mmHg in the presence of normal ejection fraction (EF). These patients may have severe or moderate AS. Differences in outcome may therefore primarily be caused by different representation of severe and moderate AS in the study groups. In any case, these data emphasize that a comprehensive evaluation including clinical, echocardiographic, and frequently CT data (calcium score) is crucial in order to correctly identify those patients with indeed severe AS within the 'low-gradient AS' subgroup (Figure 35.3.4 and Table 35.3.1).

Results of intervention

Surgical aortic valve replacement

In contemporary series, operative mortality of isolated aortic valve replacement (AVR) for AS is approximately1–3% in patients younger than 70 years and 4–8% in selected older adults.[1, 62–72]

The following factors have been shown to increase the risk of operative mortality: older age, associated co-morbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, coexisting CAD, and previous bypass or valve surgery. After successful AVR, symptoms and quality of life are in general greatly improved although after a longer time of recovery compared with TAVI. Long-term survival may be close to the age-matched general population in older patients.[47, 73] In younger patients, there is substantial improvement compared to conservative medical therapy; nevertheless a lower survival compared to age-matched controls may be expected. Risk factors for late death include age, co-morbidities, severe symptoms, LV dysfunction, ventricular arrhythmias, and untreated coexisting CAD.

In addition, poor postoperative outcome may result from prosthesis-related complications and suboptimal prosthetic valve haemodynamic performance including patient–prosthesis mismatch. In this respect, it is important to note that new data available on surgical techniques such as aortic root replacement using stentless bioprostheses[74] and surgical aortic valve replacement (SAVR) using sutureless bioprostheses[75] show that they potentially improve haemodynamic outcome. Surgery has been shown to prolong and improve quality of life, even in selected patients over 80 years of age.[69–72] Age, per se, should therefore not be considered a contraindication for surgery. Nevertheless, a

large percentage of suitable candidates previously had not been referred for surgery.[76, 77]

Transcatheter aortic valve implantation

In elderly patients with high or intermediate surgical risk, TAVI has been shown to be feasible (procedural success rates >90%) using transfemoral, transapical, or, less commonly, subclavian or direct transaortic access.[72, 78–88] In the absence of anatomical contraindications, a transfemoral approach is the preferred technique in most centres, although no randomized studies comparing access routes are available. Comparisons based on available data are limited by major differences in patient characteristics. With the development of smaller delivery systems, femoral access has become feasible in the vast majority of patients. Similarly to access route, there are limited data about direct comparisons between the available devices. Increased heart team experiences, better pre-procedural imaging work-up of the patients, and technical improvements of the respective valves and delivery systems over recent years have led to constant improvements in results with regard to early mortality and complication rates. While the 30-day mortality rate ranged from 5% to 15%[78–80, 82–85] in earlier reports, it ranges from 5% to 7% in more contemporary all-comer registries[87, 89] and has come down to 1–2% in the most recent studies of last-generation devices.[90, 91] The main procedure-related complications include stroke (approximately 1–5%), need for new pacemaker (up to 13% for the balloon expandable[81, 94] and up to 40%[85] for the self-expanding systems), and vascular complications (up to 20%).[72, 78] Paravalvular regurgitation had been common, although was reported to be trace or mild in the majority of patients and rarely clinically relevant; more than mild AR has an impact on long-term survival.[82, 84] This remains a concern and requires careful further follow-up and critical evaluation. While rates of major vascular complications could be brought down to 5% with smaller sheath sizes[88, 90] and paravalvular regurgitation, more than mild is reported as rare as 3–4% with latest-generation devices,[88, 90] pacemaker rates may also increase with new device modification and require ongoing close observation.[88, 90] Although severe procedural complications such as annular rupture, coronary obstruction, valve embolization, or ventricular perforation have become very rare (<1% for each),[92] approximately 1–2% of TAVI patients still require immediate cardiac surgery for life-threatening complications in contemporary registries.[81, 89] TAVI provides haemodynamic results, in terms of gradient and valve area, that are often superior to conventional bioprostheses.[72]

Reported 1-year survival for TAVI ranges from 60% to 85% in surgical high-risk patients, largely depending on the severity of comorbidities,[72, 78, 79, 82, 86, 92–94] and reaches 95% in intermediate-risk patients.[72] The improvement of health status and quality of life at 1 year is comparable to that achieved by SAVR but emerges more rapidly due to the less invasive nature of the procedure.[72, 92] The long-term durability of these valves still undergoes careful assessment, although 5-year results have shown no difference between transcatheter and surgical bioprostheses.[93, 95]

The Valve Academic Research Consortium statement provides a standardized definition for endpoints after TAVI which will enable a more accurate comparison between devices and approaches.[96, 97]

Patients considered not suitable for SAVR after surgical consultation clearly benefit from TAVI compared with conservative treatment including balloon valvuloplasty, as demonstrated by a randomized trial[78] (1-year mortality 31% vs 51% (number needed to treat = 5) and significantly better symptomatic improvement with fewer repeat hospitalizations).

Currently, there are five randomized studies available that compare TAVI and SAVR.[72, 88, 92, 125, 129] Table 35.3.2 summarizes key data of the randomized trials as well as large company-independent nationwide registries. Most experience exists for the different generations of the balloon expandable Edwards valve and the self-expandable CoreValve™ (Figure 35.3.6 and Figure 35.3.7).

The first randomized trial comparing TAVI using a balloon expandable valve and surgical AVR in high-risk (mean Society of Thoracic Surgeons (STS) score = 11.8), but operable patients[72] showed TAVI (use of both transfemoral and transapical route) to be non-inferior for all-cause mortality at 1 year (24.2% vs 26.8%), with marked functional improvement in both groups. The analysis of secondary endpoints showed that TAVI carried a higher risk of early cerebrovascular events (difference no longer significant at late follow-up) and vascular complications and a higher incidence of paravalvular leaks, although mostly trace and mild. Conversely, major bleeding and postoperative AF were more frequent after surgery. The interpretation of the results of the PARTNER trials[72, 78] should take into account that this study was performed with an early-generation device and that complication rates have been markedly reduced with new-generation devices.

In the second trial using a self-expanding system[92] with predominant transfemoral implantation and patients at somewhat lower risk (mean STS score = 7.3%), 1-year mortality was significantly lower in the TAVI group (14 vs 19%). While rates of vascular complications, pacemaker implantation, and paravalvular regurgitation were significantly higher with TAVI, severe bleeding, acute kidney injury, and new-onset atrial fibrillation was significantly more frequent with surgery. While these two trials studied primarily surgical high-risk patients but also included intermediate risk patients, a third, smaller study[88] again using the self-expanding system included patients older than 70 years with low to intermediate surgical risk (STS score 3, EuroScore 8.6, on average). The primary composite outcome, all-cause mortality, myocardial infarction, stroke for TAVI versus SAVR at 1 year was 13.1% versus 16.3% (p = 0.43) and mortality 4.9% versus 7.5% (p = 0.38). SAVR resulted again in more bleeding complications and atrial fibrillation, while TAVI patients had significantly more aortic regurgitation, less symptomatic benefit, and a higher need for a permanent pacemaker implantation.

The most recent trials included intermediate-risk patients. In the PARTNER 2 study[125] which used a balloon expandable valve, the mean STS score was 5.8, mean age 82 years, and frail condition was frequently present. There was no significant difference in

Table 35.3.2 Overview of current patient profiles and outcomes of TAVI

(A) Randomized clinical trials (TAVI results only are given)[72, 78, 88, 92, 95, 100–103, 127, 129]

	PARTNER A (high risk)	PARTNER B (inoperable)	PARTNER 2 (intermediate risk)	CoreValve™ (high risk)	NOTION trial (intermediate/low risk)	SURTAVI
n	348	179	1011	394	145	879
Age (years)	83.6±6.8	83.1±8.6	81.5±6.7	83.2±7.1	79.2±4.9	79.9±6.2
Female (%)	42.2	54.2	45.8	46.4	46.2	42.2
STS score (%)	11.8	11.6	5.8±2.1	7.3±3	2.9±1.6	4.4±1.5
Log ES (%)	29.3±16.5	26.4±17.2	n/a	17.6±13	8.4±4	11.9±7.6
Prosthetic valve	SAPIEN™	SAPIEN™	SAPIEN™ XT	CoreValve™	CoreValve™	CoreValve™ (16% Evolut R™)
30-day mortality (%)	3.4	5.0	3.9	3.3	2.1	2.2
30-day stroke (%)	3.8	6.7	5.5	4.9	1.4	3.4
Aortic incompetence moderate + severe (%)	13.1	15.0	3.7	10.0	15.3	5.3
New-onset pacemaker implantation (%)	4.4	3.4	8.5	19.8	34.1	25.9
Major vascular complication (%)	11.0	16.2	7.9	5.9	5.6	6.0
Major bleeding (%)	9.3	16.8	10.4	28.1	11.3	12.2
Acute kidney injury (%)	2.9	1.1	1.3	6.0	0.7	1.7
New-onset atrial fibrillation (%)	8.6	0.6	9.1	11.7	16.9	12.9
1-year mortality (%)	24.3	30.7	12.3	14.2	4.9	6.7
2-year mortality (%)	33.9	43.3	16.7	22.2	–	11.4
5-year mortality (%)	67.8	71.8	–	–	–	–

(B) Registries (*investigator initiated*, large and nationwide registries)[87, 89, 94, 120–123]

	TVT registry (USA)	UK TAVI registry	Italian TAVI registry (OBSERVANT)	France 2	GARY (German aortic valve registry)
n	12,182	3980	1652/259	3195	15,964
Years of inclusion	Nov 2011–Jun 2013	2007–2012	Dec 2010–Jun 2012	Jan 2010–Oct 2011	Jan 2011–Dec 2013
Age (years)	84	81.3±7.6	82/81.4	82.7±7	81±6
Female (%)	52	52.7	58.5/52.9	49	54
STS score (%)	7.1	–	–	14.4	6.4
Log ES (%)	–	21.9	14.1/15.5	21.9	23.3
30-day mortality (%)	7.0	6.3	5.7/8.2	9.7	5.2
Aortic incompetence moderate + severe (%)	8.5	12.0	–	16.3	5.5
New-onset pacemaker implantation (%)	6.6	5.9 (SAPIEN™); 20.1 (CoreValve™)	–	15.6	18.2
Major vascular complication (%)	6.4	3.5	–	4.7	–
Major bleeding (%)	3.5	–	–	5.7	11.4
Acute kidney injury (%)	5.5	–	–	–	3.6
New-onset atrial fibrillation (%)	6.0	–	–	–	6.4
1-year stroke (%)	4.1	2.6	–	2.3	2.6
1-year mortality (%)	23.7	18.3	13.1	24	20.5

Table 35.3.2 Continued

	TVT registry (USA)	UK TAVI registry	Italian TAVI registry (OBSERVANT)	France 2	GARY (German aortic valve registry)
2-year mortality (%)	–	27.2	–		–
5-year mortality (%)	–	53.1	–		–
All-comers inclusion	Yes	Yes	Participating hospitals	Yes	Yes (patient informed consent required)
Valves	SAPIEN™, CoreValve™	SAPIEN™, CoreValve™		SAPIEN™, CoreValve™	SAPIEN™ ~52%; CoreValve™ ~38%; Acurate, Lotus, JenaValve®, Direct flow, Portico ~10%
Follow-up rate	~65%	92%	–	–	98%
Others	Ongoing registration	Ongoing registration	Numbers are given for TF/TA approach		Ongoing registration

(C) Outcomes of TAVI versus SAVR in randomized clinical trials[72, 78, 88, 92, 95, 100-103, 125, 129]

	PARTNER A (high risk)		PARTNER 2 (intermediate risk)		CoreValve™ (high risk)		NOTION trial (intermediate/low risk)		SURTAVI (intermediate risk)	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
n	348	351	1011	1021	394	401	145	135	879	867
Mean age (years)	83.6	84.5	81.5	81.7	83.2	83.5	79.2	79.0	79.8	
Female (%)	42.2	43.3	45.8	45.2	46.4	47.1	46.2	47.4	43	
STS score (%)	11.8	11.7	5.8	5.8	7.3	7.5	2.9	3.1	4.5	
Log ES (%)	29.3	29.2	–	–	17.6	18.4	8.4	8.9	11.7	
Prosthetic valve	SAPIEN™	n/a	SAPIEN™ XT	n/a	CoreValve™	n/a	CoreValve™	n/a	CoreValve™	n/a
30-day mortality (%)	3.4	6.5	3.9	4.1	3.3	4.5	2.1	3.7	2.2	1.7
30-day stroke/TIA (%)	5.5	2.4*	5.5	6.1	4.9	6.2	1.4	3.0	3.4	5.6
Aortic incompetence moderate + severe (%)	13.1	1.7*	3.7	–	10.0	1.0*	15.3	1.8*	5.3	0.6*
New-onset pacemaker implantation (%)	3.8	3.6	8.5	6.9	19.8	7.1*	34.1	1.6*	25.9	6.6*
Major vascular complication (%)	11.0	3.2*	7.9	5.0*	5.9	1.7*	5.6	1.5	6.0	1.1*
Major bleeding (%)	9.3*	19.5	10.4	43.4*	28.1	34.5	11.3*	20.9	12.2	9.3
Acute kidney injury (%)	2.9	3.0	1.3	3.1*	6.0*	15.1	0.7*	6.7	1.7*	4.4
New-onset atrial fibrillation (%)	8.6*	16	9.1	26.4*	11.7*	30.5	16.9*	57.8	12.9*	43.4
1-year mortality (%)	24.3	26.8	12.3	12.9	14.2*	19.1	4.9	7.5	6.7	6.8
2-year mortality (%)	33.9	35.0	16.7	18.0	22.2	28.6			11.4	11.6
5-year mortality (%)	67.8	62.4	–	–	–	–	–	–	–	–
Selective patient inclusion	Yes		Yes		Yes		Yes, 17.8% of eligible patients		Yes	
Others			In patients eligible for transfemoral access, TAVI resulted in a significantly lower rate of death or disabling stroke (HR 0.79)		Patients were considered 'high risk' by heart team decision		Study underpowered		Patients with STS score 3–15% included	

* = p <0.01 versus control group.

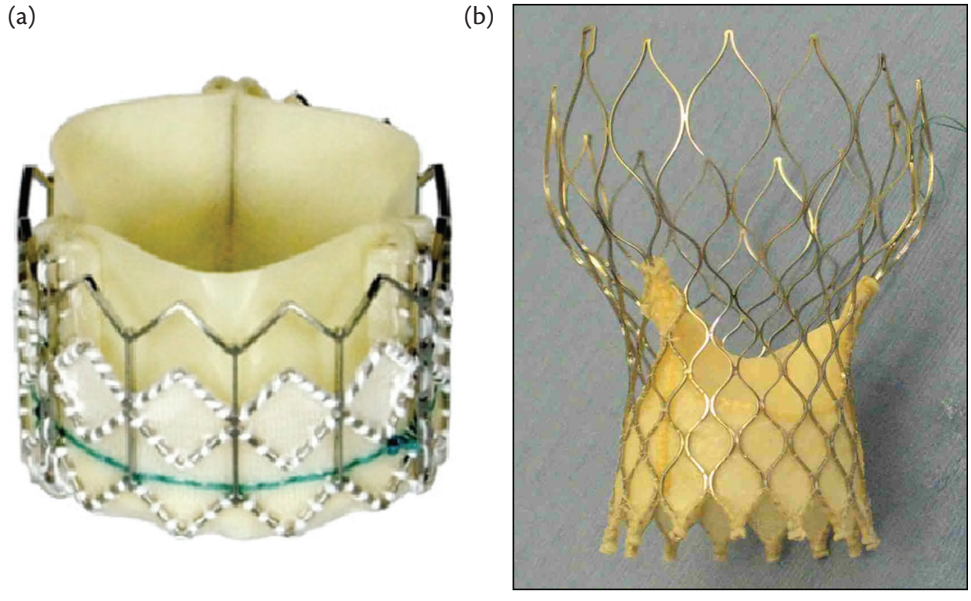

Figure 35.3.6 Stent-valve prostheses for transcatheter aortic valve implantation. (a) Edwards-SAPIEN™ valve (Edwards-Lifesciences Inc. Irvine CA, USA) consisting of three bovine pericardial leaflets mounted with a tubular slotted stainless-steel balloon expandable stent. (b) CoreValve™ revalving system (CoreValve Inc. Irvine CA, USA) which has three porcine pericardial leaflets, mounted on a self-expanding nitinol frame. Edwards-Lifesciences Inc. Irvine CA, USA. CoreValve Inc. Irvine CA, USA.

the rate of death from any cause or disabling stroke until 2 years. Patients were evaluated for their eligibility for transfemoral or transthoracic access before randomization. In the cohort eligible for transfemoral access, TAVI resulted in a significantly lower rate of death or disabling stroke than surgery in the 'as-treated analysis'. TAVI resulted in larger aortic valve areas and lower rates of acute kidney injury, severe bleeding, and new-onset atrial fibrillation, whereas surgery resulted in fewer vascular complications and less paravalvular regurgitation. There was no difference in pacemaker rates. In a propensity score analysis, the surgical group was compared to the results of the current generation of the balloon expandable valve in intermediate-risk patients.[126] With regard to the primary composite endpoint of mortality, strokes, and moderate or severe AR, TAVI was superior to SAVR. In a meta-analysis of these four described randomized trials,[127] for the primary outcome of death from any cause, TAVI as compared with SAVR was associated with a significant relative risk reduction with homogeneity across all trials irrespective of TAVI device and baseline risk. In subgroup analyses, TAVI showed a robust survival benefit over SAVR for patients undergoing transfemoral access (hazard ratio (HR) 0.80; 95% confidence interval (CI) 0.69–0.93; $p = 0.004$), but not transthoracic access (HR 1.17; 95% CI 0.88–1.56). Secondary outcomes of kidney injury, new-onset atrial fibrillation, and major bleeding favoured TAVI, while major vascular complications, incidence of permanent pacemaker implantation, and paravalvular regurgitation favoured SAVR.

The most recently published randomized trial SURTAVI[129] used a self-expanding valve in intermediate risk patients. Compared to PARTNER 2, mean STS score was even lower (4.5% vs 5.8%) and patients were slightly younger but on average still 80 years old and 52% were considered to be frail. There was no significant difference in the primary endpoint—the rate of death from any cause or disabling stroke at 2 years between TAVI and surgical AVR (12.6 vs 14.0%). The two differed, however, again in the pattern adverse events: surgery was associated with higher rates of kidney injury, atrial fibrillation, and transfusion requirements, whereas

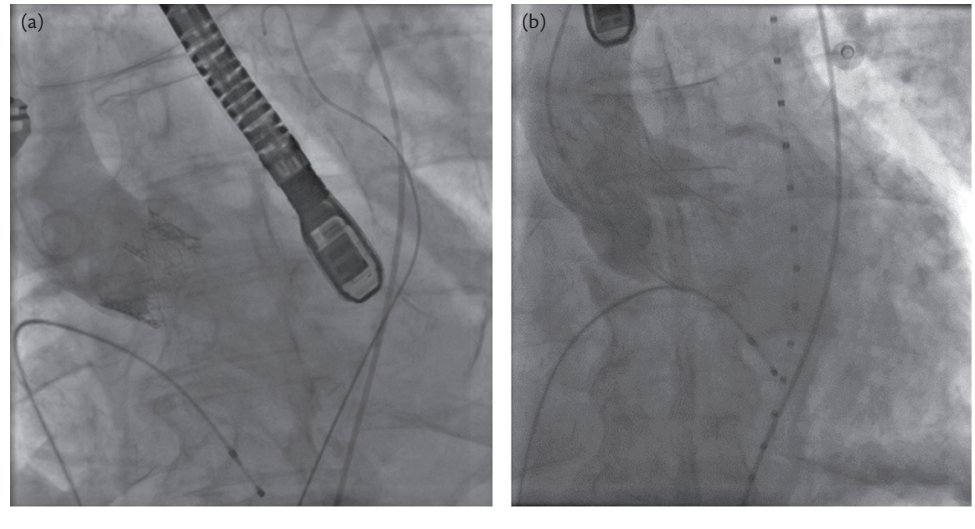

Figure 35.3.7 Aortography after transcatheter aortic valve implantation (TAVI). (a) TAVI using the balloon expandable stent. (b) TAVI using the self-expandable stented valve. In both cases, the prosthesis is deployed at the level of the aortic valve and coronary flow is not impeached. Courtesy of Dr D. Himbert.

TAVI had higher rates of residual AR and need for pacemaker implantation (still 26%). TAVI resulted in lower mean gradients and larger valve areas than surgery.

Overall, taking all randomized trials together, rates of vascular complications, pacemaker implantation, and paravalvular regurgitation were significantly higher for TAVI but the degree of excess markedly depended on the device used.[127, 129] On the other hand, severe bleeding, acute kidney injury, and new-onset atrial fibrillation were significantly more frequent with surgery while no difference was observed in the rate of cerebrovascular events.[127, 129]

Balloon aortic valvuloplasty

This intervention plays an important role in the paediatric population, but a very limited role, when used in isolation, in adults. This is because its efficacy is low, and restenosis and clinical deterioration occur within 6–12 months in most patients, resulting in a mid- and long-term outcome similar to natural history.[78, 98] The originally reported high complication rate (>10%) has been markedly reduced in contemporary series (intraprocedural deaths, 2.2%; stroke, 1.2%; tamponade, 0.5%).[99] Besides allowing bridging to a more definite treatment (SAVR, TAVI) in unstable patients, balloon aortic valvuloplasty has been reported to be helpful diagnostically when potential other causes for dyspnoea (lung disease) are present or when severe myocardial dysfunction, prerenal insufficiency, or other organ system dysfunction may be reversible with balloon aortic valvuloplasty.[99]

Indications for intervention

The indications for AVR are listed in Table 35.3.3 and Table 35.3.4 and illustrated in Figure 35.3.8.

Indications for intervention in symptomatic AS

Early therapy of aortic valve disease should be strongly recommended in all symptomatic patients with severe AS. The only exception are patients with severe co-morbidities indicating a survival less than 1 year and patients in whom severe co-morbidities

Table 35.3.3 Indications for intervention in aortic stenosis and recommendations for the choice of intervention mode

	Class[a]	Level[b]	Ref.[c]
Symptomatic aortic stenosis			
Intervention is indicated in symptomatic patients with severe, high-gradient AS (mean gradient ≥40 mmHg or peak velocity ≥ 4.0 m/s)	I	B	78, 47, 124
Intervention is indicated in symptomatic patients with severe AS, low-flow, low-gradient (<40 mmHg) with reduced EF, and evidence of flow (contractile) reserve excluding pseudo-severe AS	I	C	
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal EF after careful confirmation of severe AS* (Figure 35.3.1 and Table 35.3.1)	IIa	C	
Intervention should be considered in symptomatic patients with severe AS low-flow, low-gradient, and LV dysfunction without flow (contractile) reserve particularly when CT calcium scoring confirms severe AS	IIa	C	
Intervention should not be performed in patients with severe co-morbidities when the intervention is unlikely to improve the quality of life or survival	III	C	
Choice of intervention in symptomatic aortic stenosis			
Aortic valve interventions should only be performed in centres with departments of cardiology and cardiac surgery on site and structured collaboration between the two including a heart team (heart valve centres)	I	C	
The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality (aspects to be considered are listed in Table 35.3.4). In addition, the local expertise and outcome data for the given intervention must be taken into account	I	C	
SAVR is recommended in patients at low surgical risk (STS or ES II <4% or logistic ES I <10%** and no other risk factors not included in these scores such as frailty, porcelain aorta or sequelae of chest radiation)	I	B	124
Transcatheter aortic valve implantation (TAVI) is recommended in patients who are not suitable for SAVR as assessed by the heart team	I	B	78, 128
In patients who are at increased surgical risk (STS or ES II ≥4% or logistic ES I ≥10%** or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the heart team according to the individual patient characteristics (Table 35.3.4) with TAVI being favoured in elderly patients suitable for transfemoral access	I	B	78, 72, 95, 103, 92, 88, 125–127, 129
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe AS who require urgent major non-cardiac surgery	IIb	C	
Balloon aortic valvotomy may be considered as a diagnostic means in patients with severe AS and other potential cause for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, prerenal insufficiency or other organ dysfunction that may be reversible with balloon aortic valvotomy, when performed in centres that are able to escalate to TAVI	IIb	C	

(*continued*)

Table 35.3.3 Continued

	Class[a]	Level[b]	Ref.[c]
Asymptomatic patients with severe AS (refers only to patients eligible for surgical valve replacement!)			
SAVR is indicated in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) not due to another cause	I	C	
SAVR is indicated in asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise clearly related to AS	I	C	
SAVR should be considered in asymptomatic patients with severe AS and an abnormal exercise test showing a decrease in blood pressure below baseline	IIa	C	
SAVR should be considered in asymptomatic patients, with normal EF and none of the above-mentioned exercise test abnormalities, if the surgical risk is low, and one of the following findings is present: ◆ Very severe AS defined by a peak transvalvular velocity >5.5 m/s ◆ Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year ◆ Markedly elevated brain natriuretic peptide levels (>3-fold age and sex-corrected normal range) confirmed by repeated measurements without other explanations ◆ Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation	IIa	C	
Concomitant aortic valve surgery at the time of other cardiac/ascending aorta surgery			
AVR is indicated in patients with severe AS undergoing CABG, surgery of the ascending aorta or of another valve	I	C	
AVR should be considered in patients with moderate AS*** undergoing CABG, surgery of the ascending aorta or of another valve after heart team decision	IIa	C	

[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
* In patients with a small valve area but low gradient despite preserved LVEF, explanations for this finding other than the presence of severe AS are frequent and must be carefully excluded. See text (evaluation of AS) and Figure 35.3.1 and Table 35.3.1.
** STS score (calculator: http://riskcalc.sts.org/stswebriskcalc/#/calculate); EuroSCORE II (calculator: http://www.euroscore.org/calc.html); logistic EuroSCORE I (calculator: http://www.euroscore.org/calcge.html). Scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc.[130] EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard; it is nevertheless provided here for comparison since it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality.
*** Moderate AS is defined as valve area 1.0–1.5 cm^2 (0.6 cm^2/m^2 to 0.9 cm^2/m^2 BSA) or mean aortic gradient 25–40 mmHg in the presence of normal flow conditions. However, clinical judgement is required.
AS, aortic stenosis; AVR, aortic valve replacement; BSA, body surface area; CABG, coronary artery bypass graft surgery; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

Table 35.3.4 Aspects to be considered by the heart team for the decision between SAVR and TAVI in patients at increased surgical risk (see Table 35.3.3)

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II <4% (logistic Euro SCORE I <10%)*		+
STS/EuroSCORE II ≥4% (logistic Euro SCORE I ≥10%)*	+	
Presence of severe co-morbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Prior cardiac	+	
Frailty**	+	
Restricted mobility and conditions that may impact the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable access (any) for TAVI		+

(*continued*)

Table 35.3.4 Continued

	Favours TAVI	Favours SAVR
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavourable for TAVI		+
Presence of thrombi in aorta or left ventricle		+
Cardiac conditions in addition to AS that require consideration for concomitant intervention		
Severe coronary artery disease requiring revascularization by coronary artery bypass grafting		+
Severe primary mitral valve disease		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy suggesting myectomy		+

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
* STS score (calculator: http://riskcalc.sts.org/stswebriskcalc/#/calculate); EuroSCORE II (calculator: http://www.euroscore.org/calc.html); logistic EuroSCORE I (calculator: http://www.euroscore.org/calcge.html). Scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc.[130] EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard; it is nevertheless provided here for comparison since it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality.
** Although several tools for frailty assessment have been proposed and evaluated (mostly including slow walking speed, weakness, inactivity, exhaustion, and shrinking—as measured by physical performance tests and questionnaires[104–106]) it remains currently uncertain which one should be recommended for general use in clinical practice and whether they are superior to clinical judgement by the heart team in this setting.

or their general condition at high age make it unlikely that the intervention will improve quality of life.

As long as the mean gradient remains higher than 40 mmHg, there is virtually no lower EF limit for intervention.

The management of patients with low gradient AS (valve area <1 cm^2, mean gradient <40 mmHg) is more challenging. In patients with low-flow, low-gradient AS and reduced EF (valve area <1 cm^2, mean gradient <40 mmHg, EF <40%), in whom the depressed EF is predominantly caused by excessive afterload (afterload mismatch), LV function usually improves after intervention.[22, 26, 107] Conversely, improvement in LV function after intervention is uncertain if the primary cause is scarring due to extensive myocardial infarction or cardiomyopathy. In patients with low gradients and evidence of flow reserve, intervention is definitely advised when severe AS is confirmed at increasing flow (true severe AS; see 'Evaluation').[22] Patients who are classified as pseudo-severe AS at increasing flow should undergo conventional heart failure treatment and not aortic valve intervention.[108] Although the outcome of patients without flow reserve is compromised by a higher operative mortality, AVR—as well as TAVI—has been shown to improve EF and clinical status also in such patients.[22, 23, 107] Final decision-making should take into account the patient's clinical condition (in particular, the presence and extent of co-morbidities), the degree of valve calcification (CT calcium score), the extent of coronary disease, and the feasibility of revascularization. The ability to identify the patients with severe aortic stenosis in this subgroup by CT calcium scoring and the availability of TAVI have lowered the threshold to intervene.

Patients with low-flow, low-gradient AS, and preserved EF (valve area <1 cm^2, mean gradient <40 mmHg, EF ≥50%, stroke volume index ≤35 mL/m^2) are the most challenging subgroup. Data on their natural history (see 'Natural history') and outcome after surgery remain controversial.[17, 18, 20, 25, 26] In such cases, surgery should be performed only when symptoms are present and if comprehensive evaluation suggests significant valve obstruction (Figure 35.3.4 and Table 35.3.1).

Patients with normal-flow, low-gradient AS, and preserved EF (valve area <1 cm^2, mean gradient <40 mmHg, EF ≥50%, stroke volume index >35 mL/m^2) data should be re-evaluated. If normal flow is confirmed these patient will in general not have severe AS and not benefit from intervention.[18–20] In these patients, surgery or intervention is not recommend.

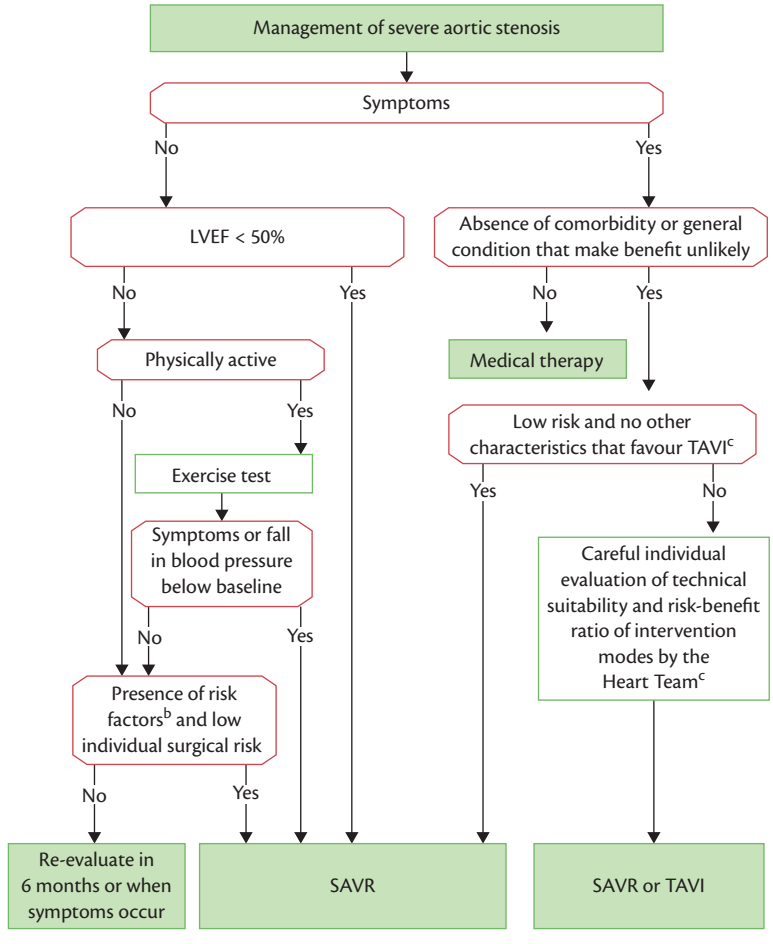

Figure 35.3.8 Management of severe aortic stenosis. AS, aortic stenosis; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a] See Figure 35.3.4 and Table 35.3.1 for definition of severe AS.
[b] Surgery should be considered (IIa C) if one of the following is present: peak velocity >5.5m/s; severe valve calcification + peak velocity progression ≥0.3 m/s/year; markedly elevated neurohormones (>3-fold age- and sex-corrected normal range) without other explanation; severe pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg).
[c] See Table 35.3.3 andTable 35.3.4.

Choice of intervention mode in symptomatic AS

Aortic valve interventions should only be performed in centres with departments of cardiology and cardiac surgery on site and structured collaboration between them including a heart team of dedicated cardiologists, cardiac surgeons, cardiac anaesthesiologists, and cardiac imaging specialists.[110] Good team collaboration between these departments is vital to achieve good outcomes. The definition of heart valve centres is provided in Chapter 35.1.

The choice of the intervention mode should take into account the cardiac and extracardiac characteristics of the patient, the individual risk of surgery, which is assessed by the judgement of the heart team in addition to scores, the feasibility of TAVI, and the local experience and outcome data.

There is still little experience with TAVI in patients at low surgical risk, particularly when younger than 75 years. Such patients have so far rarely been included in studies and registries. Younger patients obviously differ in characteristics. With decreasing age, for example, bicuspid valves become more predominant which were in general excluded in clinical trials. Experience with intervention in this anatomy is therefore still limited and worse results have been reported compared to tricuspid valves.[109] Thus, results of the currently available studies and registries on TAVI cannot simply be applied to younger patients. In addition, the lack of long-term outcome data becomes critical in younger patients. In particular, the lack of durability data and the eventual negative long-term effects of higher pacemaker and paravalvular regurgitation rates need to be considered in this context. Therefore, surgery remains currently the first choice in surgical low-risk patients and patients younger than 75 years. In case preoperative assessment identifies an increased risk for surgery by risk scores or patient characteristics that may favour TAVI (Table 35.3.4), this should be discussed by the heart team.

Patients not suitable for SAVR should undergo TAVI as long as comprehensive evaluation of co-morbidities and general condition makes improvement of quality of life and of survival by intervention likely.

Available data from randomized controlled trials and large registries in elderly patients at increased surgical risk show that TAVI is superior to medical therapy in extreme risk patients,[78] non-inferior or superior to surgery in high-risk patients,[72, 95, 103, 92] and, more recently, non-inferior to surgery and may be even superior when transfemoral access is possible in intermediate risk patients.[88, 125–127, 129] This favours the use of TAVI over surgery in elderly patients at increased surgical risk particularly when suitable for transfemoral access. The final decision between SAVR and TAVI (including the choice of access route) should, however, be made by the heart team after careful individual evaluation of technical suitability and weighing of risks and benefits of

SAVR versus TAVI as well as local experience and outcome data. Table 35.3.4 provides aspects that should be considered for the individual decision. Although major attempts have been made to evaluate existing surgical risk scores[67, 110] or to develop new risk scores, none of them has turned out to be very helpful as a single tool for patient selection and individual decision between TAVI and SAVR. In particular, they do not include the important aspects of frailty and conditions such as porcelain aorta, history of chest radiation, or patent coronary bypass grafts. In addition, there is limited consideration of the severity of co-morbidities. Thus, they can only be considered as one piece of information within the comprehensive patient evaluation.

Balloon valvuloplasty may be considered as a bridge to surgery or TAVI in haemodynamically unstable patients or in patients with symptomatic severe AS who require urgent major non-cardiac surgery. Balloon aortic valvuloplasty may also be considered diagnostically in patients with severe AS and other potential cause for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, prerenal insufficiency, or other organ dysfunction that may be reversible with Balloon aortic valvuloplasty.

Asymptomatic AS

Management of asymptomatic severe AS remains a matter of controversy. Currently available studies do not provide convincing data to support the general recommendation of early SAVR, even in patients with asymptomatic very severe AS.[46–49, 111, 112] A recent retrospective study of asymptomatic AS using propensity score matching suggests a substantial improvement of outcome with SAVR compared to a conservative management.[113] However, these results are solely driven by the poor outcome of patients in the conservative group who developed symptoms during follow-up but nevertheless did not undergo SAVR. Thus, the study highlights the importance of appropriate follow-up to make sure that patients receive treatment when they develop symptoms but does not support early elective surgery in asymptomatic patients. The decision to operate on asymptomatic patients requires careful weighing of the benefits against the risks. The population currently considered for TAVI are symptomatic elderly patients with increased surgical risk. TAVI is not recommended in asymptomatic patients. Thus, this section only refers to asymptomatic patients who are candidates for SAVR.

Early elective surgery is indicated in asymptomatic patients with depressed LV function not due to other causes.[48] These patients are, however, very rare (<1% of AS patients) and the relatively poor outcome and observed questionable improvement with SAVR raises the suspicion that these patients may frequently have other undiagnosed cardiac problems in addition to their AS.[114]

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.[31, 38, 58]

Surgery should be considered in patients at low operative risk, with normal exercise performance, and the following:

- Very severe AS defined by a peak velocity greater than 5.5m/s,[49, 112] or
- A combination of severe valve calcification with a rapid increase in peak transvalvular velocity of at least 0.3 m/s per year,[47] or
- Markedly elevated natriuretic peptide levels (greater than threefold age and gender-corrected normal range) confirmed by repeated measurements without other explanations,[40–42] or
- Severe pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg confirmed by invasive measurement) without other explanation.[53–57]

An increase of mean pressure gradient with exercise by greater than 20 mmHg[32, 33] has also been reported to be a predictor of symptom development. The use of this criterion as an indication for early elective surgery has, however, become less well established. The individual changes of gradient with exercise remain complex and determined by AS severity as well as the ability to increase flow. The added value of exercise echo compared to earlier listed recommended criteria assessed at rest has been questioned by more recent data [34].

In patients without the preceding predictive factors, watchful waiting appears safe as early surgery is unlikely to be beneficial.

Medical therapy

The progression of degenerative AS is an active process, sharing a number of similarities with atherosclerosis. Although several retrospective reports have shown beneficial effects of statins and angiotensin-converting enzyme inhibitors, randomized trials have consistently shown that statins do not affect the progression of AS.[115, 116] Statin therapy should therefore not be used in AS patients where its only purpose is to slow progression. On the other hand, modification of atherosclerotic risk factors must be strongly recommended following the guidelines of secondary prevention in atherosclerosis.[117]

Symptomatic patients require early intervention, because no medical therapy for AS is able to improve outcome compared with the natural history. However, patients who are unsuitable candidates for surgery or TAVI, or who are currently awaiting a surgical or TAVI procedure, may be treated with digoxin, diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers if they experience symptoms of heart failure. Coexisting hypertension should be treated. However, treatment should be carefully titrated to avoid hypotension and patients should be frequently re-evaluated. Maintenance of sinus rhythm is important.

Serial testing

In the asymptomatic patient, the wide variability of the rate of progression of AS heightens the need for patients to be carefully educated about the importance of follow-up and reporting symptoms as soon as they develop. Stress tests should determine the recommended level of physical activity. Follow-up visits should include echocardiography with a focus on haemodynamic progression, LV function and hypertrophy, and the ascending aorta. Type and interval of follow-up should be determined on the basis of the initial examination.

Asymptomatic severe AS should be re-evaluated at least every 6 months for the occurrence of symptoms (change in exercise tolerance, ideally using exercise testing if symptoms are doubtful) and change in echo parameters. Measurement of natriuretic peptides should be considered.

In the presence of significant calcification, mild and moderate AS should be re-evaluated yearly. In younger patients with mild AS and no significant calcification, intervals may be extended to 2–3 years.

Special patient populations

Combined AVR and coronary artery bypass grafting (CABG) carries a higher risk than isolated AVR.[63–66] However, AVR late after CABG is also associated with significantly increased risk. Although there are no prospective randomized trials, data from retrospective analyses indicate that patients in whom CABG is indicated and who have moderate AS (mean gradient in the presence of normal flow 25–40 mmHg, valve area 1.0–1.5 cm^2) will in general benefit from concomitant AVR. It has also been suggested that if age is less than 70 years and more importantly an average rate of AS progression of 5 mmHg per year is documented, patients may benefit from valve replacement at the time of coronary surgery once the baseline peak gradient exceeds 30 mmHg.[118] Individual judgement is recommended, taking into consideration BSA, haemodynamic data, leaflet calcification, progression rate of AS, patient life expectancy and associated co-morbidities, as well as the individual risk of either concomitant valve replacement or late reoperation.

Patients with severe symptomatic AS and diffuse CAD that cannot be revascularized should not be denied SAVR or TAVI, even though this is a high-risk group.

A few studies have recommended the potential use of percutaneous coronary intervention in place of CABG in patients with AS. However, currently the available data are not sufficient to recommend this approach, apart from selected high-risk patients with acute coronary syndromes or in patients with non-severe AS.

Combined percutaneous coronary intervention and TAVI have been shown to be feasible, but require more data before a firm recommendation can be made. Whether to proceed, as well as the chronology of interventions, should be the subject of individualized discussion based on the patient's clinical condition, coronary anatomy, and myocardium at risk.

When MR is associated with severe AS, its severity may be overestimated in the presence of the high ventricular pressures and careful quantification is required. As long as there are no morphological leaflet abnormalities (flail or prolapse, post-rheumatic changes, or signs of infective endocarditis), mitral annulus dilatation, or marked abnormalities of LV geometry, surgical intervention on the mitral valve is in general not necessary, and non-severe secondary MR mostly improves after the aortic valve is treated.

Concomitant aneurysm/dilatation of the ascending aorta requires the same treatment as in AR (see Chapter 35.2).

For congenital AS, see the ESC Guidelines on grown-up congenital heart disease.[119]

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Chapter 35.4 Mitral regurgitation

Mitral regurgitation (MR) is the second most frequent valve disease after aortic stenosis in hospitalized patients[1] and appears to be the first in the general population.[2]

Aetiology

It is essential to distinguish between primary (organic) MR, which is the direct result of abnormalities of the mitral valve apparatus and secondary (functional and ischaemic) MR, which is due to left ventricular (LV) disease and remodelling.

Primary mitral regurgitation

Degenerative MR is the most common aetiology in developed countries with the increasing life expectancy of their population.[1] The disease phenotype encompasses the spectrum from leaflet prolapse or flail in the absence of excessive tissue to diffuse myxomatous degeneration that is characterized by excessive valve thickening and tissue proliferation. Pathological examination shows leaflet infiltration by mucopolysaccharides and accumulation of proteoglycans in the absence of inflammation. Non-specific alteration of collagen and elastin leads to increased elasticity and increased tension on the chordae tendineae which can become elongated and subsequently rupture. Mitral valve prolapse occurs in connective tissue disorders such as Marfan and Ehlers–Danlos syndromes. Although most cases of mitral valve prolapse are sporadic, familial mitral valve prolapse has been observed with autosomal dominant inheritance and genetic heterogenicity, linked to chromosomes 11, 13, 16, and the X chromosome.[3, 4] Mitral annular calcification can be present in patients with myxomatous disease and its incidence increases with age.

In rheumatic heart disease, which has become rare in Western countries after the decline of rheumatic fever, MR is frequently associated with various degrees of MS. Regurgitation is essentially due to valvular and subvalvular retraction rather than thickening. Similar lesions may be observed in rheumatoid arthritis, lupus erythematosus, antiphospholipid syndrome, carcinoid disease, and drug-induced valve disease.[5]

Infective endocarditis remains common and can result in leaflet perforation and chordal rupture. It is discussed in Section 36 and also covered by specific European Society of Cardiology (ESC) Guidelines.[6]

The rupture of a papillary muscle, usually involving a head of the posteromedial papillary muscle, is a dramatic complication of acute myocardial infarction, which occurs less frequently since the implementation of acute reperfusion strategies. Acute or chronic papillary muscle ischaemia or dysfunction in isolation does not result in MR.

Secondary mitral regurgitation

In secondary MR (previously also referred to as 'functional MR'), valve leaflets and chordae are structurally normal and MR results from geometrical distortion of the subvalvular apparatus secondary to LV enlargement and remodelling due to idiopathic cardiomyopathy or coronary artery disease (CAD). In the latter, secondary MR has also been termed ischaemic MR, although this does not imply the presence of ongoing myocardial ischaemia. Thus secondary MR is not primarily a valvular disease, but results from an imbalance between tethering (apical and lateral papillary muscle displacement, annular dilatation) and closing forces, due to LV dysfunction (reduced contractility or LV dyssynchrony, or both).[7–9] Tethering may also be the result of a localized scar leading to changes in ventricular geometry—this is mostly seen in patients with inferior myocardial infarction. In patients with long-standing atrial fibrillation, atrial enlargement may lead to annular dilatation even in the presence of preserved ventricular function, which in turn may cause mitral regurgitation. In older patients with secondary MR, some extent of degenerative changes, such as valve thickening and calcification, may coexist.

The paradigm of a structurally normal valve in functional MR has recently been challenged, since the observation of structural changes in the mitral leaflets of patients with functional MR.[10]

Pathophysiology

MR consists of systolic backflow of blood from the LV to the left atrium as a result of incomplete mitral valve closure and a pressure gradient between the LV and the left atrium. MR can result from dysfunction of one or often several of the following components: the annulus, the leaflets, the chordae tendineae, the papillary muscles, and the LV. The mechanisms of regurgitation can be valve prolapse due to redundant leaflets and elongation or rupture of chordae; loss of valvular tissue by retraction, perforation, or tethering on the leaflets (usually the posterior valve by chordal retraction); or LV remodelling causing geometric valvular distortion. The Carpentier classification[11] has subcategorized the mechanisms by leaflet movement and is useful to systematically describe valve function (Figure 35.4.1).

Regurgitant volume is determined by the regurgitant area, the systolic pressure gradient across the MR orifice, and the duration of systole. A systolic ventriculoatrial pressure gradient is present throughout isovolumic contraction, ejection, and isovolumic

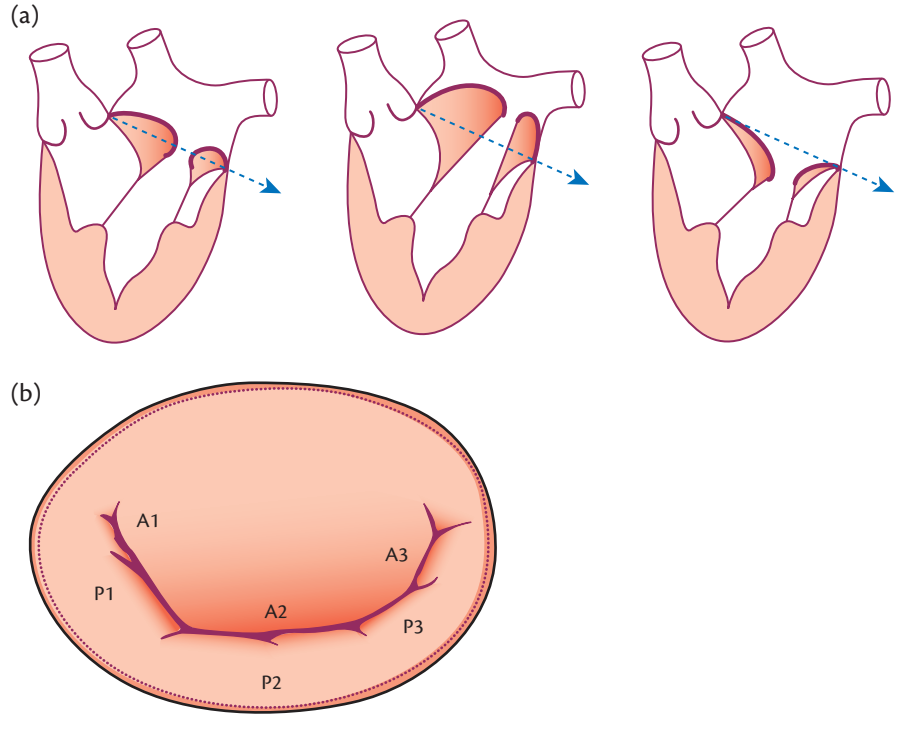

Figure 35.4.1 Carpentier classification in MR. (a) Functional anatomy subcategorized by leaflet movement; type I: normal leaflet motion; type II: leaflet prolapse; type III: restricted leaflet motion. (b) Anatomical location: the posterior leaflets segments are designated as P1, P2, and P3. P1 is adjacent to the anterolateral commissure, P2 is the middle scallop, and P3 is adjacent to the posteromedial commissure. The anterior leaflet has less clearly defined segments, designated as A1, A2, and A3, corresponding to the adjacent posterior leaflet segments.

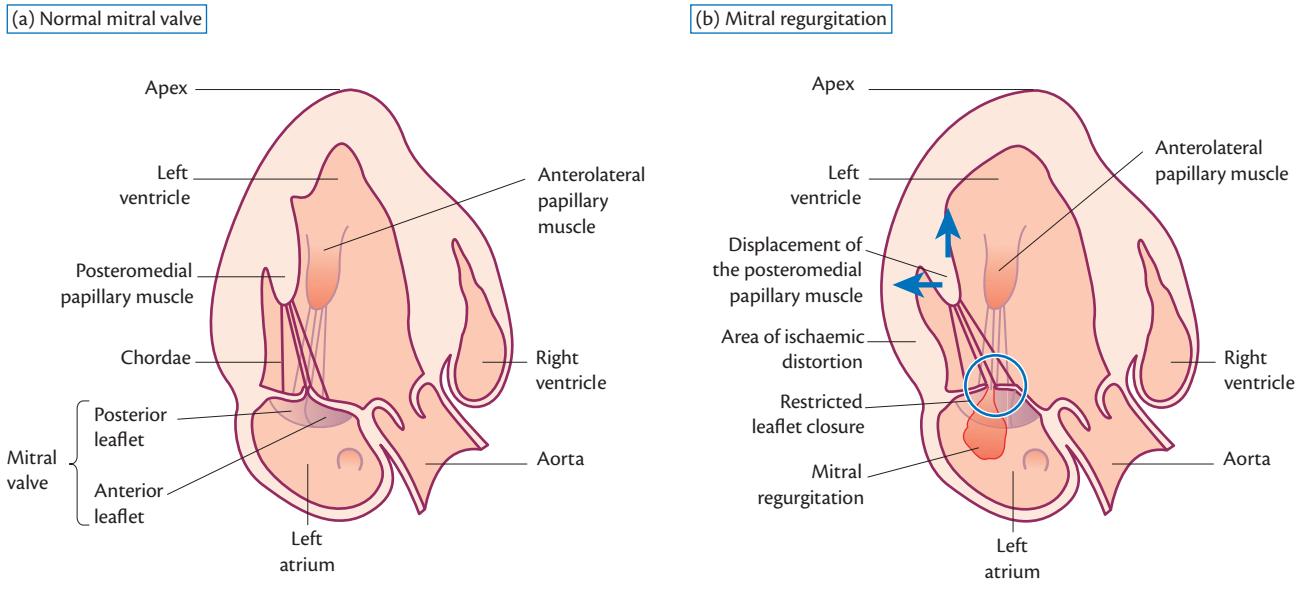

Figure 35.4.2 Pathophysiology of ischaemic MR. A normal mitral valve is shown in (a). Ischaemic MR, in which the leaflets cannot close effectively, is shown in (b). The orientation of the illustration is typical of ultrasound imaging.
Adapted with permission from Levine RA. Dynamic mitral regurgitation—more than meets the eye. N Eng J Med 2004;351:1681–4.

relaxation. When the regurgitant orifice area is small, MR predominates in early systole.[12] In the presence of bileaflet prolapse, the onset of MR may occur in mid systole. The regurgitant orifice increases during systole in valve prolapse. In ischaemic MR, it peaks in early and late systole,[13] and increases in parallel with LV enlargement or rise in afterload. The effective regurgitant orifice area (EROA) is dynamic, and is influenced by changes in loading conditions or contractility.[12, 13]

Progression of functional MR is weakly linked to annular enlargement but more importantly to increased mitral tenting caused by LV remodelling, papillary muscle displacement, and increased chordal traction[14] (Figure 35.4.2).

Acute mitral regurgitation

Acute MR, resulting from papillary muscle chordal rupture, leaflet tear, or perforation, induces an immediate decrease in afterload. LV emptying increases, and left atrial pressure rises acutely, which is transmitted back to the pulmonary circulation. LV function is normal and ejection fraction (EF) is increased. Forward stroke volume is reduced, resulting in tachycardia to maintain cardiac output.

Chronic mitral regurgitation

MR causes LV volume overload. The total stroke volume is increased and the forward stroke volume is maintained or decreased. Diastolic function is supranormal.[15] LV remodelling is characterized by a large radius-to-thickness ratio and a small mass-to-volume ratio resulting in normal and no longer decreased afterload. Thus in chronic organic MR, altered LV function may be present despite a normal EF. Eccentric LV hypertrophy develops and occurs from a decrease in protein degradation rather than an increase in the rate of protein synthesis.[16] Atrial compliance progressively increases. Regurgitant volume is thus handled without a large increase in left atrial pressure and pulmonary congestion.

The haemodynamic state may remain compensated for many years. However, as concentric hypertrophy does not develop, the increased volume is not compensated by increased thickness: the radius-to-thickness ratio remains high, which maintains increased systolic and diastolic stress.

Neurohormonal mechanisms develop[17] and sympathetic nervous system activity is especially increased. LV dysfunction can occur by loss of contractile elements, myocyte dysfunction, and abnormal calcium handling.[18] When chronic MR decompensates, afterload increases and heart failure may develop.

General aspects of MR evaluation

History

Acute severe MR usually results in severe dyspnoea, acute pulmonary oedema, or congestive heart failure.

Patients with chronic severe organic MR may remain asymptomatic for years.[19] Typical symptoms involve a decreased exercise capacity and dyspnoea. In advanced disease stages, LV contractile dysfunction may develop—sometimes even in the absence of symptoms. Patients with MR have a predisposition to develop atrial fibrillation. In secondary MR, symptoms are related to the underlying disease process. MR is a dynamic condition and its severity may vary over time in relation to arrhythmias, ischaemia, hypertension, or exercise. Improvement of LV function may be accompanied by a reduction of MR. Dynamic chronic ischaemic MR can lead to acute pulmonary oedema in the absence of acute myocardial ischaemia.[20]

Physical examination

Systolic blood pressure is usually normal and pulse pressure is not increased.

In chronic severe primary MR, the apical impulse is displaced to the left. The main finding of auscultation is a systolic high-pitched murmur, loudest at the apex. It typically radiates to the axilla, but the radiation of the murmur depends on the direction of the regurgitant jet. If MR is at least moderate, the murmur is holosystolic, beginning at the onset of the first heart sound and continuing after the second heart sound. Its peak intensity is usually heard in late systole in valve prolapse. If the prolapse is not holosystolic, the typical feature is a mid- or late systolic click, generated by the tensing of the chordae and billowing of the mitral leaflets, followed by a late systolic murmur. Both click and murmur vary in intensity and timing with manoeuvres that induce changes in LV volume. Although the loudness of the murmur correlates to some extent with regurgitant severity, it is not reliable for quantification of MR severity. In severe MR, a third heart sound and a short diastolic rumble reflect the rapid and voluminous LV filling. In secondary MR, auscultatory signs are highly dynamic; the murmur is usually of low intensity and peak intensity is usually heard in early systole. The third heart sound is frequent.

In acute MR, the murmur is shortened by a rapid reduction in the pressure gradient between LV and left atrium; it may even be inaudible in papillary muscle rupture with low output.

Evidence of pulmonary congestion or of congestive heart failure is only seen in patients with decompensated disease.

Electrocardiography

Patients in sinus rhythm may present with signs of LV and left atrial hypertrophy. Atrial fibrillation is common. In ischaemic MR, Q waves may be seen, most frequently in the inferior and/or lateral leads; and a left bundle branch block may be present.

Chest radiograph

Chronic severe MR leads to cardiomegaly due to LV and left atrial enlargement, and radiological signs of left heart failure when cardiac dysfunction is present. In acute MR, heart volume may be normal, with evidence of interstitial or alveolar pulmonary oedema.

Because of the fundamental differences between primary and secondary MR[21] and the aspects to consider for further evaluation and treatment[22], the management of the two entities will be further discussed in separate subsections. In the rare cases where both mechanisms are present, the predominant one should guide the management.

Primary mitral regurgitation

Specific aspects of evaluation of primary MR

Acute MR

Acute MR due to papillary muscle rupture should be suspected in patients presenting with acute pulmonary oedema or shock following acute myocardial infarction. Physical examination may be misleading, in particular, the murmur may be soft or inaudible and echocardiographic colour Doppler flow may underestimate the severity of the lesion. The diagnosis is suggested by the demonstration of hyperdynamic LV function in non-infarcted areas in the presence of acute heart failure (HF) and confirmed by the documentation of the ruptured papillary muscle by echo.[23]

Acute MR may also be caused by infective endocarditis or trauma.

Chronic mitral regurgitation

Clinical examination usually provides the first clues that MR is present and may be significant, as suggested by the intensity and duration of the systolic murmur and the presence of the third heart sound.

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in Chapter 35.1. Specific issues in MR are as follows:

Echocardiography is the principal investigation and must include an assessment of severity, mechanism, consequences, and repairability.[7]

The criteria for defining severe primary MR are described in Chapter 35.1. The quantification of severity requires integration of Doppler and morphological information with careful cross-checking of the validity of such data against the effects on the LV, left atrial, and pulmonary pressures.[7] Quantification should be performed in an integrative way, including qualitative, semi-quantitative (including the vena contracta—the narrowest part of the jet), and quantitative parameters—including the proximal isovelocity surface area (PISA) method for the assessment of the regurgitant volume and EROA. However, the limitations of each of these methods need to be considered.[24, 25] For quantitative parameters, interobserver agreement has been reported to be close to 50% only.[24] Doppler echocardiographic findings suggestive of severe MR in the absence of signs of LV volume overload, need to be interpreted cautiously—in particular in asymptomatic patients—since these patients may not have severe MR.[25] These limitations are particularly important when surgery is considered in asymptomatic patients. Planimetry of the regurgitant jet should be abandoned as this measurement is poorly reproducible and depends on numerous factors.

A precise anatomical description of the different lesions, which must be related to the segmental and functional anatomy according to the Carpentier classification in order to assess the feasibility of repair, should be performed (Figures 35.4.3–35.4.5). Transthoracic echocardiography also assesses mitral annular dimensions.[7]

The required information can mostly be obtained by transthoracic echocardiography,[26] but transoesophageal echocardiography (TOE) is more precise for classification of valvular lesions and the subvalvular apparatus. Three-dimensional echocardiography provides additional information for selecting the appropriate repair strategy.[7]

The consequences of MR on ventricular function are assessed using echocardiography by measuring LV size and EF. Left atrial

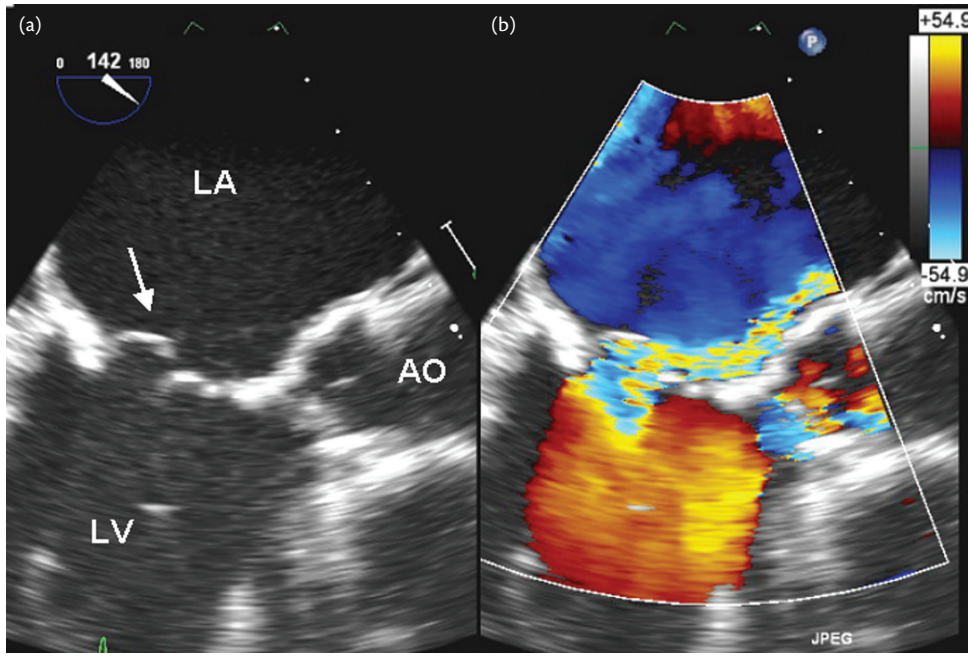

Figure 35.4.3 Transoesophageal echocardiography in MR. (a) Severe mitral valve prolapse with a flail of posterior leaflet (P2 segment) (arrow). (b) Colour flow imaging showing severe MR with an eccentric jet directed in the opposite direction to the prolapse segment. Ao, aorta; LA, left atrium; LV, left ventricle.
Courtesy of Dr E. Brochet.

volume, systolic pulmonary arterial pressure, tricuspid regurgitation and annular size, and right ventricular function are important parameters. The results of mitral valve repair must be assessed intraoperatively by two-dimensional TOE (which can be complemented by three-dimensional TOE), to document a successful repair, ensure sufficient height of coaptation, absence of MR, absence of systolic anterior motion, and wall motion abnormalities.[27]

Determination of functional capacity and symptoms assessed by cardiopulmonary exercise testing may aid the assessment.[28] Exercise echocardiography is useful to quantify exercise-induced changes in MR, in systolic pulmonary artery pressure, and in LV function.[29–31] It may be particularly helpful in patients with symptoms and uncertainty about the severity of MR based on measurements at rest. In asymptomatic patients, the significant increase of pulmonary artery pressure with exercise (>60 mmHg) has been demonstrated to be of prognostic value.[31] The use of global longitudinal strain measured by the speckle tracking method could be of potential interest for the detection of subclinical LV dysfunction but is limited by inhomogeneous algorithms used by different echo systems.

Neurohormonal activation in MR has been evaluated, with several studies suggesting the value of elevated brain natriuretic

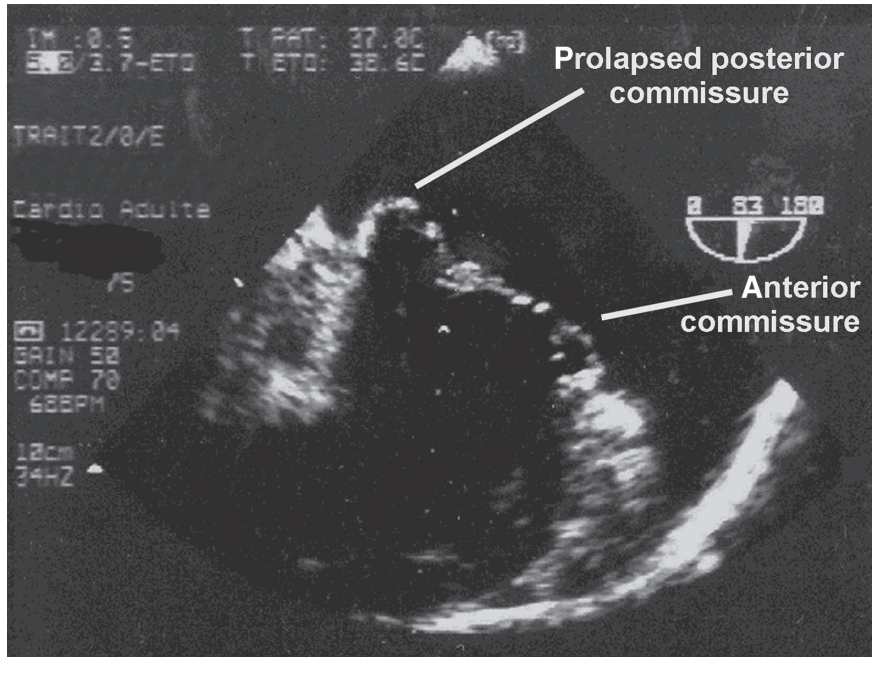

Figure 35.4.4 Prolapse of the posterior commissure. Transoesophageal echocardiography.
Courtesy of Dr B. Cormier.

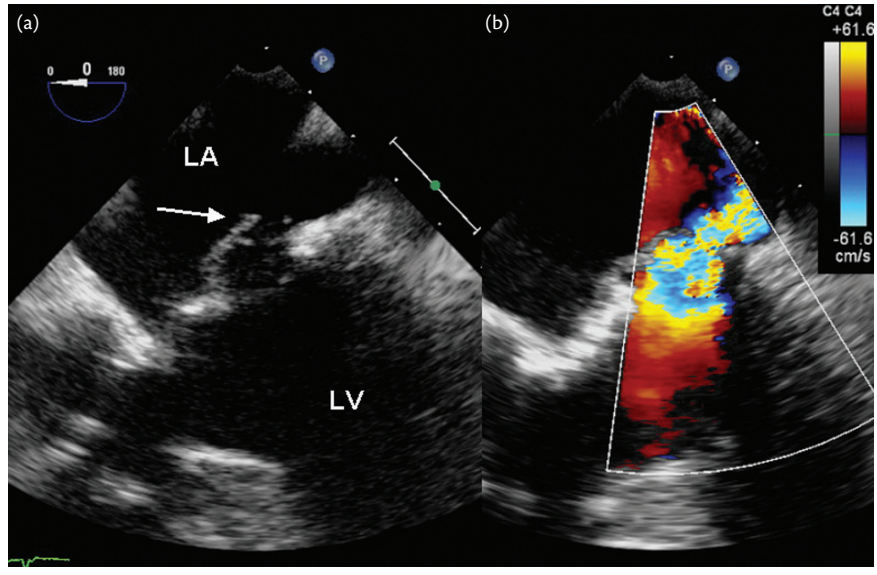

Figure 35.4.5 Mitral valve prolapse with a flail of anterior leaflet. Transoesophageal echocardiography. (a) Severe mitral valve prolapse with a flail of posterior leaflet (P2 segment) (arrow). (b) Colour flow imaging showing severe MR with an eccentric jet directed in the opposite direction to the prolapse segment. LA, left atrium; LV, left ventricle.
Courtesy of Dr E. Brochet.

peptide (BNP) levels and a change in BNP as predictors of outcome (particularly of symptom onset). A cut-off BNP value of 105 pg/mL or greater determined in a derivation cohort was prospectively validated in a separate cohort, and helped to identify asymptomatic patients at higher risk[32] of developing HF, LV dysfunction, or death on mid-term follow-up. Low plasma BNP has a high negative predictive value and may be helpful for the follow-up of asymptomatic patients.[33]

Natural history

Acute MR is poorly tolerated and carries a poor prognosis in the absence of intervention. In patients with chordal rupture, the clinical condition may stabilize after an initial symptomatic period. However, unoperated, it carries a poor prognosis owing to subsequent development of pulmonary hypertension.

In asymptomatic severe chronic MR, the estimated 5-year rates of death from any cause, death from cardiac causes, and cardiac events (death from cardiac causes, HF, or new atrial fibrillation with medical management) have been reported to be 22±3%, 14±3%, and 33±3%, respectively.[21] In addition to symptoms, the following were all found to be predictors of poor outcome: age, atrial fibrillation, severity of MR (particularly EROA), pulmonary hypertension, left atrial dilatation, increased left ventricular end-systolic diameter (LVESD), and low LVEF.[21, 34–39]

Surgical techniques in degenerative MR

Surgical access, valve exposure, and evaluation

TOE represents a major diagnostic tool in the evaluation of the mitral valve and is essential to define and predict the reparability of the valve. TOE assesses the anatomy and mobility of the leaflets, the size of the annulus, the subvalvular apparatus and the size and direction of the regurgitation jets (Figure 35.4.6 and Figure 35.4.7).

Mitral valve surgery is usually performed through a full median sternotomy, although, less invasive accesses, such as the right lateral thoracotomy and partial sternotomy, are currently used in many centres. Extracorporeal circulation with direct aortic and bicaval cannulation is used. An appropriate exposure of the mitral valve plays a key role during surgery. The exposure of the mitral valve is usually achieved by a direct left atriotomy, just behind the right interatrial grove. Alternatively, a transseptal incision (though the right atrium, especially when intervention on the tricuspid valve is also necessary) and a superior approach (roof of left atrium) are also adopted by many surgeons.

After the valve is exposed, saline solution can be injected into the LV through the mitral orifice to visualize the area of leaflet non-coaptation, testing the leaflet mobility and checking the subvalvular apparatus. The same test is usually repeated after different steps of the valve repair and once it is completed, to test the final result.

A careful valve analysis is performed by using hooks to gently pull or to manipulate the mitral leaflets in order to evaluate their mobility and to identify chordal rupture, elongation, or retraction. The subvalvular apparatus is also assessed. The commissural regions are carefully checked for fusion or prolapse. Finally, eventual dilatation of the annulus is evaluated.

Repair techniques

In case of mitral prolapse due to degenerative disease, this should be considered as a spectrum of lesions, starting from a single scallop involvement (usually P2) (Figure 35.4.8) to multisegment prolapse, up to Barlow's disease (Figure 35.4.9).

Carpentier first introduced a classification to define the mechanisms of MR according to leaflets' movement (Figure 35.4.1). Moreover, he described three major targets for mitral valve repair: (1) restitution of physiological leaflet motion, (2) establishment of an adequate line of leaflet coaptation, and (3) stabilization of the annulus while maintaining an adequate size of the mitral orifice.

Quadrangular or triangular resection of the posterior leaflet

Prolapse of the middle scallop (P2) of the posterior leaflet represents the most frequent cause of mitral regurgitation in

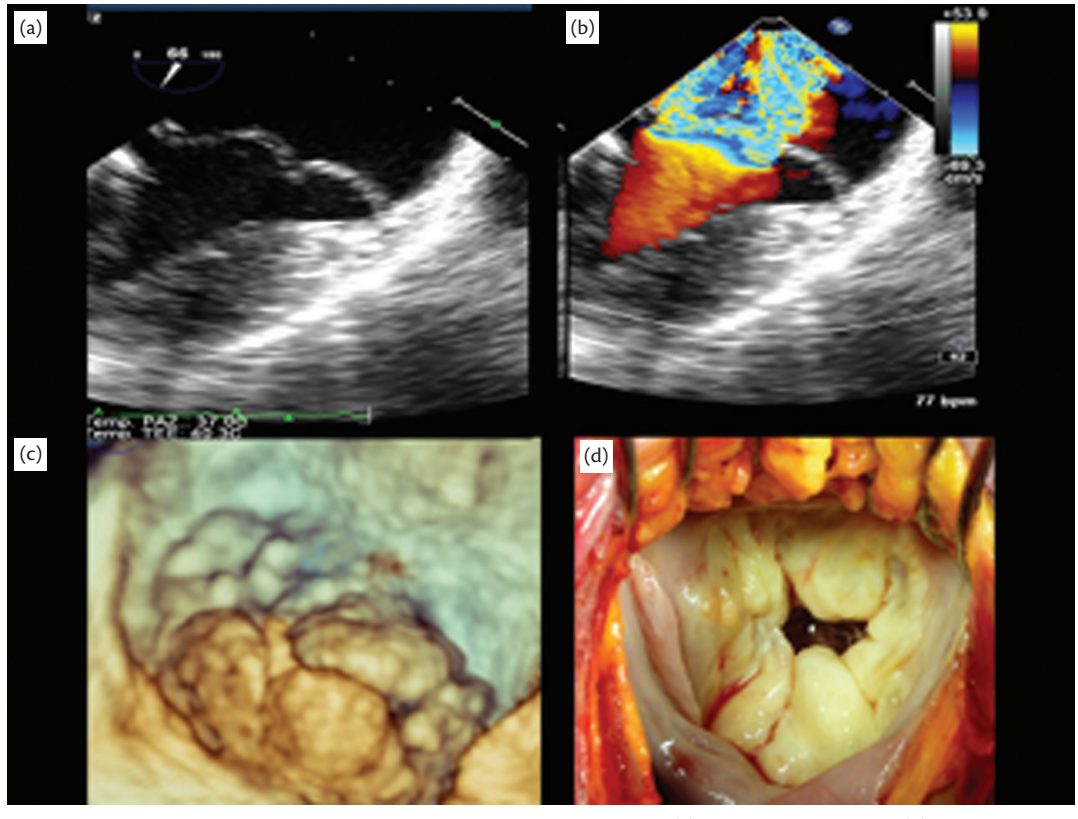

Figure 35.4.6 Myxomatous mitral valve with bileaflet prolapse and severe valve regurgitation. (a) Two-dimensional TOE. (b) Colour Doppler TOE. (c) Real-time three-dimensional TOE. (d) Intraoperative finding.
De Bonis, M. et al. Nat. Rev. Cardiol. 9, 133–146 (2012); published online 22 November 2011; doi:10.1038/nrcardio.2011.169

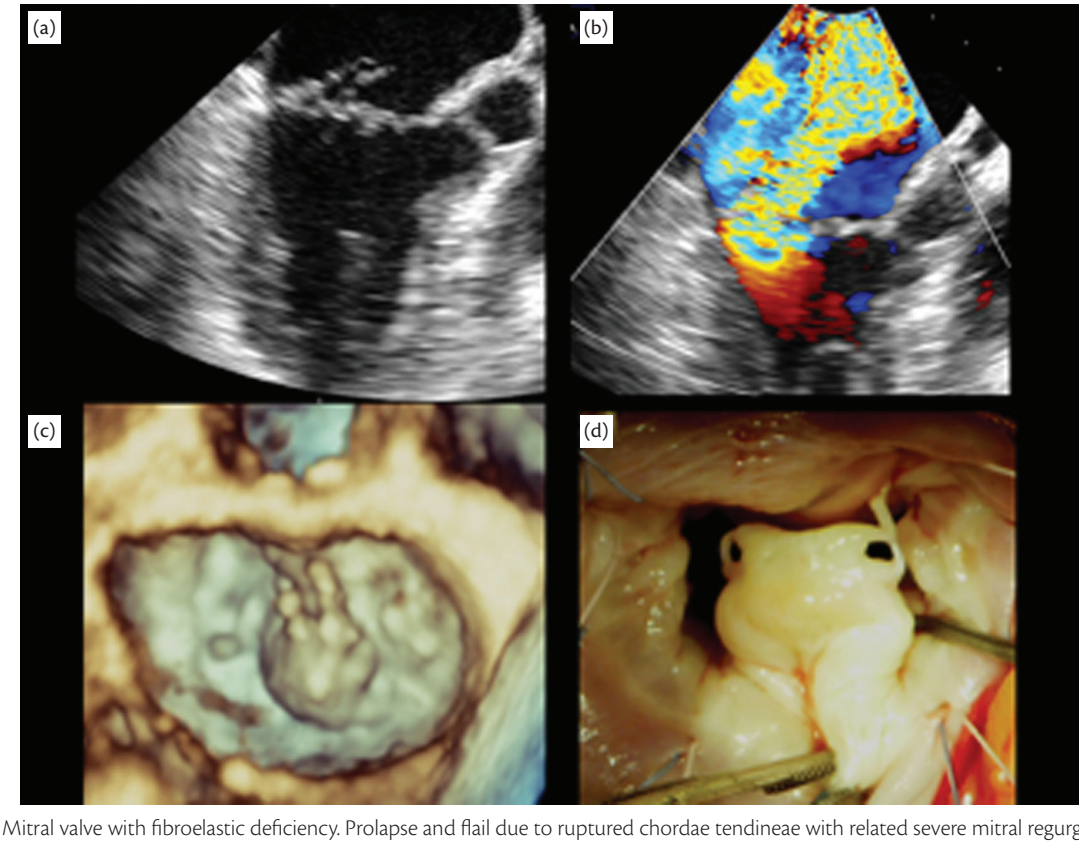

Figure 35.4.7 Mitral valve with fibroelastic deficiency. Prolapse and flail due to ruptured chordae tendineae with related severe mitral regurgitation. (a) Two-dimensional TOE. (b) Colour Doppler TOE. (c) Real-time three-dimensional TOE. (d) Intraoperative finding.
De Bonis, M. et al. Nat. Rev. Cardiol. 9, 133–146 (2012); published online 22 November 2011; doi:10.1038/nrcardio.2011.169

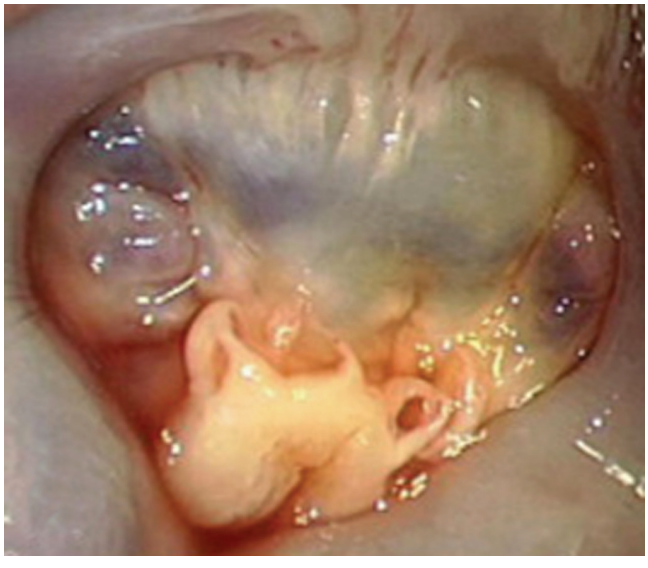

Figure 35.4.8 Flail of a single scallop (P2) of the posterior leaflet due to chordal rupture—intraoperative finding.

degenerative mitral valve disease. This condition may result from elongation or rupture of chordae. In the presence of a small prolapse or flail, triangular resection may be used to repair the posterior leaflet. If the prolapse is relatively large, a quadrangular resection of the prolapsing segment of the posterior leaflet with sliding plasty can be adopted to better cover the annulus area where excision has been performed and to decrease the height of the posterior leaflet (Figure 35.4.10). The adjacent area of normal leaflet without elongated chordae is first identified and advancement flaps are created cutting along the annulus towards the lateral sides of the remnants of the posterior leaflet. Following their reinsertion into the posterior annulus with a continuous polypropylene suture, the posterior leaflet continuity is re-established by re-approximation of the two edges, either with continuous or interrupted sutures.

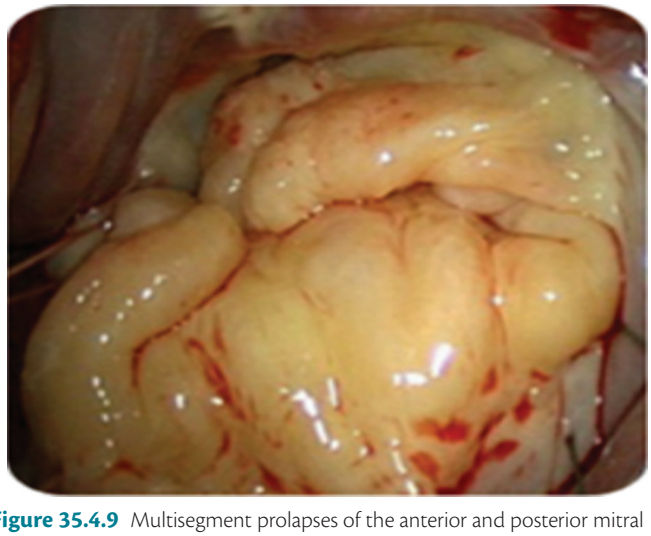

Figure 35.4.9 Multisegment prolapses of the anterior and posterior mitral valve leaflet in Barlow's disease—intraoperative finding.

Triangular resection of the anterior leaflet

A triangular resection of the anterior leaflet, usually the central scallop, may be used for a redundant prolapsing anterior leaflet. It may also be used for ruptured chordae of the anterior leaflet. A small triangle is excised from the free edge of the anterior leaflet extending the incision near the annulus. However, this technique has largely been abandoned in favour of artificial chordae to correct the prolapse.

Artificial chordae implantation and chordal transposition

In degenerative MR, chordae tendineae may be elongated or ruptured. Chordal replacement with a polytetrafluorethylene (PTFE) suture is currently one of the most popular techniques for the treatment of diseased chordae (Figure 35.4.11). PTFE neochordae support the free margins of the prolapsing leaflet and can be implanted in either anterior or posterior papillary muscles, respecting the policy of not crossing the midline or native chordae, to prevent excess traction. A variety of different techniques have been reported to establish the correct size of PTFE neochordae. This concept of 'respect rather than resect' the leaflet tissue is becoming a more and more accepted approach. In many instances, the abnormal redundant leaflet tissue is displaced into the ventricle to maintain a good coaptation surface between leaflets and to avoid systolic anterior motion. However limited leaflet resection in combination with PTFE remains the preferred technique in many centres.

Native chordae from the posterior leaflet can also be transferred to the anterior mitral leaflet to repair a prolapsing segment from an elongated or torn chord. The chosen chord from the posterior mitral leaflet is resected with a portion of the above leaflet tissue and transposed on the anterior mitral leaflet. Alternatively, secondary chordae may be transferred to the prolapsing free edge to correct the lesion (Figure 35.4.12).

Edge-to-edge repair

With this technique, developed by Alfieri, the matching edges of both leaflets are sutured together at the site of regurgitation. If the regurgitant jet is located in the central portion of the mitral valve (between A2 and P2), this correction generates a double-orifice valve. By contrast, when the regurgitation is in the commissural area (paracommissural), the edge-to-edge suture leads to a single-orifice valve with a relatively smaller area.

Prosthetic annular ring

In surgical mitral repair, annuloplasty plays a very important role and is routinely carried out by means of a prosthetic ring or band. The aim of annuloplasty is to restore the normal ratio between annular diameters and regain normal annular shape. Lack of annuloplasty has been associated with reduced durability of repair, although some evidence suggests that annuloplasty could be avoided in selected patients.

Results of surgery

Despite the absence of a randomized comparison between the results of valve replacement and repair in the setting of degenerative MR, it is widely accepted that, when feasible, valve repair

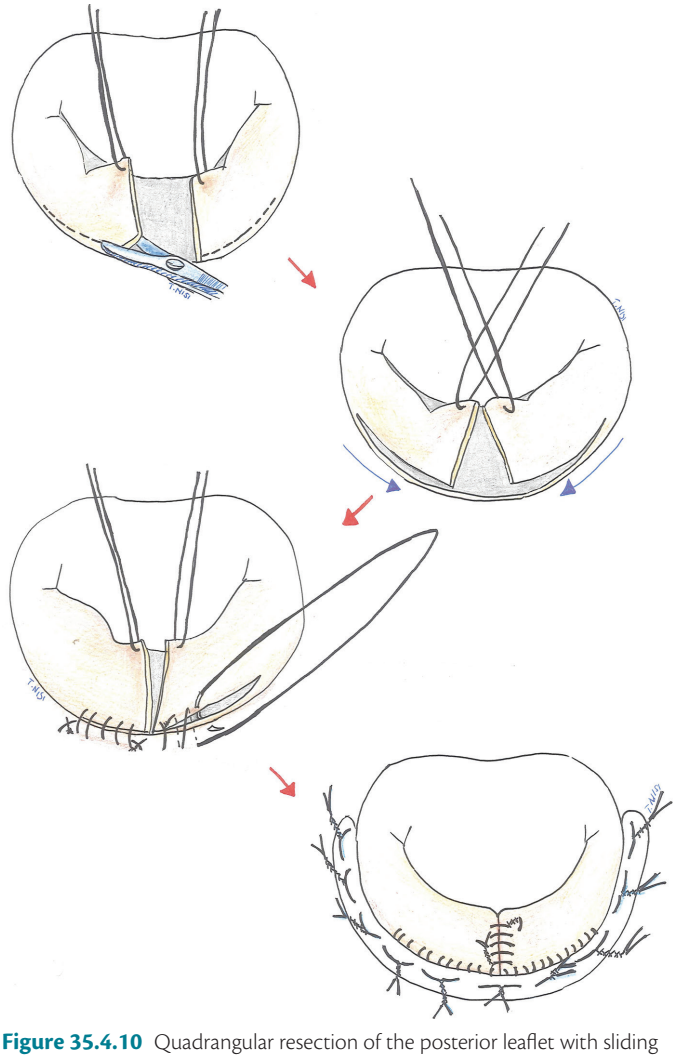

Figure 35.4.10 Quadrangular resection of the posterior leaflet with sliding plasty. After resecting the prolapsing segment, the remaining portions of the posterior leaflet are detached from the annulus for an extension of about 1.5–2 cm. A portion of their basal tissue is removed to reduce the height of the posterior leaflet. These flaps are then reattached to the annulus and the edges of the quadrangular resection are reapproximated to fill the gap.
From La valvulopatia mitralica. Elisabetta Lapenna, Michele De Bonis, Giovanna Di Giannuario, Andrea Giacomini, Teodora Nisi, Denti Paolo, Fumero Andrea, Giovanni La Canna, Ottavio Alfieri. In: Trattato di chirurgia cardiaca by Luigi Chiariello. Società Editrice Universo. ISBN 9788865151297/8865151293. Publisher: Seu, 2016.

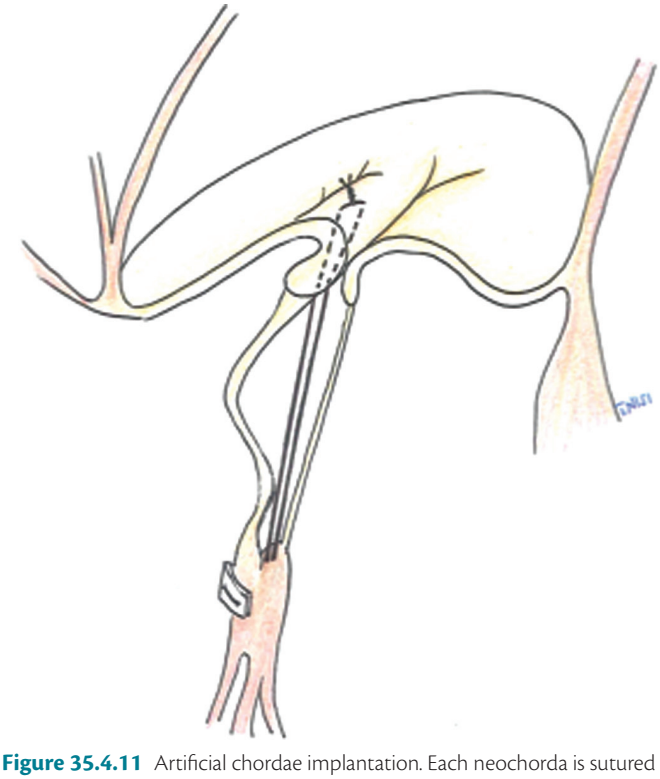

Figure 35.4.11 Artificial chordae implantation. Each neochorda is sutured to the fibrous portion of the papillary muscle and then at the free edge of the leaflet in correspondence of the prolapsing portion.
From La valvulopatia mitralica. Elisabetta Lapenna, Michele De Bonis, Giovanna Di Giannuario, Andrea Giacomini, Teodora Nisi, Denti Paolo, Fumero Andrea, Giovanni La Canna, Ottavio Alfieri. In: Trattato di chirurgia cardiaca by Luigi Chiariello. Società Editrice Universo. ISBN 9788865151297/8865151293. Publisher: Seu, 2016.

is the optimal surgical treatment in patients with severe primary MR. When compared with valve replacement, repair has a lower perioperative mortality, improved survival, better preservation of postoperative LV function, and lower long-term morbidity.

Besides symptoms, the most important predictors of postoperative outcome are age, atrial fibrillation, preoperative LV function, pulmonary hypertension, and repairability of the valve. The best results of surgery are observed in patients with a preoperative EF greater than 60%. While a cut-off of LVESD of 45 mm or greater is generally accepted, in a series of MR due to flail leaflet, a LVESD of 40 mm or larger has been shown to be independently associated with increased mortality with medical treatment as opposed to mitral surgery.[39] In addition to the initial measurements, the temporal changes of LV dimensions and systolic function should also be taken into account when making decisions about the timing of surgery,[40] but require further validation.

The probability of a durable valve repair is of crucial importance. Degenerative MR due to segmental valve prolapse can usually be repaired with a low risk of reoperation. The repairability of rheumatic lesions, extensive valve prolapse, and, even more so, MR with leaflet calcification or extensive annulus calcification is more challenging.[35] In current practice, surgical expertise in mitral valve repair is growing and becoming widespread.[41]

Patients with predictable complex repair should undergo surgery in experienced repair centres with high repair rates and low operative mortality.[41–43] According to an analysis of the Society of Thoracic Surgeons database, high volume centres, which were defined by a volume of more than 140 annual mitral valve procedures, had a surgical mortality of less than 1% for mitral repair surgery.[42] Ultimately, attention must be paid to surgeon-specific volume and experience, and an annual surgical specific volume of more than 50 mitral procedures was associated with a predicted repair rate of 80%.[44] Finally, the learning curve and overall experience of an individual surgeon needs to be considered, since lowest mortality and morbidity may be reached after a total of 300 mitral valve surgeries.[45] When repair is not feasible, mitral valve replacement with preservation of the subvalvular apparatus is preferred.

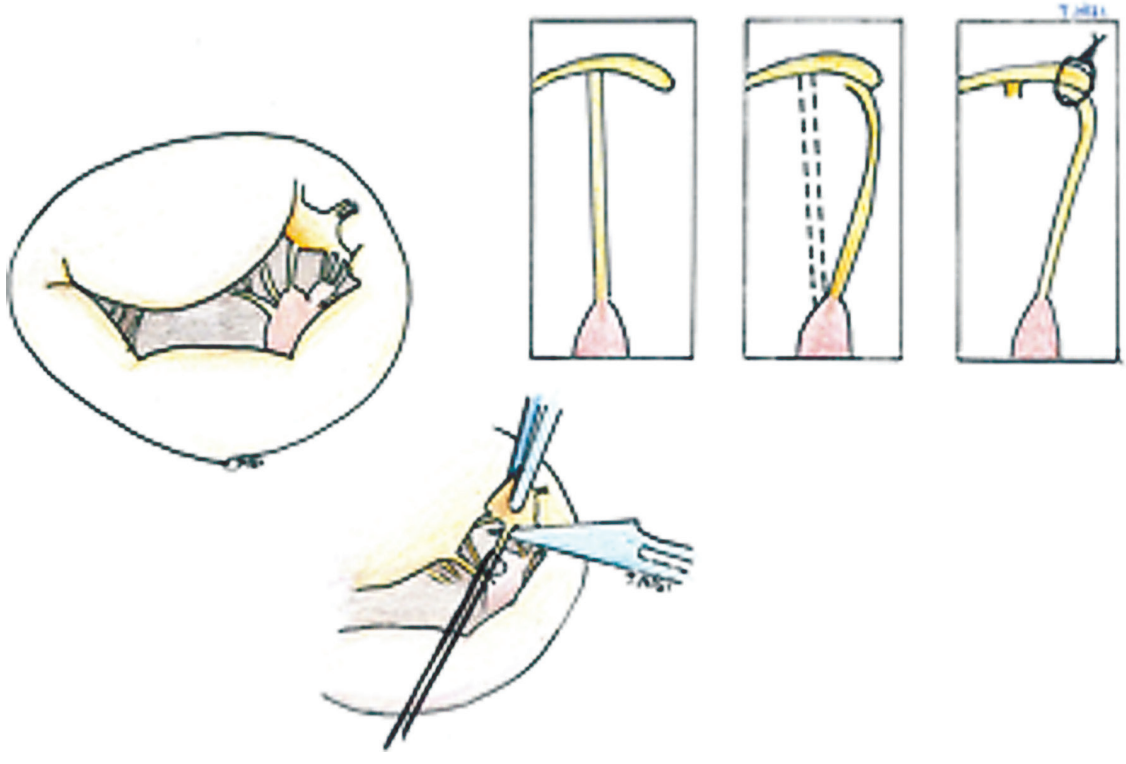

Figure 35.4.12 Transfer of secondary chordae. A secondary chorda is transferred to the prolapsing free edge to correct the lesion.
From La valvulopatia mitralica. Elisabetta Lapenna, Michele De Bonis, Giovanna Di Giannuario, Andrea Giacomini, Teodora Nisi, Denti Paolo, Fumero Andrea, Giovanni La Canna, Ottavio Alfieri. In: Trattato di chirurgia cardiaca by Luigi Chiariello. Società Editrice Universo. ISBN 9788865151297/8865151293. Publisher: Seu, 2016.

Transcatheter and percutaneous intervention

Catheter-based interventions have been developed to correct organic MR either through a transapical or a percutaneous approach. Among the percutaneous procedures, the edge-to-edge repair is the only one adopted worldwide.[46] The applicability of the procedure is limited because precise echocardiographic criteria have to be respected to make a patient eligible[46] and the acute achievement of an optimal outcome, as defined by the Mitral Valve Academic Research Consortium criteria, remains difficult to predict.[47] Percutaneous edge-to-edge repair for degenerative MR is generally safe with low rates of procedural and 30-day mortality and complications.[46, 48–50] Post-procedural mitral stenosis is very rare and means the hospital stay is short. However, efficacy is suboptimal and more than 50% of patients are left with residual or recurrent MR greater than or equal to 2/4 at 1 and 4 years.[46, 48–50] When compared with surgical treatment, percutaneous edge-to-edge repair is associated with a higher rate of MR requiring repeat surgery and MR grade 3–4 at 1 and 4 years.[46, 48–50] Mitral valve repair after an unsuccessful clip procedure has been reported, although valve replacement may be necessary in the majority of patients. In high-risk patients, early mortality following edge-to-edge treatment has been high (up to 9%)[50, 51] and 1-year survival 80%,[50] mirroring the advanced age and multiple comorbidities of the populations studied. Additional studies are needed to establish the best therapeutic option in this high-risk subset.

Indications for intervention

Urgent surgery is indicated in patients with acute severe MR. Rupture of a papillary muscle necessitates urgent surgical treatment after stabilization of the haemodynamic status, using an intra-aortic balloon pump, positive inotropic agents, and, when possible, vasodilators. Valve surgery consists of valve replacement in most cases.[23]

The indications for surgery in severe chronic primary MR are shown in Table 35.4.1 and Figure 35.4.13.

The decision of whether to replace or repair depends mostly on valve anatomy and surgical expertise. However, mitral repair should be the preferred technique.

Surgery is indicated in patients who have symptoms due to chronic MR, but no contraindications to surgery.

When LVEF is less than 30%, a durable surgical repair can still improve symptoms, although the effect on survival is largely unknown. In this situation, the decision of whether to operate will take into account the response to medical therapy, surgical risk, and the likelihood of successful valve repair.

Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary MR who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by the heart team, avoiding futility.

The management of asymptomatic patients is controversial as there are no randomized trials to support any particular course of action. However, surgery can be proposed in selected

Table 35.4.1 Indications for intervention in severe primary mitral regurgitation

	Class[a]	Level[b]
Mitral valve repair should be the preferred technique when the results are expected to be durable	I	C
Surgery is indicated in symptomatic patients with LVEF >30%[38, 81, 82]	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm* and/or LVEF ≤60%)[37, 82]	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45 mm and LVEF >60%) and atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension[c] (systolic pulmonary pressure at rest >50 mmHg)[53, 83]	IIa	B
Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40–44 mm* when a durable repair is likely, surgical risk is low, the repair is performed in heart valve centres, and at least one of the following findings is present: ◆ flail leaflet, or ◆ presence of significant left atrial dilatation (volume index ≥60 mL/m² BSA) in sinus rhythm	IIa	C
Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when likelihood of successful repair is high and co-morbidity low	IIa	C
Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when likelihood of successful repair is low and co-morbidity low	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the heart team, avoiding futility	IIb	C

BSA, body surface area; LV, left ventricle; LVE, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; SPAP, systolic pulmonary artery pressure.
[a] Class of recommendation.
[b] Level of evidence.
[c] If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement.
* Cut-offs refer to averaged sized adults and may require adaption in patients with unusually small or large stature.

asymptomatic patients with severe MR, in particular when repair is likely and surgical risk low.

In patients with signs of LV dysfunction (LVEF ≤60% and/or LVESD ≥45 mm), surgery is indicated, even in patients with a high likelihood of valve replacement. Lower LVESD values can be used in patients of small stature.

If LV function is preserved, surgery should be considered in asymptomatic patients with atrial fibrillation[52] related to MR or pulmonary hypertension (systolic pulmonary arterial pressure >50 mmHg at rest). Echocardiographic measures of pulmonary pressure show disagreement with invasive measures.

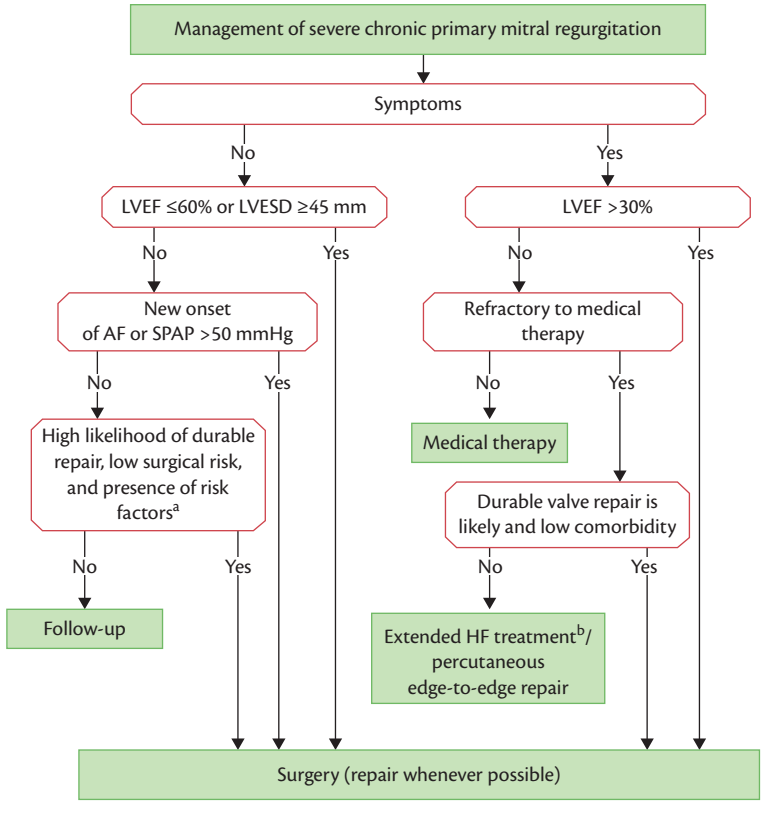

Figure 35.4.13 Management of severe chronic primary mitral regurgitation. AT, atrial fibrillation; BSA, body surface area; CRT, cardiac resynchronization therapy; HF, heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; SPAP, systolic pulmonary arterial pressure.
[a] When there is a likelihood of durable valve repair at a low-risk, valve repair should be considered (IIa C) in patients with LVESD ≥40 mm and one of the following is present: flail leaflet or LA volume ≥60 mL/m² BSA at sinus rhythm.
[b] Extended HF management includes the following: CRT; ventricular assist devices; cardiac restraint devices; heart transplantation.

If surgery is indicated solely by pulmonary hypertension, the pulmonary pressure measurement should thus be confirmed by right heart catheterization.

Surgery should be considered in asymptomatic patients with preserved LVEF (≥60%) and LVESD 40–44 mm,[39] when a durable repair is likely, surgical risk low, repair performed in a heart valve centre, and at least one of the following findings is present:

- Flail leaflet, or
- Presence of significant left atrial dilatation (volume index ≥60 mL/m² body surface area (BSA))[53] in sinus rhythm.

Pulmonary hypertension on exercise (systolic pulmonary artery pressure ≥60 mmHg) has been found to be associated with an increased event-rate.[30] However, this threshold may be physiological in elderly patients even in the absence of mitral regurgitation and a discrepancy with invasive measures cannot be excluded. Consequently, criteria that may indicate surgery have not been well enough defined to include it in current recommendations.

In other asymptomatic patients, severe MR can be safely followed with a careful watchful waiting approach until symptoms occur or previously recommended cut-off values are reached.[19] Ideally, such a strategy[54] can be implemented in heart valve centers.[55] Some registry-based series suggest a better outcome with an early surgical approach.[56] Nevertheless, a series performed in centres with excellent surgical outcomes could not find a difference in overall survival between an early surgical approach and watchful waiting using propensity analysis.[57] In the absence of randomized studies, early elective surgery for asymptomatic patients with no other indication for surgery, remains a subject of debate.

Close clinical follow-up is recommended when there is doubt about the feasibility of valve repair. In this latter group, operative risk or prosthetic valve complications, or both of these, probably outweigh the advantages of correcting MR at an early stage. These patients should be reviewed carefully and surgery indicated when symptoms or objective signs of LV dysfunction occur.

When guideline indications for surgery are reached, early surgery—within 2 months—is associated with better outcomes since the development of even mild symptoms by the time of surgery is associated with deleterious changes in cardiac function after surgery.[58]

Finally, solid data on the value of surgery are currently lacking for patients with mitral valve prolapse and preserved LV function with recurrent ventricular arrhythmias despite medical therapy.

Medical therapy

In acute MR, reduction of filling pressures can be obtained with nitrates and diuretics. Sodium nitroprusside reduces afterload and regurgitant fraction, as does an intra-aortic balloon pump. Inotropic agents and an intra-aortic balloon pump should be added in case of hypotension.

There is no evidence to support the use of vasodilators, including angiotensin-converting enzyme inhibitors (ACEIs), in chronic MR without HF and therefore they are not recommended in this group of patients. However, when HF has developed, ACEIs are beneficial and should be considered in patients with advanced MR and symptoms who are not suitable for surgery or when residual symptoms persist following surgery. Beta blockers and spironolactone (or eplerenone) should also be considered as appropriate.[59]

Serial testing

Asymptomatic patients with moderate MR and preserved LV function can be followed-up on a yearly basis and echocardiography should be performed every 1–2 years. Asymptomatic patients with severe MR and preserved LV function (EF > 60%) should be followed clinically and echocardiographically every 6 months, the follow-up being shorter if no previous evaluation is available and in patients with values close to the cut-off limits or demonstrating significant changes since their last review. Patients should be instructed to report any change in functional status in a prompt manner. The ideal setting for follow-up is within heart valve center.[55]

Secondary mitral regurgitation

Specific aspects of evaluation of secondary MR

In chronic secondary MR, the murmur is frequently soft and its intensity is unrelated to the severity of MR. Ischaemic MR is a dynamic condition and its severity may vary depending upon changes in loading conditions: hypertension, medical therapy, or exercise. The dynamic component can be assessed and quantified by exercise echocardiography. Acute pulmonary oedema may result from dynamic changes in ischaemic MR and the resulting increase in pulmonary vascular pressure.[20]

Echocardiographic examination is useful for establishing the diagnosis and differentiating secondary from primary MR in patients with coronary disease or HF.

In secondary MR, lower thresholds of severity (using quantitative methods: ≥20 mm² for EROA and ≥30 mL for regurgitant volume as compared to severe primary MR: EROA ≥40 mm²; regurgitant volume ≥60 mL) have been found to be associated with a higher mortality.[7, 60] However, in these patients it is not entirely clear whether survival is directly impacted by MR or by LV function and—in contrast to primary MR—whether treatment of MR can improve survival. Furthermore, the assessment of the true extent of LV systolic function is complicated by MR and the associated reduced afterload. Indeed, so far no survival benefit has been confirmed for MR treatment in secondary MR. For isolated mitral valve treatment (surgery or percutaneous edge-to-edge repair) in secondary MR, thresholds for treatment need to be validated in clinical trials.

The final assessment of the degree of secondary MR should be performed after optimized medical treatment. Severity of tricuspid regurgitation and right ventricular size and function should also be evaluated. As ischaemic MR is a dynamic condition, echocardiographic quantification of MR during exercise may provide information about dynamic characteristics, and have prognostic importance. An exercise-induced increase of 13 mm² or more of the EROA has been suggested to be associated with an increase in

the relative risk of death and hospitalization for cardiac decompensation.[61] The prognostic value of exercise tests to predict the results of surgery, however, remains to be evaluated. The prognostic importance of dynamic MR is not necessarily applicable to secondary MR due to idiopathic cardiomyopathy and data are more limited as compared with secondary MR in ischaemic heart disease.

An assessment of the coronary status is necessary to evaluate options of revascularization. In patients who require revascularization, the threshold for repairing additional MR can obviously be lower than in the case of isolated mitral valve intervention. This has also to be kept in mind when applying different definitions of MR severity compared to primary MR.

In patients with a low LVEF, it is also mandatory to assess the presence and extent of myocardial viability (by dobutamine echocardiography, single-photon emission computed tomography, positron emission tomography, or cardiovascular magnetic resonance).

In patients with CAD undergoing revascularization, the decision to treat (or not treat) ischaemic MR should be made before surgery, as general anaesthesia may reduce the severity of regurgitation significantly. In addition, intraoperative testing using acute volume and inotrope challenge may be performed.

Natural history

Patients with chronic ischaemic MR have a poor prognosis.[60] The presence of severe CAD and LV dysfunction have prognostic importance. The causative role of MR in the poor prognosis, however, remains uncertain. Nevertheless, increasing MR severity is associated with worse outcome.[60, 62]

In patients with secondary MR due to non-ischaemic aetiology, data regarding the natural history are more limited than in ischaemic MR. A precise analysis is difficult because of the limited number of small series including many confounding factors. Some studies have shown an independent association between significant MR and a poor prognosis.[62, 63]

Results of surgery

Surgery for secondary MR remains a challenge, particularly when concomitant revascularization is not an option, owing to significant operative mortality, high rates of recurrent MR, and the absence of proven survival benefit.[64–66] Operative mortality is higher than in primary MR and the long-term prognosis is worse due, at least in part, to more severe comorbidities.

Indications and the preferred surgical procedure remain controversial. Most studies show that severe ischaemic MR is not usually improved by revascularization alone and that persistence of residual MR carries an increased mortality risk. However, the impact of valve surgery on survival remains unclear since most studies failed to demonstrate improved long-term clinical outcome following surgical correction of secondary MR.[64–66] The presence of significant myocardial viability should be taken into consideration when deciding whether to operate as it is a predictor of good outcome after repair combined with bypass surgery.[67] The optimal surgical approach remains controversial.[68] Mitral valve repair performed with an undersized rigid complete ring to restore leaflet coaptation and valve competence can be performed with acceptable perioperative risk but should be reserved to carefully selected patients without echocardiographic risk factors for residual or recurrent MR. Preoperative predictors of recurrent secondary MR after isolated undersized annuloplasty include factors reflecting mitral valve deformation, local and global left ventricular remodelling (LVEDD >65 mm, posterior mitral leaflet angle >45°, distal anterior mitral leaflet angle >25°, systolic tenting area >2.5 cm^2, coaptation distance (distance between the annular plane and the coaptation point) >10 mm, end-systolic interpapillary muscle distance >20 mm, and systolic sphericity index >0.7, basal aneurysms and dyskinesia).[69–71] In patients at high likelihood of MR recurrence, valve replacement should be considered.

In recent observational studies, survival after repair was comparable to replacement, with higher rates of MR recurrence after valve repair.[72, 73] Restrictive annuloplasty was recently compared to chordal-sparing mitral valve replacement in a randomized study of patients with secondary ischaemic MR and demonstrated no difference in clinical outcome and LV reverse remodelling at 1 year but was associated with a markedly higher recurrence rate.[68] However, patients with predictors of repair failure were not excluded and the patients with the most reverse ventricular remodelling were patients undergoing repair who did not experience MR recurrence. Repair failure is thus high in unselected patients and undersized annuloplasty should be reserved to patients without preoperative predictors of recurrent MR.

Percutaneous intervention

Percutaneous edge-to-edge repair for secondary MR is a low-risk option in selected patients with secondary MR and eligible anatomical criteria to improve symptoms, functional capacity, and quality of life, and induce reverse LV remodelling.[74] Although some degree of MR reduction is achieved in the majority of patients, its efficacy remains suboptimal with at least 2+ residual and recurrent MR in more than 50% of the patients at 12 months.[74] Suboptimal results may in part be due to treatment of patients with very advanced disease. The futility of the procedure needs to be questioned in particular for patients with advanced LV remodelling and very severely reduced ventricular function.

Similarly to surgery, a survival benefit compared to optimal medical therapy has not yet been demonstrated and randomized trials (i.e. COAPT, RESHAPE, and MITRAFR[75]) are ongoing to further clarify this issue.

Promising data have been reported for direct percutaneous annuloplasty.[76] Current data on coronary sinus annuloplasty report suboptimal outcomes and the use of coronary sinus devices should be discouraged.

Indications for intervention

The heterogeneous data regarding secondary MR result in less evidence-based management than in primary MR and highlight the importance of heart team-based decision-making. An enlarged heart-team that includes heart failure and electrophysiology

Table 35.4.2 Indications for mitral valve intervention in chronic secondary mitral regurgitation[a]

	Class[b]	Level[c]
Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF >30%	I	C
Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF <30% but with an option for revascularization, and evidence of myocardial viability	IIa	C
When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk	IIb	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility	IIb	C
In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the heart team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for ventricular assist device or heart transplant according to individual patient characteristics	IIb	C

CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction.
[a] See 'Specific aspects of evaluation of secondary MR' in the text for quantification of secondary mitral regurgitation, which must always be performed under optimal treatment.
[b] Class of recommendation.
[c] Level of evidence.

specialists is recommended. Recommendations are summarized in Table 35.4.2.

In patients with CAD undergoing revascularization, the evaluation and decision to treat (or not to treat) ischaemic MR should be made before surgery, as general anaesthesia may reduce the severity of regurgitation significantly. When MR severity is assessed intraoperatively, the use of acute volume and inotrope challenge may be helpful. At the time of bypass surgery, treatment of severe secondary MR is indicated. Surgery should also be considered in symptomatic patients with severe secondary MR not due to primary ventricular disease but to annular dilatation that is caused by long-standing atrial fibrillation and preserved LV systolic function.

Mitral valve surgery may be considered in patients with severe secondary MR who have a LVEF of at least 30% who remain symptomatic despite optimal medical therapy (including cardiac resynchronization therapy (CRT) if indicated), who have a low surgical risk, when revascularization is not indicated.[77]

Percutaneous edge-to-edge repair may be considered in these latter patients when surgical risk is not low, avoiding futility.

When those patients with no option for revascularization have already developed severe LV dysfunction (EF ≤30%), percutaneous edge-to-edge repair may be considered, mainly to improve symptoms in patients with symptomatic severe secondary MR despite optimal medical therapy (including CRT if indicated), who fulfil the echo criteria of eligibility, avoiding futility. Similarly to surgery, a survival benefit compared to 'optimal' medical therapy according to current guidelines[78] has not yet been proved. Surgery may be considered in such patients when they are not candidates for edge-to-edge repair and when the surgery is performed in centres that can provide a ventricular assist device if pump function does not resume after surgery. In these cases, the heart team should also carefully evaluate the options of a ventricular assist device or heart transplant according to the individual patient's characteristics.

There is continuing debate regarding the management of moderate ischaemic MR in patients undergoing coronary artery bypass grafting. A recent randomized trial could not show a benefit of concomitant valve surgery.[79] Long-term results of either approach are unknown. In patients with a low EF, mitral valve surgery is more likely to be considered if myocardial viability is present and if comorbidity is low. In patients capable of exercising, exercise echocardiography should be considered whenever possible. Exercise-induced dyspnoea and a large increase in MR severity and systolic pulmonary artery pressure favour combined surgery.

In all other patients and in particular patients with advanced LV remodelling and a very poor ventricular function (i.e. an EF ≤15%), optimal medical treatment followed by extended HF treatment (CRT, ventricular assist devices, heart transplantation) or palliative therapy should be determined by the heart team according to the patient's characteristics.

Medical treatment

Optimal medical therapy is mandatory; it should be the first step in the management of all patients with secondary MR and should be given in line with the ESC Guidelines in the management of HF.[59]

The indications for resynchronization therapy should be in accordance with related guidelines.[59] In responders, CRT may immediately reduce MR severity through increased closing force and resynchronization of papillary muscles.[80] A further reduction in MR and its dynamic component can occur through a reduction in tethering force in relation to LV reverse remodelling. If symptoms persist after optimization of conventional HF therapy, mitral valve intervention should be considered.

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Chapter 35.5 Mitral stenosis

Although the prevalence of rheumatic fever has greatly decreased in Western countries, mitral stenosis (MS) still results in significant morbidity and mortality worldwide.[1, 2] The treatment of MS has been revolutionized since the development of percutaneous mitral balloon commissurotomy (PMC).

Aetiology

In rheumatic MS, the anatomical lesions combine to varying degrees: fusion of one or both commissures; thickening, fibrosis, and calcification of the valves; and shortening, thickening, and fusion of the subvalvular apparatus. Other valves are also involved in over one-third of cases, the most frequent associated lesions being tricuspid disease and aortic regurgitation.[2, 3]

Degenerative calcific mitral valve disease, either MS or mixed disease, is mainly encountered in elderly patients, in particular those with cardiovascular risk factors. It is usually observed in conditions inducing mitral valve stress such as arterial hypertension, hypertrophic cardiomyopathy, or aortic stenosis. It may also be observed in patients with severe chronic kidney disease or more rarely in congenital metabolic disorders or Marfan syndrome.[4, 5] In degenerative MS, calcification predominates on the mitral annulus, which causes few or no haemodynamic consequences in most cases (Figure 35.5.1). There is no commissural fusion in degenerative MS and significant MS may be the consequence of reduced annular dilatation in diastole and the extension of calcification to mitral leaflets reducing anterior leaflet motion.

Among the rare aetiologies of MS, drug-induced valvular disease may occasionally present as MS, even with commissural fusion.[6, 7] Inflammatory diseases such as rheumatoid arthritis or lupus erythematosus also result in restrictive mitral valve disease, often combining stenosis without commissural fusion and regurgitation.[1] Other rare aetiologies include carcinoid disease, Fabry disease, mucopolysaccharidosis, Whipple disease, or obstruction of the valve by an atrial tumour or a large vegetation.

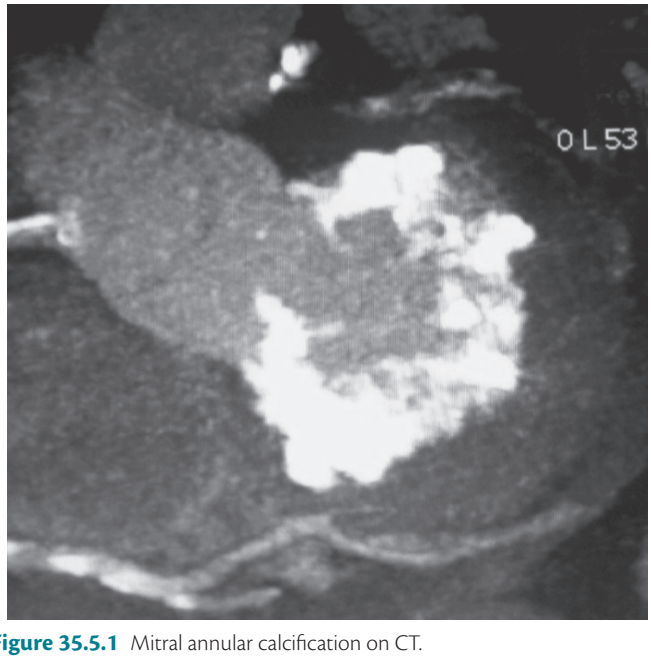


Figure 35.5.1 Mitral annular calcification on CT.
Courtesy of M. Urena-Alcazar.

Pathophysiology

After a rheumatic attack, the alterations of the valve slowly progress, mostly driven by the abnormal flow dynamics caused by the initial and eventually repeated rheumatic insults.

Normal mitral valve area is 4–6 cm^2. A diastolic transvalvular gradient between the left atrium and the left ventricle (LV) appears when the valve area approaches 2 cm^2 or less. MS is considered clinically significant when the valve area is less than 1.5 cm^2, or less than 1 cm^2/m^2 body surface area in large individuals. Valve obstruction progressively limits cardiac output and increases pressure in the left atrium, which, in turn, raises pulmonary circulation pressure. Pulmonary oedema, related to transudation from the pulmonary capillaries, occurs when mean capillary wedge pressure is approximately greater than 25 mmHg. The transvalvular gradient and its consequences are highly dependent on heart rate and transvalvular flow. Exercise limitation is multifactorial and heterogeneous for a given degree of stenosis. This heterogeneity may be explained by differences in the evolution of stroke volume during exercise[8] and differences in atrioventricular compliance.[9] A low net compliance is mainly the consequence of a low compliance of the left atrium and is associated, even more than at rest, with a higher pulmonary pressure at exercise and more severe symptoms. The degree of pulmonary hypertension is variable and often greater than the passive increase caused by elevated left atrial pressures. This could be due to initially reversible morphological changes in pulmonary vasculature, reactive pulmonary vasoconstriction, or reduced lung compliance.[10] Chronic pulmonary hypertension causes right ventricular (RV) hypertrophy, which, possibly exacerbated by tricuspid regurgitation, causes failure of the RV.

Intrinsic LV contractility is usually preserved; however, chronic afterload elevation and preload reduction, related to MS and ventricular interactions, can cause LV dysfunction in up to 25% of cases.

Atrial fibrillation, which is not strictly linked to the severity of MS, is a consequence of left atrial dilatation and hypertrophy, as well as rheumatic insult to the atria, internodal tracts, and sinoatrial node. Atrial fibrillation causes haemodynamic compromise through decreased cardiac output due to the loss of atrial contraction and shortening of diastole. It also increases thromboembolic risk as a result of left atrial enlargement, blood stagnation, and increased concentrations of prothrombotic markers.

Diagnosis

The patient with MS may feel asymptomatic for years and then present with a gradual decrease in activity. The diagnosis is usually established by physical examination, chest X-ray, ECG, and echocardiography.

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in Chapter 35.1.

Specific issues in MS are as follows:

History

Usually, symptoms appear gradually over years, with patients first reporting dyspnoea on exertion, which is the consequence of the abnormal elevation of the left atrial and capillary wedge pressure. Patients frequently adapt their level of functional capacity and deny dyspnoea despite objective effort limitation. Pregnancy, emotional stress, sexual intercourse, infection, or the onset of atrial fibrillation may all be precipitating factors of marked dyspnoea or pulmonary oedema. Haemoptysis, paroxysmal cough, as well as chest discomfort, is infrequent.

Atrial fibrillation often begins in paroxysms and eventually becomes chronic. Embolic events, which may be the presenting complaint in 20% of cases, are most often cerebral and leave sequelae in one-third of cases.

At a more advanced stage, patients may complain of fatigue due to low cardiac output, weakness, or abdominal discomfort due to hepatomegaly when RV failure is present. Hoarseness may occasionally be observed in the case of severe enlargement of the left atrium (i.e. Ortner syndrome).

Physical examination

The main signs of auscultation are appreciated at the apex. The low-pitched rumbling diastolic murmur (typically holodiastolic, decrescendo with a presystolic accentuation in sinus rhythm) can be palpated when it is of high intensity. The loudness of the murmur depends on the level of the transmitral gradient. It may be of low intensity or even inaudible in patients with low output, emphysema, or obesity. The opening snap occurs 0.013–0.03 s after the second heart sound—the more severe the stenosis, the shorter the interval, as increased left atrial pressure causes earlier opening of the mitral valve. The accentuated first heart sound (a high-pitched sound due to the fact that ventricular systole closes the mitral valve) may be blunted in patients with severe calcification which alters both the opening and closing of the valve.

Pulmonary hypertension causes both a louder second heart sound at the base and a murmur of tricuspid regurgitation located at the xiphoid. This can be differentiated from a murmur of mitral regurgitation by its respiratory variation. In patients with RV failure, the dilated ventricle can be palpated at the xiphoid, as can a systolic impulse of the pulmonary artery at the third left intercostal space.

Pulmonary rales are present in patients with severe symptoms and at an advanced stage, and mitral facies with intermittent malar flushes, jugular distension, and peripheral cyanosis may be seen. Respiratory failure, cachexia, and the discovery of severe pulmonary hypertension dominate examination.

Auscultation should also search for a holosystolic murmur at the apex suggesting mitral regurgitation. Finally, it should look for an associated aortic valve disease resulting in either a mid-systolic or a diastolic murmur at the level of the left sternal border.

Electrocardiography

Patients who are in sinus rhythm demonstrate signs of left atrial enlargement with a prolonged P wave and a negative deflection in lead V1 and left axial deviation of the P wave. Atrial fibrillation is frequent. Signs of RV hypertrophy are usually present in cases of severe pulmonary hypertension.

Chest radiography

The cardiac silhouette is only mildly enlarged during the early stages. As severity increases, signs of left atrial enlargement can be observed: (1) straightening of the left heart border, (2) double contour of the left atrium, and (3) widening of the carinal angle of the trachea. As the disease progresses, signs of RV enlargement can follow. Redistribution of pulmonary vascular flow towards the upper lung fields, a progressively enlarged pulmonary trunk, and signs of interstitial pulmonary and alveolar oedema are all indicative of the elevation of pulmonary pressures. Usually, fluoroscopy is necessary to visualize valve calcification.

Echocardiography

Echocardiography is the main method used to assess the severity and consequences of MS, as well as the extent of anatomical lesions.

Valve area should be measured using planimetry and the pressure half-time method, which are complementary. Planimetry, when it is feasible, is the method of choice, in particular immediately after PMC. Continuity equation and proximal isovelocity could be used when additional assessment is needed. Measurements of mean transvalvular gradient, calculated using Doppler velocities, are highly rate and flow dependent, but are useful to check consistency in the assessment of severity, particularly in patients in sinus rhythm. MS does not usually have clinical consequences at rest when the valve area is larger than 1.5 cm^2, while these may occur with a valve area less than that which corresponds to 'moderate to severe MS' in the European Association of Echocardiography/American Society of Echocardiography recommendations for echocardiographic assessment of valve stenosis[11] (Figure 35.5.2) (Video 35.5.1 (online) and Video 35.5.2 (online)).

A comprehensive assessment of valve morphology is important for the treatment strategy. Scoring systems have been developed to help assess suitability, taking into account valve thickening, mobility, calcification, subvalvular deformity, and commissural areas[12–14] (Table 35.5.1) (Video 35.5.3 (online)).

Echocardiography also evaluates pulmonary artery pressures, associated mitral regurgitation, and left atrial size. Due to the frequent association of MS with other valve diseases, a comprehensive evaluation of the tricuspid and aortic valves is mandatory.

Transthoracic echocardiography (TTE) usually provides sufficient information for routine management. Transoesophageal echocardiography (TOE) should be performed to exclude left atrial thrombus before PMC or after an embolic episode, if TTE provides suboptimal information on anatomy or, in selected cases, to guide the procedure, especially transseptal puncture.

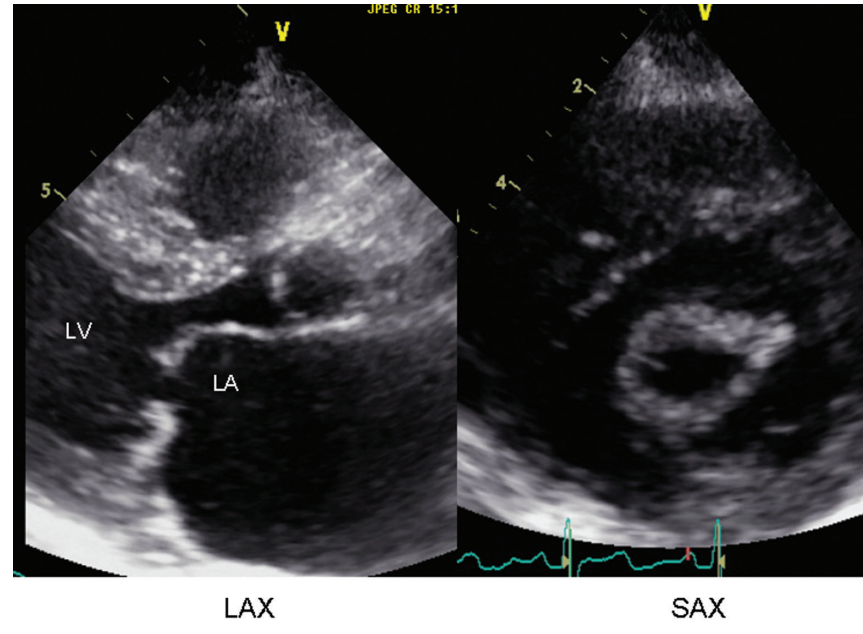


Figure 35.5.2 Echographic analysis of mitral stenosis. Transthoracic echocardiography. Parasternal long-axis (left) and short-axis (right) views showing MS. Note on the short-axis view the bilateral commissural fusion without calcification. LA, left atrium; LAX, long-axis view; LV, left ventricle; SAX, short-axis view.
Courtesy of Dr E. Brochet.

Table 35.5.1 Echocardiography scores

(A) Assessment of mitral valve anatomy according to the Wilkins score

Grade	Mobility	Thickening	Calcification	Subvalvular thickening
1	Highly mobile valve with only leaflet tips restricted	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness	Minimal thickening just below the mitral leaflets
2	Leaflet mid and base portions have normal mobility	Mid leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins	Thickening of chordal structures extending to one third of the chordal lengths
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid portions of the leaflets	Thickening extended to distal third of the chords
4	No or minimal forward movement of the leaflets in diastole	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles

The total score is the sum of the four items and ranges between 4 and 16.
From Wilkins GT, Weyman AE, et al. Br Heart J 1988;60(4):299–308.

(B) Assessment of mitral valve anatomy according to the Cormier score

Echocardiographic group	Mitral valve anatomy
Group 1	Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e. thin chordae ≥10 mm long)
Group 2	Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e. thickened chordae <10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

From Iung B, Cormier B, Ducimetiere P, et al. Circulation 1996;94(9):2124–30.

(C) Echo score 'revisited' for immediate outcome prediction

Echocardiographic variables	Points for score (0 to 11)
Mitral valve area ≤1 cm^2	2
Maximum leaflet displacement ≤12 mm	3
Commissural area ratio ≥1.25	3
Subvalvular involvement	3

Risk groups: low (score 0–3); intermediate (score 5); high (score 6–11).
From Nunes et al. Circulation 2014;129:886–95.

Three-dimensional echocardiography improves the evaluation of valve morphology (especially visualization of commissures), optimizes accuracy and reproducibility of planimetry, and could be useful for guiding (TOE) and monitoring (TTE) PMC in difficult cases[15–17] (Video 35.5.4 (online)). Echocardiography also plays an important role in monitoring the results of PMC during the procedure (Video 35.5.5 (online) and Video 35.5.6 (online)).

Stress testing

Stress testing is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of MS. Exercise echocardiography may provide additional objective information by assessing changes in mitral gradient and pulmonary pressures.[18] Recent experience suggests that the limiting symptoms (dyspnoea or fatigue) are more related to the pattern of increase of mean gradient and systolic pulmonary pressure than to the level at peak exercise.[19] Dobutamine stress may be used when exercise echocardiography is not feasible. However, there is still a need for validation through prognostic studies to refine indications in asymptomatic patients.

Other non-invasive tests

The role of magnetic resonance imaging and computed tomography (CT) for planimetry of the valve area is under investigation.[20] CT accurately assesses the location and severity of valve and especially annular calcification.[21] Its usefulness in the detection of left atrial appendage thrombosis[22] or assessment of valve anatomy in rheumatic MS has not been validated so far.

Natural history

In developing countries, severe rheumatic MS is commonly observed in infants or young adults, whereas in industrialized countries, symptoms are usually delayed until the fifth decade of life. Studies on natural history are old and non-controlled.[23] The rate of progression of stenosis is variable: ranging from 0.1 to 0.3 cm^2/year, higher rates being observed in patients with severe anatomical deformity and high transmitral gradient. Survival in asymptomatic patients with rheumatic MS is usually good up to 10 years. However, progression is highly variable with a risk of sudden deterioration, which may be precipitated by pregnancy or complications such as atrial fibrillation or systemic embolism.[23, 24] Among patients with few symptoms, survival was 42% at 10 years and the incidence of heart failure was approximately 60%. Symptomatic patients have poor prognosis with a 5-year survival of only 44%.[23] The progression was highly variable with gradual deterioration in one-half of patients, and sudden deterioration, precipitated by a complication, in the rest. Atrial fibrillation can occur in asymptomatic patients and is often preceded by supraventricular arrhythmias. The occurrence of atrial fibrillation increases with age and left atrial enlargement, and the incidence of thromboembolism is also higher with age, atrial fibrillation, larger left atrium, smaller valve area, and, most significantly, the presence of left atrial spontaneous echo contrast.[24]

Mitral annular calcification is an independent predictor of cardiovascular events, in particular atrial fibrillation, myocardial infarction, and stroke.[4]

Intervention

Percutaneous mitral commissurotomy

Since its introduction in the early 1980s, successful results of PMC have led to its worldwide adoption.

Transseptal catheterization is one of the most crucial steps of the procedure and the Inoue balloon technique has become the most popular method (Figure 35.5.3).

PMC, which results in commissural splitting (Figure 35.5.4), usually provides at least a 100% increase in valve area, with a final

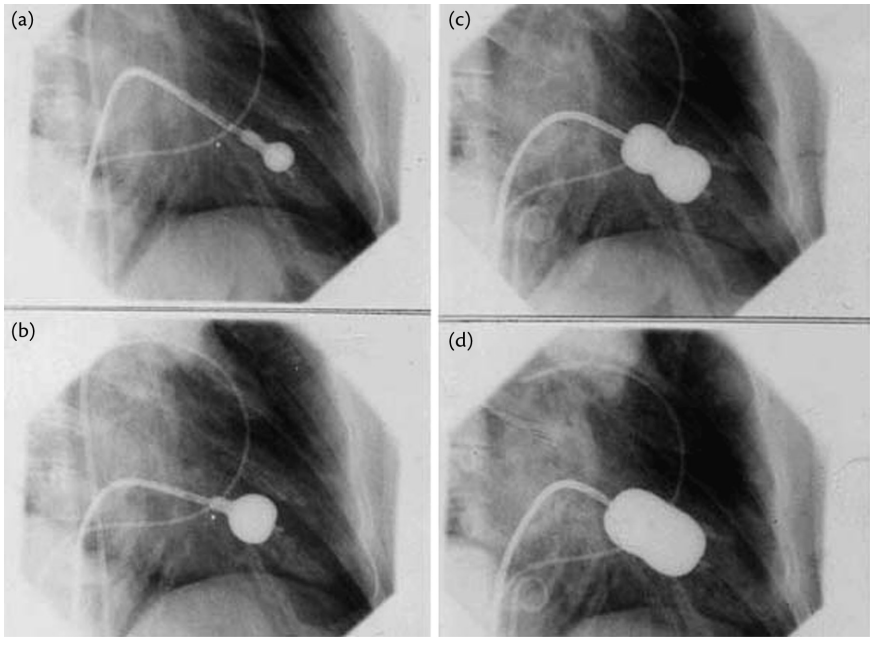


Figure 35.5.3 Percutaneous mitral commissurotomy using the Inoue balloon technique. Right anterior oblique view. (a) The distal part of the balloon is inflated with contrast in the centre of the mitral valve; (b) the distal part is further inflated and the balloon is pulled back into the mitral orifice; (c) inflation occurs in the central portion; (d) at full inflation the waist on the balloon disappears.

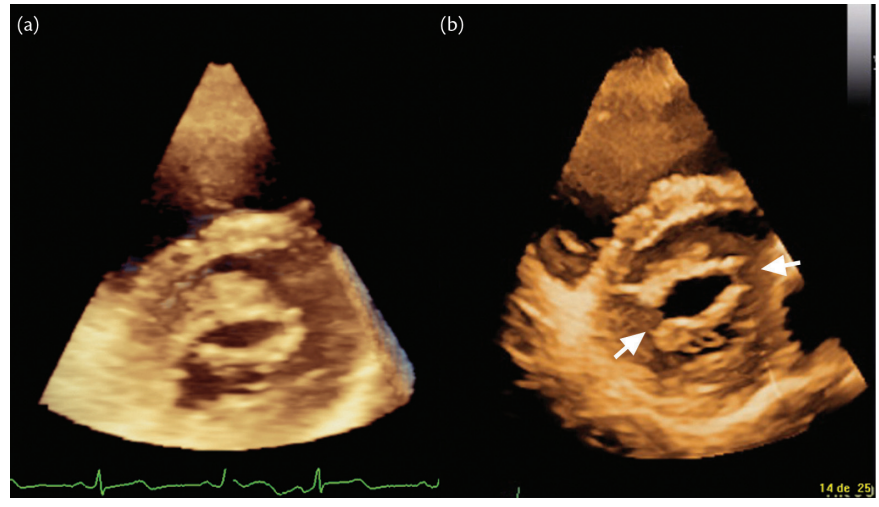


Figure 35.5.4 Echographic evaluation after percutaneous mitral commissurotomy (PMC). Real-time three-dimensional TTE before (a) and after (b) PMC. Note the well-defined opening of both commissures with real-time three-dimensional TTE after PMC (white arrows).
Courtesy of Dr E. Brochet.

valve area of approximately 2 cm^2. The improvement in valve function results in an immediate decrease in pulmonary pressures, both at rest and during exercise.

Technical success and complications are related to patient selection and the operator's experience. Therefore PMC should be performed by experienced operators, in high-volume centres. Good initial results, defined as a valve area larger than 1.5 cm^2 with no mitral regurgitation greater than 2/4, are achieved in over 80% of cases. Major complications include procedural mortality (0.5–4%), haemopericardium (0.5–10%), systemic embolism (0.5–5%), and severe mitral regurgitation (2–10%). Emergency surgery is rarely needed (<1%).[25, 26]

Series reporting the longest follow-up after PMC were performed in European populations with a mean age of 49 and 55 years and a high proportion of patients with suboptimal anatomical conditions[12, 27] (Figure 35.5.5). In these series of patients who had successful PMC, 20-year rates of cardiovascular survival without intervention (repeat PMC or surgery) were estimated at 38±2% and 36±5%, respectively. The corresponding rates were 33±2% and 21±5% when considering New York Heart Association (NYHA) class I or II at last follow-up.

Valve morphology is one of the predictors of late clinical outcome, but it is only one factor among others. Besides anatomical factors, baseline predictors of poor late outcome are higher age and the consequences of MS, such as a high functional class and the presence of atrial fibrillation.

Even in patients with good immediate results, the degree of valve opening has an impact on late outcome. Besides post-procedural valve area, mean mitral gradient after PMC is also a strong independent predictor of late clinical results.[12, 27] The persistence of a high gradient following PMC despite good valve opening can be related to limited valve reserve in conjunction with a loss of pliability, which is likely to influence late restenosis. The degree of commissural opening is strongly linked to post-procedural valve area and gradient[28] but does not have an incremental prognostic value for late event-free survival in multivariate analysis.

The different predictive factors of late functional results can be combined using a scoring system. The likelihood of good functional outcomes estimated in individual patients according to baseline characteristics and also the immediate results of PMC should be taken into consideration to identify the optimal treatment[12–14] (Table 35.5.2).

When the immediate results are unsatisfactory, surgery is usually required shortly thereafter.[12, 29] Conversely, after successful PMC, long-term results are good in the majority of cases

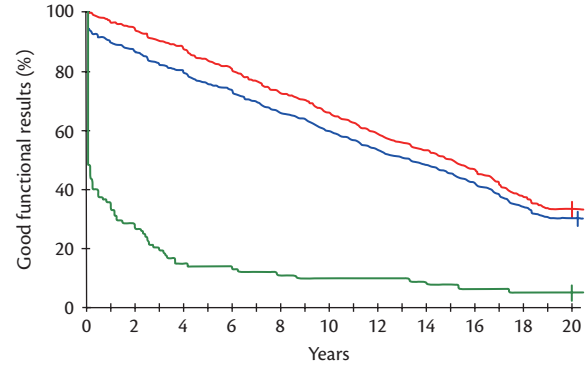


Figure 35.5.5 Twenty-year results of percutaneous mitral commissurotomy (PMC) survival without re-intervention and NYHA class I–II. The components of the score are given in Table 35.5.1. Good functional results, defined as survival without cardiovascular death, without operation and in NYHA class I or II, were observed in 29.4% of patients at 20 years. This result is shown in the survival rate graph, with the number of exposed patients. The green curve represents the subgroup with poor immediate results, with a sharp drop corresponding to the large proportion of early repeat surgery after the initial PMC. Those who did not have a repeat intervention mostly became symptomatic or died. On the other hand, for the total population, notably the portion with 'good' immediate results, one observes a linear survival rate, suggesting progressive deterioration, with about 29% of good results after 20 years.
Adapted from Bouleti C. Circulation 2012;125;2119–27.

Table 35.5.2 Predictive factors of poor late functional results after good immediate results of percutaneous mitral commissurotomy

	Adjusted hazard ratio (95% CI)	*p*	Points for score (0/13)
Age (years) and final MVA (cm²)			
<50 and MVA ≥2.00	1	<0.0001	0
<50 and MVA 1.50–2.00 *or* 50–70 and MVA >1.75	2.1 (1.6–2.9)		2
50–70 and MVA 1.50–1.75 *or* ≥70 and MVA ≥1.50	5.1 (3.5–7.5)	<0.0001	5
Valve anatomy and sex			
No valve calcification	1	0.18	0
Valve calcification:			
Female	1.2 (0.9–1.6)	<0.0001	0
Male	2.3 (1.6–3.2)		3
Rhythm and NYHA class			
Sinus rhythm *or* Atrial fibrillation and NYHA class I–II	1	<0.0001	0
Atrial fibrillation and NYHA class III–IV	1.8 (1.4–2.3)		2
Final mean mitral gradient (mmHg)			
≤3	1	0.05	0
3–6	1.1 (1.0–1.8)	<0.0001	1
≥6	2.5 (1.8–3.5)		3

CI, confidence interval, MVA, mitral valve area, NYHA, New York Heart Association.
Good immediate results of percutaneous mitral commissurotomy are defined by a valve area ≥1.5 cm² with no regurgitation >2/4
From Bouleti C et al. Circulation 2012;125(17):2119–27.

and can be predicted by preoperative anatomical and clinical characteristics, and the quality of the immediate results.[12, 14] When functional deterioration occurs, it is late and mainly related to restenosis.[12, 29–31] Successful PMC also reduces embolic risk.[24, 32]

Surgery

The first operation performed 50 years ago was closed mitral valve commissurotomy.[33] This operation was effective and easily accessible, which explains its high use until recently in developing countries. Today it has been almost completely replaced by open-heart mitral commissurotomy using cardiopulmonary bypass, which enables surgeons not only to correct commissural fusion, but also to act on chordal and papillary fusion, and to even improve leaflet mobility and pliability by enlarging the leaflets using pericardial patches. The use of prosthetic rings is controversial in these cases. In series from experienced centres, mostly including young patients, long-term results are good with a rate of reoperation for valve replacement of 0–7% at 36–53 months, and 10-year survival rates of 81–90%.[34]

In current practice, surgery for MS is mostly valve replacement (approximately 95%) as a result of increasingly elderly presentation and unfavourable valve characteristics for valve repair. Besides the early and late morbidity related to cardiac surgery, operative mortality for valve replacement ranges from 3% to 10% and correlates with age, functional class, pulmonary hypertension, and presence of coronary artery disease. Long-term survival is related to age, functional class, atrial fibrillation, pulmonary hypertension, preoperative LV/RV function, and prosthetic valve complications.

Indications for intervention

The type of treatment, as well as its timing, should be decided on the basis of clinical characteristics (including functional status, predictors of operative risk, presence of concomitant heart valve disease, and results of PMC), valve anatomy, and local expertise.

Indications for intervention are as follows (Table 35.5.3 and Figure 35.5.6):

- In general, indication for intervention should be limited to patients with clinically significant MS (moderate to severe) (valve area <1.5 cm²) However, PMC may be also considered in symptomatic patients with valve area larger than1.5 cm² if symptoms cannot be explained by another cause and if the anatomy is favourable (recommendation class IIb, level of evidence C).
- Intervention should be performed in symptomatic patients. Most patients with favourable valve morphology currently undergo PMC; however, open commissurotomy may be preferred by experienced surgeons in young patients with mild-to-moderate mitral regurgitation. Decision-making as to the type of intervention in patients with suboptimal anatomy is still a matter of debate and must take into account the multifactorial nature of predicting the results of PMC.[12, 14, 27] PMC should be considered as an initial treatment for selected patients with mild-to-moderate calcification or severe involvement of the subvalvular apparatus, who have otherwise favourable clinical characteristics, especially in young patients and even more so young females, in whom postponing valve replacement is particularly attractive[35] (Figure 35.5.7). In such cases, surgery should be considered reasonably soon if the results of PMC are suboptimal and follow-up should be closer.

PMC is the procedure of choice when surgery is contraindicated, or as a bridge to surgery in high-risk, critically ill patients.

Surgery is indicated in patients who are unsuitable for PMC. In such cases, tricuspid disease should be treated according to the recommendations in Chapter 35.6.

Due to the small but definite risk inherent in PMC, truly asymptomatic patients (as assessed using stress testing) are not usually candidates for the procedure, except in cases where there is increased risk of systemic embolism or haemodynamic decompensation (Figure 35.5.6). In such patients, PMC should only be performed if they have favourable characteristics and if performed by experienced operators.

In asymptomatic patients with MS, surgery is limited to those rare patients at high risk of complications or who experience

Table 35.5.3 Indications for percutaneous mitral commissurotomy and mitral valve surgery in clinically significant (moderate or severe) mitral stenosis (valve area ≤1.5 cm²)

	Class[a]	Level[b]
PMC is indicated in symptomatic patients without unfavourable characteristics* for PMC	I	B[12, 14, 27]
PMC is indicated in any symptomatic patients with contraindication or high risk for surgery Mitral valve surgery is indicated in symptomatic patients who are not suitable for PMC	I I	C C
PMC should be considered as initial treatment in symptomatic patients with suboptimal anatomy but no unfavourable clinical characteristics for PMC*	IIa	C
PMC should be considered in asymptomatic patients without unfavourable clinical and anatomical characteristics* for PMC and ◆ high thromboembolic risk (previous history of systemic embolism, dense spontaneous contrast in the left atrium, new-onset or paroxysmal atrial fibrillation) and/or ◆ high risk of haemodynamic decompensation (systolic pulmonary pressure >50 mmHg at rest, need for major non-cardiac surgery, desire for pregnancy)	IIa	C

NYHA, New York Heart Association; PMC, percutaneous mitral commissurotomy.
[a] Class of recommendation.
[b] Level of evidence.
* Unfavourable characteristics for PMC can be defined by the presence of several of the following characteristics:
– Clinical characteristics: old age, history of commissurotomy, NYHA class IV, permanent atrial fibrillation, severe pulmonary hypertension.
– Anatomical characteristics: echo score >8, Cormier score 3 (calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, severe tricuspid regurgitation.

symptoms at a low level of exercise, with low risk for surgery and with contraindications to PMC.

The most important contraindication to PMC is left atrial thrombosis (Box 35.5.1). However, when the thrombus is located in the left atrial appendage, PMC may be considered in patients with contraindications to surgery or those without urgent need for intervention in whom oral anticoagulation can be safely given for 1–3 months, provided repeat TOE shows the thrombus has disappeared. Surgery is indicated if the thrombus persists and will also comprise exclusion of the left atrial appendage after thrombectomy.

The potential role of transcatheter mitral valve implantation in high-risk patients with contraindications for both surgery and PMC is to be determined. Currently this new technique is at a very early stage of evaluation and has not been performed in

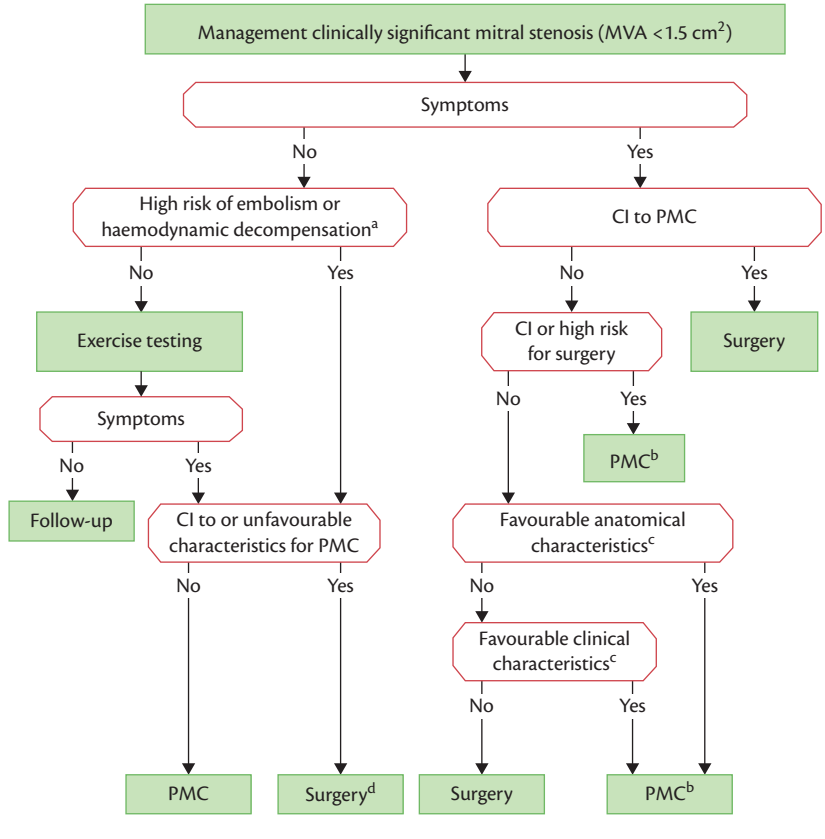
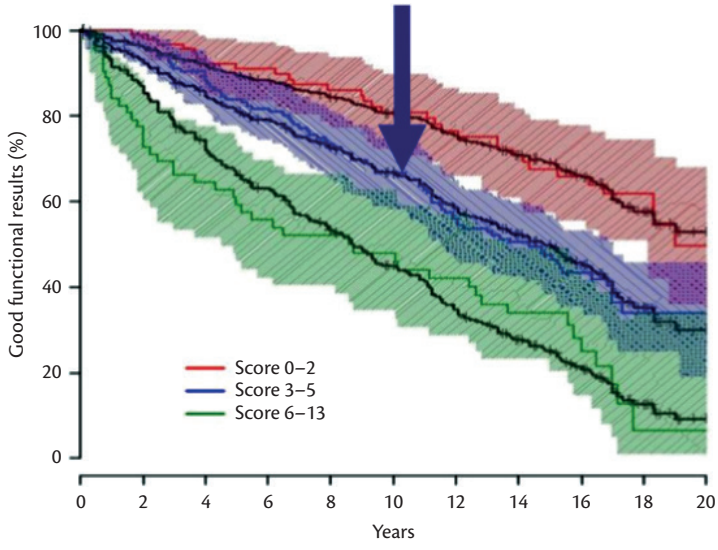


Figure 35.5.6 Management of moderate or severe mitral stenosis (valve area ≤1.5cm²). CI, contraindication; MS, mitral stenosis; PMC, percutaneous mitral commissurotomy.
[a] High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the left atrium, new-onset atrial fibrillation. High-risk of haemodynamic decompensation: systolic pulmonary pressure >50 mmHg at rest, need for major non-cardiac surgery, desire for pregnancy.
[b] Surgical commissurotomy may be considered by experienced surgical teams or in patients with contra-indications to PMC.
[c] See table of recommendations on indications for PMC and mitral valve surgery in clinically significant mitral stenosis in section 7.2.
[d] Surgery if symptoms occur for a low level of exercise and operative risk is low.



No. at Risk											
Score 0–2	81	78	71	66	62	58	53	49	37	20	6
Score 3–5	146	138	122	111	94	81	71	53	28	10	3
Score 6–13	69	55	47	36	32	28	22	17	10	1	0

Years after PMC	Predicted	Observed (95% CI)
5	81	84 (78–90)
10	67	65 (57–73)
15	50	46 (38–55)

Figure 35.5.7 Prediction of long-term results of percutaneous mitral commissurotomy (PMC). Above, actuarial curve showing the outcomes according to the score described in Table 35.5.2 .Below, predicted and observed outcomes of a patient with moderately calcified valve but favourable anatomical characteristics (score 3–5).
Adapted with permission from Bouleti C. Circulation 2012;125(17):2119–27.

patients with native MS with the exception of valve implantation in massive annular calcification.

Medical therapy

Diuretics transiently ameliorate dyspnoea. Digoxin, beta blockers, or heart rate-regulating calcium channel blockers can improve exercise tolerance. Anticoagulation with a target international normalized ratio between 2 and 3 is indicated in patients with either new-onset or paroxysmal atrial fibrillation in native MS as well as after PMC or surgical commissurotomy.[36]

In patients with sinus rhythm, oral anticoagulation is indicated when there has been prior systemic embolism, or a thrombus is present in the left atrium (recommendation class I, level of evidence C) and should also be considered when TOE shows dense spontaneous echo contrast or an enlarged left atrium (M-mode diameter >50 mm or left atrial volume >60 mL/m^2) (recommendation class IIa, level of evidence C).[37] Aspirin and other antiplatelet agents are not valid alternatives. Patients with moderate-to-severe MS and atrial fibrillation, also called 'valvular atrial fibrillation,[38] were excluded from trials on the non-vitamin K antagonist oral anticoagulants (NOACs) and should therefore be kept on vitamin K antagonists.

Cardioversion is not indicated before intervention in patients with severe MS, as it does not durably restore sinus rhythm. If atrial fibrillation is of recent onset and the left atrium is only moderately enlarged, cardioversion should be performed soon after successful intervention.

Infective endocarditis prophylaxis is indicated as appropriate[39] (see Chapter 36.11).

In countries with a high prevalence of rheumatic disease, rheumatic fever prophylaxis should be given to young patients and should be continued after PMC or surgical commissurotomy. The duration

Box 35.5.1 Contraindications for percutaneous mitral commissurotomy

- Mitral valve area larger than 1.5 cm^{2*}
- Left atrial thrombus
- More than mild mitral regurgitation
- Severe or bicommissural calcification
- Absence of commissural fusion
- Severe concomitant aortic valve disease, or severe combined tricuspid stenosis and regurgitation requiring surgery
- Concomitant coronary artery disease requiring bypass surgery.

* PMC may be considered in patients with valve area >1.5 cm^2 with symptoms which cannot be explained by another cause and if the anatomy is favourable.

for which prophylactic antibiotic therapy should be continued is controversial. It seems to be rarely necessary after 21 years.

Serial testing

Asymptomatic patients with clinically significant MS, who have not undergone intervention, should be followed up yearly by means of clinical and echocardiographic examinations and at longer intervals (2–3 years) in case of moderate stenosis.

Management of patients after successful PMC is similar to that of asymptomatic patients. Follow-up should be closer if asymptomatic restenosis occurs. When PMC is not successful and symptoms persist, surgery should be considered early unless there are definite contraindications.

Special patient populations

When restenosis with symptoms occurs after surgical commissurotomy or PMC, reintervention in most cases requires valve replacement but PMC can be proposed in selected candidates.

In patients with restenosis following prior closed- or open-heart commissurotomy, even if the results are less satisfying than in native valves, a 19% rate of 20-year good functional results after successful PMC was reported[40] and supports the use of PMC in patients with favourable characteristics. Surgery is indicated in patients who are not suitable for PMC.[41]

Restenosis after previous PMC becomes more frequent. Repeat PMC gives good mid-term clinical results in selected patients, particularly in young patients with mild or no calcification.[42] Thus, re-PMC can be proposed in selected patients with favourable characteristics if the predominant mechanism is commissural refusion, and in cases with an initially successful PMC if restenosis occurs after several years. In the other patients, surgery is the preferred option if not contraindicated. Finally, PMC may have a palliative role in patients who present with suboptimal valve anatomy for PMC, but who are not surgical candidates.[43]

In the elderly, echocardiographic examination should pay particular attention to confirm the rheumatic aetiology and distinguish it from degenerative MS.

In rheumatic MS when surgery is high risk or contraindicated but life expectancy is still acceptable, PMC is a useful option, even if only palliative. In patients with favourable valve morphology, PMC can be attempted first, resorting to surgery if results are unsatisfactory. In other patients, surgery is preferable.[12, 44]

In patients with degenerative MS with severe calcified mitral annulus, surgery is very high risk due to complications such as posterior wall rupture and trauma to coronary arteries.[45] Since there is no commissural fusion in these cases, degenerative MS is not amenable to PMC. If degenerative MS is severe, very preliminary experience has suggested that transcatheter valve implantation may be considered in symptomatic patients who are inoperable if the anatomy is suitable (i.e. nearly circular calcification as assessed by CT), sufficiently large LV cavity, absence of septal bulging and narrow aorto-mitral angle as assessed by CT)[46] (Figure 35.5.8) (Video 35.5.7 (online) and Video 35.5.8 (online)). These findings need to be confirmed by larger studies with follow-up before making any firm recommendations.

For information on MS during pregnancy see Chapter 35.11.

In patients with severe MS combined with severe aortic valve disease, surgery is preferable when it is not contraindicated. The management of the patients where surgery is contraindicated is difficult and requires a comprehensive and individualized evaluation by the heart team. If transcatheter aortic valve implantation (TAVI) is considered as an option on the aortic valve, a subsequent PMC may be attempted in the rare patients with rheumatic MS—in the other cases either medical therapy or TAVI alone or implantation of a transcatheter bioprosthesis in mitral position, with all the reservations made earlier, may be considered if the symptoms persist after TAVI.[47]

In cases with severe MS with moderate aortic valve disease, PMC can be performed as a means of postponing the surgical treatment of both valves.

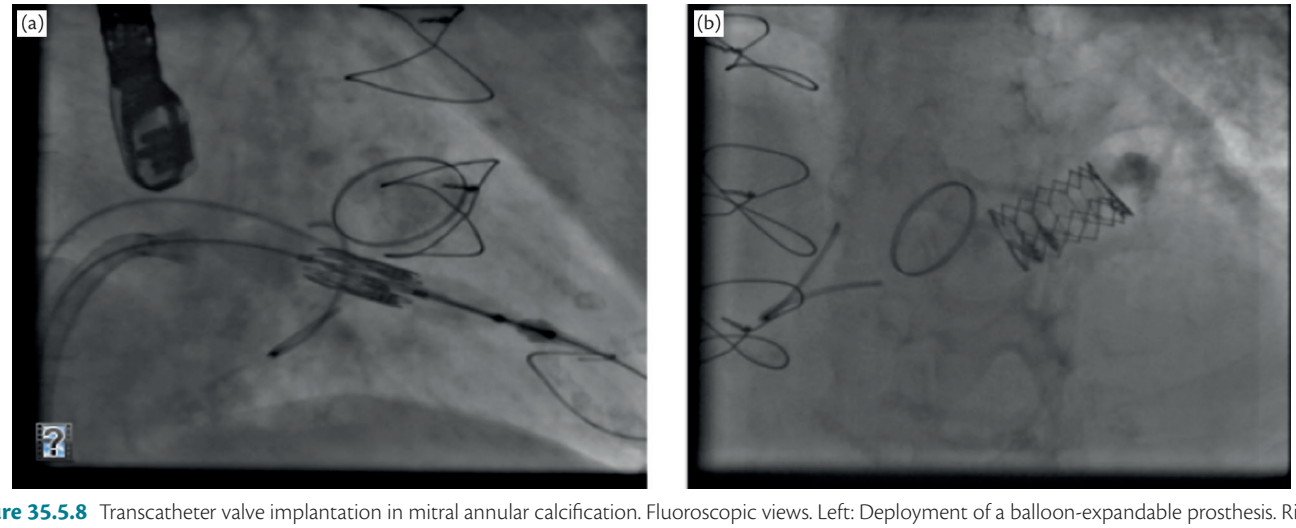


Figure 35.5.8 Transcatheter valve implantation in mitral annular calcification. Fluoroscopic views. Left: Deployment of a balloon-expandable prosthesis. Right anterior oblique view –Right: After implantation the balloon-expandable prosthesis is implanted within the annular calcification. Antero-posterior view. Courtesy of D. Himbert.

In patients with severe tricuspid regurgitation, PMC may be considered in selected patients with sinus rhythm, moderate atrial enlargement, and functional tricuspid regurgitation secondary to pulmonary hypertension. In other cases, surgery on both valves is preferred.[48]

Valve replacement is the only surgical option for the treatment of the other rare cases of severe MS of non-rheumatic origin where commissural fusion is absent.

➔ The videos will be available on launch of the digital version of *The ESC Textbook of Cardiovascular Medicine 3e*

Video 35.5.1 (online)

Severe mitral stenosis.

Video 35.5.2 (online)

Mitral stenosis: bicommissural opening after percutaneous mitral commissurotomy.

Video 35.5.3 (online)

Transthoracic echocardiography of mitral stenosis. This video illustrates the ability of X-plane or biplane imaging to provide simultaneously both parasternal long- and short-axes of the mitral valve at the tip of the leaflets.

Video 35.5.4 (online)

Two- and three-dimensional transoesophageal echocardiography (TOE) examination of mitral stenosis. Top right and left: two-dimensional TOE four-chamber view showing typical appearance of pliable mitral stenosis. Bottom left: Doppler measurement of mitral gradient during TOE. Bottom right: three-dimensional TOE en face view of mitral stenosis.

Video 35.5.5 (online)

Transthoracic echocardiography (TTE) examination of mitral stenosis after percutaneous mitral commissurotomy. Top panel: TTE parasternal short-axis view showing complete opening of the anterolateral commissure (left) with mild commissural jet of mitral regurgitation (right). Bottom left: three-dimensional TTE parasternal oblique short-axis view showing the extent of commissural opening. Right: mean mitral gradient of 4 mmHg after percutaneous mitral commissurotomy.

Video 35.5.6 (online)

Three-dimensional transoesophageal echocardiography left atrial view of mitral stenosis during Inoue balloon inflation.

Video 35.5.7 (online)

Fluoroscopic right anterior oblique view. Balloon inflation during transcatheter mitral valve implantation in degenerative calcified mitral stenosis.

Video 35.5.8 (online)

Three-dimensional transoesophageal echocardiography oblique view showing transcatheter implantation in degenerative calcified mitral stenosis.

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Chapter 35.6 Tricuspid regurgitation

Aetiology

Trivial tricuspid regurgitation (TR) is frequently detected by echocardiography in normal subjects. Pathological TR is more often secondary, rather than due to a primary valve lesion.[1] Secondary TR is the consequence of right ventricular (RV) pressure or volume overload, or both, in the presence of structurally normal leaflets. Pressure overload is most often caused by pulmonary hypertension resulting from left-sided heart disease or, more rarely, cor pulmonale or idiopathic pulmonary arterial hypertension. RV volume overload possibly relates to atrial septal defects or intrinsic disease of the RV. Possible causes of primary TR are infective endocarditis[2,3] (especially in intravenous drug addicts), rheumatic heart disease, carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, Ebstein's anomaly, drug-induced valve diseases, thoracic trauma, and iatrogenic diseases.[1, 4]

Pathophysiology

TR induces RV and atrial dilatation, both of which tend to increase annular dilatation, which causes a further increase of TR. Severe TR can also induce ventricular interdependency and reduction in both right-sided stroke volume and left ventricular (LV) preload. Haemodynamic abnormalities increase during inspiration.

Evaluation

History

Even severe TR may be well tolerated for a long period of time. It is most often discovered during an echocardiographic examination for another cause.[5]

Predominant symptoms are those of associated diseases. Dyspnoea and fatigue are common. Symptoms more specifically related to TR are right-sided congestion and hepatalgia. Anorexia and weight loss may occur at a later stage.

Physical examination

Although they are load dependent, clinical signs of right heart failure are of value in evaluating the severity of TR.

Three signs are typical: (1) a soft holosystolic murmur best heard along the left sternal border and in the xiphoid region increasing with inspiration, due to the increase of the venous return (Carvallo's sign); (2) systolic jugular vein expansion; and (3) a pulsatile and enlarged liver with hepatojugular reflux. The murmur could be mild, or even absent, in severe TR when turbulent flow disappears. Peripheral cyanosis, leg oedema, or even ascites may be observed in response to the increased right atrial pressure.

Electrocardiography

Atrial fibrillation and incomplete right bundle branch block are frequent.

Chest radiograph

Marked cardiomegaly is usually present due to enlargement of the right cavities.

Echocardiography

Echocardiography is the ideal technique to evaluate TR.

As for mitral regurgitation, the presence of structural abnormalities of the valve distinguishes between primary and secondary TR. In primary TR, the aetiology can usually be identified from specific abnormalities such as vegetations in infective endocarditis,[3] leaflet thickening and retraction in rheumatic and carcinoid disease, prolapsing/flail leaflet in myxomatous or post-traumatic disease, and dysplastic tricuspid valve in congenital diseases such as Ebstein's anomaly.[4] Since secondary TR is due to annular dilatation and increased tricuspid leaflet tethering in relation to RV pressure or volume overload (or both), the degree of dilatation of the annulus, the RV dimension and function, and the degree of tricuspid valve deformation should also be measured.[1] Significant tricuspid annular dilatation is defined by a diastolic diameter of at least 40 mm or at least 21 mm/m^2 in the four-chamber transthoracic view.[1, 6–8] Three-dimensional echocardiography may

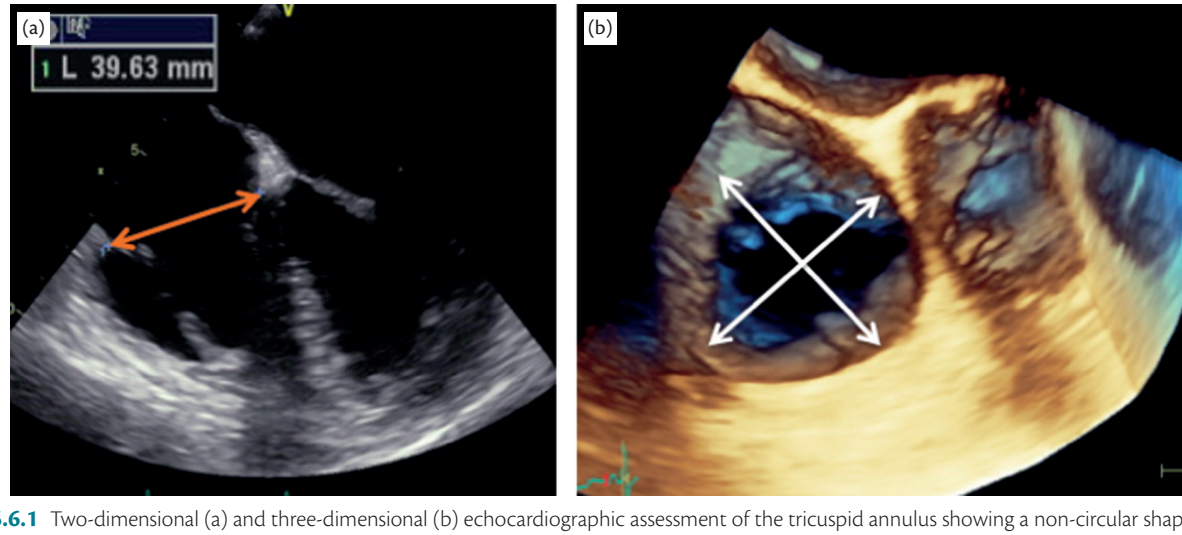

Figure 35.6.1 Two-dimensional (a) and three-dimensional (b) echocardiographic assessment of the tricuspid annulus showing a non-circular shape.

be used to evaluate the shape and size of the tricuspid annulus, but so far no studies have reported its clinical value to predict postoperative TR evolution after isolated left-sided valve surgery (Figure 35.6.1). In secondary TR, a coaptation distance larger than 8 mm characterizes patients with significant tethering (distance between the tricuspid annular plane and the point of coaptation in mid-systole from the apical four-chamber view).[9]

Evaluation of TR severity (integration of multiple qualitative and quantitative parameters) and pulmonary systolic pressure should be carried out as currently recommended.[17] Briefly, colour flow mapping of the regurgitant jet lacks discrimination between mild and moderate regurgitations. Systolic flow reversal in the hepatic veins identifies severe TR but lacks sensitivity for less severe regurgitations. The accuracy of the continuity equation is limited due to the non-circular shape of the tricuspid annulus and the difficulties of its measurement. The width of the vena contracta seems to be the most reliable quantitative index; a vena contracta diameter larger than 7 mm is a good marker of severe TR. The proximal flow convergence method has been validated in only one study, criteria for severe TR were an effective regurgitant orifice area larger than 40 mm and a regurgitant volume greater than 45 mL.[1]

Evaluations of the RV dimensions and function should be conducted, despite existing limitations of current indices of RV function. Tricuspid annular plane systolic excursion (< 17 mm), tricuspid annulus systolic velocity (<9.5 cm/s), and RV fractional area (<35%) could be used to identify patients with RV dysfunction.[10]

The presence of associated lesions (looking carefully at the associated valve lesions, particularly on the left side) and LV function should be assessed.

In experienced labs, three-dimensional measurements of RV volumes can be considered, which are very similar to those obtained by CMR.[10] However, CMR, when available, is the preferred method for evaluating RV size and function and represents the gold standard for assessing RV volumes and function.

Today, catheterization is not needed to diagnose or estimate TR severity, but should be obtained in patients in whom isolated TV surgery is contemplated for secondary TR to evaluate pulmonary vascular resistance.

Natural history

TR induces progressive RV and RA dilatation, both of which tend to increase annular dilatation, which causes a further increase of TR. Severe TR can also induce ventricular interdependency and reduction in both right-sided stroke volume and LV preload. Haemodynamic abnormalities increase during inspiration. Prolonged burden of volume overload may thus result in ventricular dysfunction and irreversible myocardial damage.[11, 12]

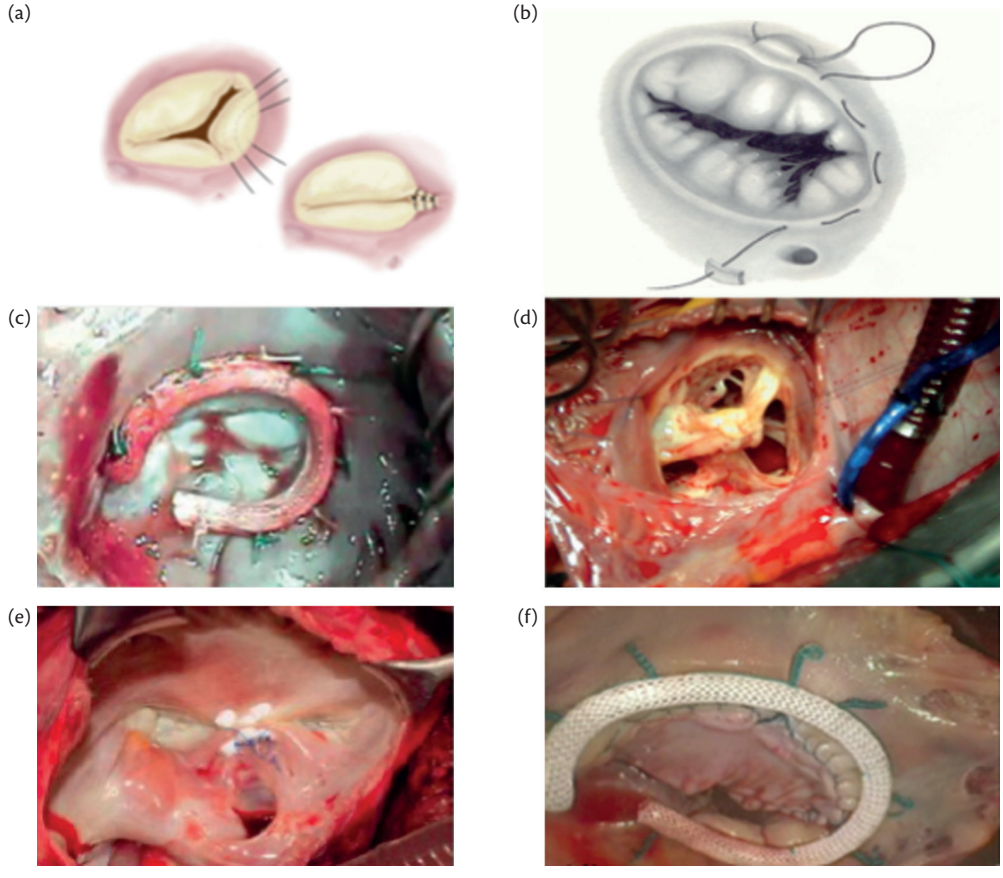

Figure 35.6.2 Surgical techniques to treat tricuspid regurgitation. (a) Kay suture annuloplasty (bicuspidization). (b) De Vega suture annuloplasty. (c) Ring annuloplasty. (d) Clover technique. (e) Double-orifice repair. (f) Leaflet augmentation with a pericardial patch.

Starck CT, Kempfert J, Falk V. Tricuspid valve interventions: surgical techniques and outcomes. EuroIntervention 2015;11(Suppl W):W128–32 and De Bonis M, Lapenna E, La Canna G, Grimaldi A, Maisano F, Torracca L, Caldarola A, Alfieri O. A novel technique for correction of severe tricuspid valve regurgitation due to complex lesions. Eur J Cardiothorac Surg 2004;25:760–5.

Table 35.6.1 Indications for tricuspid valve surgery

	Class[a]	Level[b]
Recommendations on tricuspid stenosis		
Surgery is indicated in symptomatic patients with severe tricuspid stenosis[c]	I	C
Surgery is indicated in patients with severe tricuspid stenosis undergoing left-sided valve intervention[d]	I	C
Recommendations on primary tricuspid regurgitation		
Surgery is indicated in patients with severe primary tricuspid regurgitation undergoing left-sided valve surgery	I	C
Surgery is indicated in symptomatic patients with severe isolated primary tricuspid regurgitation without severe right ventricular dysfunction.	I	C
Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery	IIa	C
Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary tricuspid regurgitation and progressive right ventricular dilatation or deterioration of right ventricular function	IIa	C
Recommendations on secondary tricuspid regurgitation		
Surgery is indicated in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery	I	C
Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with dilated annulus (≥40 mm or >21 mm/m^2 by two-dimensional echocardiography) undergoing left-sided valve surgery	IIa	C
Surgery may be considered in patients undergoing left-sided valve surgery with mild or moderate secondary tricuspid regurgitation even in the absence of annular dilatation when previous recent right heart failure has been documented.	IIb	C
After previous left-sided surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe tricuspid regurgitation who are symptomatic or have progressive right ventricular dilatation/dysfunction, in the absence of severe right or LV dysfunction, and severe pulmonary vascular disease/hypertension.	IIb	C

LV, left ventricular; PMC, percutaneous mitral commissurotomy.
[a] Class of recommendation.
[b] Level of evidence.
[c] Percutaneous balloon valvuloplasty can be attempted as a first approach if tricuspid stenosis is isolated.
[d] Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve.

Although data are limited, the natural history of primary TR suggests that severe TR has a poor prognosis, even if it may be well tolerated functionally for years.[12, 13] Flail tricuspid valve (classically associated with severe TR) is associated with decreased survival and increased risk of heart failure.[13] TR may diminish or disappear as RV failure improves, following the treatment of its cause. However, TR may persist or worsen even after successful correction of left-sided lesions. Pulmonary hypertension, increased RV pressure and dimension, reduced RV function, atrial fibrillation, pacemaker leads, the severity of tricuspid valve deformation (tricuspid annulus diameter, coaptation height), and incomplete subvalvular preservation of the mitral valve are important risk factors for persistence or late worsening of secondary TR.[6–9, 14, 15] Several reports, including one small randomized study, have shown that, in patients undergoing mitral valve surgery, the use of prophylactic tricuspid annuloplasty in the presence of a dilated tricuspid annulus (≥40 mm or >21 mm/m^2 on echo or 70 mm during intervention) and mild–moderate TR was associated with a reduced rate of TR progression, improved RV remodelling, and better functional outcomes.[7, 16–20]

Medical therapy

Diuretics reduce signs of congestion. Specific therapy of the underlying disease is warranted. Drugs reducing pulmonary artery pressures or pulmonary vascular resistance, or both, might be considered in patients with severe functional TR and severe pulmonary hypertension.

Results of surgery

Ring annuloplasty is key to surgery for TR (Figure 35.6.2). Better long-term results are observed with prosthetic rings than with the suture annuloplasty, the incidence of residual TR being, respectively, 10% versus 20–35% at 5 years.[7, 8, 19, 20] Current experience favours the use of ring annuloplasty for severe TR related to isolated tricuspid annular dilatation.[20] When the tricuspid valve leaflets are significantly tethered, complementary tricuspid valve procedures with the objective of reducing residual postoperative TR (i.e. enlargement of the anterior leaflet) may be useful.[21] In more advanced forms of tethering and RV dilatation, valve replacement should be considered. The use of large bioprostheses over mechanical valves is currently favoured.[22] Adding a tricuspid repair, if indicated during left-sided surgery, does not increase operative risks. Ten-year survival ranges from 30% to 50%, the predictors being preoperative functional class, LV and RV function, and prosthetic complications.[20–22] In the presence of trans-tricuspid pacemaker leads, the technique used should be adapted to the patient's condition and the surgeon's experience. Reoperation on the tricuspid valve in cases of persistent TR after mitral valve surgery carries a high risk, mostly due to the late referral and the consequently poor clinical conditions of the patient (including renal and hepatic impairment, age, and the

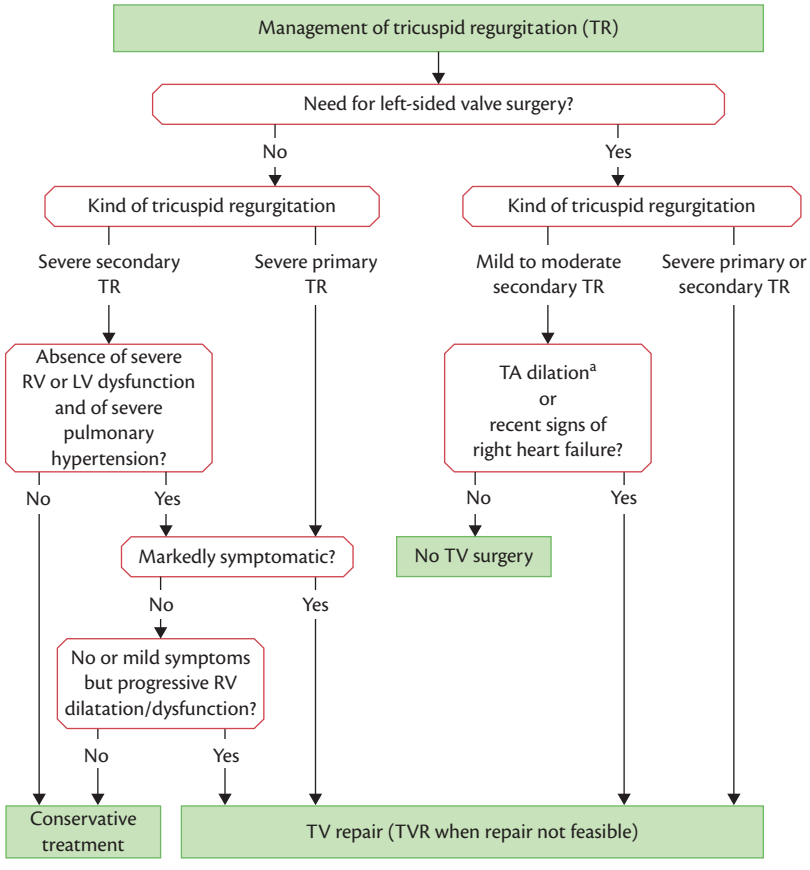

Figure 35.6.3 Indication for surgery in tricuspid regurgitation. LV, left ventricular; RV, right ventricular; TA, tricuspid annulus; TR, tricuspid regurgitation; TV, tricuspid valve; TVR, tricuspid valve replacement.
[a] TA 40 mm or <21 mm/m^2.

number of previous cardiac interventions). Those patients may well have poor long-term results related to the presence of irreversible RV dysfunction before reoperation, or LV, myocardial, or valvular dysfunction. To improve the surgical outcome and the prognosis of the patients in this challenging scenario, the treatment of severe late TR following left-sided valve surgery should be considered earlier, even in asymptomatic patients, if there are signs of progressive RV dilatation/dysfunction and in the absence of left-sided valve dysfunction, severe RV or LV dysfunction, and severe pulmonary vascular disease/hypertension.

Indications for surgery

The timing of surgical intervention remains controversial, mostly due to the limited data available and their heterogeneous nature (Table 35.6.1 and Figure 35.6.3).

As a general principle, if technically possible, valve repair is preferable to valve replacement and surgery should be carried out early enough to avoid irreversible RV dysfunction.

The need for correction of secondary TR is usually considered at the time of surgical correction of left-sided valve lesions. Tricuspid valve surgery is indicated in patients with severe TR. Tricuspid surgery should be considered in patients with mild or moderate TR and significant dilatation of the annulus (≥40 mm or >21 mm/m^2 on echocardiography or >70 mm on direct intraoperative measurement).[16–19] Tricuspid valve repair at the time of left-sided valve surgery may also be considered in patients with prior recent right heart failure even in the absence of annular dilatation. Any primary TR of moderate or more degree requires repair at the time of surgical correction of left-sided valve lesions.

Surgery limited to the tricuspid valve is recommended in symptomatic patients with severe primary TR. Though these patients respond well to diuretic therapy, delaying surgery is likely to result in irreversible RV damage, organ failure, and poor results of late surgical intervention. Although cut-off values are less well defined (similar to mitral regurgitation), asymptomatic patients with severe primary TR should be followed carefully to detect progressive RV enlargement and development of early RV dysfunction, prompting surgical intervention.

In persistent or recurrent severe TR after previous left-sided valve surgery, isolated operation on the tricuspid valve should be considered in patients who are symptomatic or have progressive RV dilatation or dysfunction, in the absence of left-sided valve dysfunction, severe RV or LV dysfunction, or severe pulmonary vascular disease.

For the management of Ebstein's abnormality see the article by Baumgartner and colleagues.[4]

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Chapter 35.7 Tricuspid stenosis

Tricuspid stenosis (TS), although still present in developing countries, is rarely observed in the West.[1] Detection requires careful evaluation, as it is almost always associated with left-sided valve lesions that dominate the presentation.

Aetiology

TS is often combined with tricuspid regurgitation, most frequently of rheumatic origin, and almost always associated with left-sided valve lesions, particularly mitral stenosis, that dominate the presentation. The anatomical changes of rheumatic TS resemble those of mitral stenosis. Carcinoid disease may cause mixed tricuspid valve disease, frequently associated with pulmonic stenosis.[1] Other aetiologies are rare: congenital, drug-induced valve diseases, Whipple's disease, endocarditis, or large right atrial tumour.

Pathophysiology

Normal valve area is around 7–8 cm^2, a pressure gradient occurs if it is smaller than 2 cm^2. TS usually induces a small (<5 mmHg) diastolic pressure gradient between the right atrium and ventricle, which increases during inspiration due to the increase of venous return, and is limited by venous compliance and reduced cardiac output. A mean pressure gradient greater than 5 mmHg is considered indicative of significant TS and is usually associated with symptoms.

Evaluation

History

The main symptoms and clinical signs are often those of the associated valvular lesions. Increased venous pressure results in the symptoms of right heart failure. Low cardiac output causes fatigue.

Physical examination

The diastolic murmur is of low intensity and increases with inspiration, preceded by a subtle opening snap. Presystolic jugular distension, Harzer's sign, systemic venous congestion, oedema, or even anasarca may be seen in the most severe cases.

Electrocardiography

In patients in sinus rhythm, the most frequent abnormality is right atrial hypertrophy or, more frequently, biatrial hypertrophy. Atrial fibrillation is present in one-half of cases.

Chest X-ray

The cardiac silhouette is enlarged with right atrial dilatation. Coexistent mitral stenosis results in left atrial enlargement, but the degree of pulmonary congestion is less than usual.

Echocardiography

Echocardiography provides the most useful information. TS is often overlooked and requires careful evaluation.

In rheumatic disease, the leaflets are thickened with reduced motion and frequent commissural fusion, the chordae are shortened and thickened, and diastolic doming is seen.[1] In carcinoid syndrome, retraction of leaflets or subvalvular apparatus, or both, towards the apex persists during systole. Echocardiographic evaluation of the anatomy of the valve and its subvalvular apparatus is important to assess valve reparability. The pressure half-time method is less valid for the assessment of the severity of TS than of MS and the continuity equation is rarely applicable because of the frequency with which associated regurgitation is present. Planimetry of the valve area is usually impossible unless three-dimensional echocardiography is used. No generally accepted grading of TS severity exists. A mean gradient of 5 mmHg or higher at normal heart rate is considered indicative of clinically significant TS.[1]

Catheterization is no longer used for evaluating TS severity and has been replaced by echocardiography.

Medical therapy

Diuretics are useful in the presence of heart failure but are of limited efficacy.

Surgery

The lack of pliable leaflet tissue is the main limitation for valve repair. Even though this is still a matter of debate, biological prostheses for valve replacement are usually preferred over mechanical ones because of the higher risk of thrombosis carried by the latter and the satisfactory long-term durability of the former in the tricuspid position.[2, 3]

Percutaneous intervention

Percutaneous balloon tricuspid dilatation has been performed in a limited number of cases, either alone or alongside percutaneous mitral commissurotomy, but this frequently induces significant regurgitation. There is a lack of data on evaluation of long-term results.[4]

Indications for intervention

Intervention on the tricuspid valve is usually carried out at the time of intervention on the other valves in patients who are symptomatic despite medical therapy. Conservative surgery or valve replacement according to anatomy and surgical expertise in valve repair is preferred to balloon commissurotomy, which can only be considered as a first approach in the rare cases of isolated TS or when additional mitral stenosis can also be treated interventionally (see Table 35.6.1 in Chapter 35.6).

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Chapter 35.8 Combined and multiple valve diseases

Significant stenosis and regurgitation can be found on the same valve. Disease of multiple valves may be encountered in several conditions, but particularly in rheumatic heart disease and, less frequently, in degenerative valve disease. There is a lack of data

on mixed and multiple valve diseases. This does not allow for evidence-based recommendations.[1]

The general principles for the management of mixed or multiple valve disease are as follows:

- When either stenosis or regurgitation is predominant, management follows the recommendations concerning the predominant valvular heart disease (VHD). When the severity of both stenosis and regurgitation is balanced, indications for interventions should be based upon symptoms and objective consequences, rather than the indices of severity of stenosis or regurgitation.
- Besides the separate assessment of each valve lesion, it is necessary to take into account the interaction between the different valve lesions. As an illustration, associated mitral regurgitation may lead to underestimation of the severity of aortic stenosis, since decreased stroke volume due to mitral regurgitation lowers the flow across the aortic valve and, hence, the aortic gradient. This underlines the need to combine different measurements, including assessment of valve areas, if possible using methods that are less dependent on loading conditions, such as planimetry.
- Indications for intervention are based on global assessment of the consequences of the different valve lesions, that is, symptoms or presence of left ventricular dilatation or dysfunction. Intervention can be considered for non-severe multiple lesions associated with symptoms or leading to left ventricular impairment.
- The decision to intervene on multiple valves should take into account the extra surgical risk of combined procedures.
- The choice of surgical technique should take into account the presence of the other VHD; repair remains the ideal option.

The management of specific associations of VHD is detailed in other chapters in Section 35.

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Chapter 35.9 Prosthetic valves

Valve substitutes and surgical techniques

There is no perfect valve substitute. Every valve prosthesis introduces a new disease process, whether they are mechanical (Figure 35.9.1), now mainly bileaflet valves, or biological (Figure 35.9.2). The latter include homografts, pulmonary autografts, and porcine, pericardial bovine, or equine xenografts. Stentless bioprostheses may have better haemodynamics,[1] but no improvement in long-term durability has been demonstrated so far. A new class of sutureless bioprostheses has the potential to simplify minimally invasive aortic valve replacement and reduce cross-clamp and cardiopulmonary bypass times.[2] Compared with conventional surgical valves, sutureless valves have a larger effective orifice area which results in lower gradients and may improve left ventricular mass regression.[3] However, higher rates of pacemaker implantation have been reported as compared to conventional bioprostheses.[4]

Minimally invasive surgery was developed as an alternative to full sternotomy and refers to different techniques using a smaller chest incision including mini-sternotomy, minithoracotomy, endoscopic video-assisted approach, or even robotic surgery. There is, however, a lack of adequate comparative studies.[5–7]

The two transcatheter-implantable prostheses which are most widely used are made of pericardial tissue inserted into a bare-metal balloon-expanding stent or a nitinol self-expanding stent. Continuous technical improvements have led to smaller devices. More recent devices have been designed to facilitate implantation, in particular with repositionable and retrievable valves, and to reduce the frequency of valve-related complications[8] (Figure 35.9.3).

All mechanical valves require lifelong anticoagulation using a vitamin K antagonist (VKA). In biological valves long-term anticoagulation is not required, unless atrial fibrillation or other indications are present, but they are subject to structural valve deterioration (SVD) over time.

Homografts and pulmonary autografts, mainly used in the aortic position in adults, account for < 1% of AVRs in large databases. Homografts are subject to SVD, which occurs more rapidly in young patients. A randomized trial showed superior durability of stentless bioprostheses over homografts.[9] Technical concerns, limited availability, and increased complexity of reintervention restrict the use of homografts. Although debated, the main indication for homografts is acute infective endocarditis with perivalvular lesions.[10]

The transfer of the pulmonary autograft in the aortic position (Ross procedure) provides excellent haemodynamics, but requires expertise and has carries a risk of early stenosis of the pulmonary homograft, a risk of recurrence of AR due to subsequent dilatation of the native aortic root and the risk of rheumatic involvement.[11, 12] Although the Ross operation is occasionally carried out in selected adults (professional athletes or women contemplating pregnancy), its main advantage is in children as the valve and new aortic annulus appear to grow with the child, which is not the case with homografts. Potential candidates for a Ross procedure should be referred to centres that are experienced and successful in performing this operation.

In practice, the choice is between a mechanical and a stented biological prosthesis in the majority of patients.

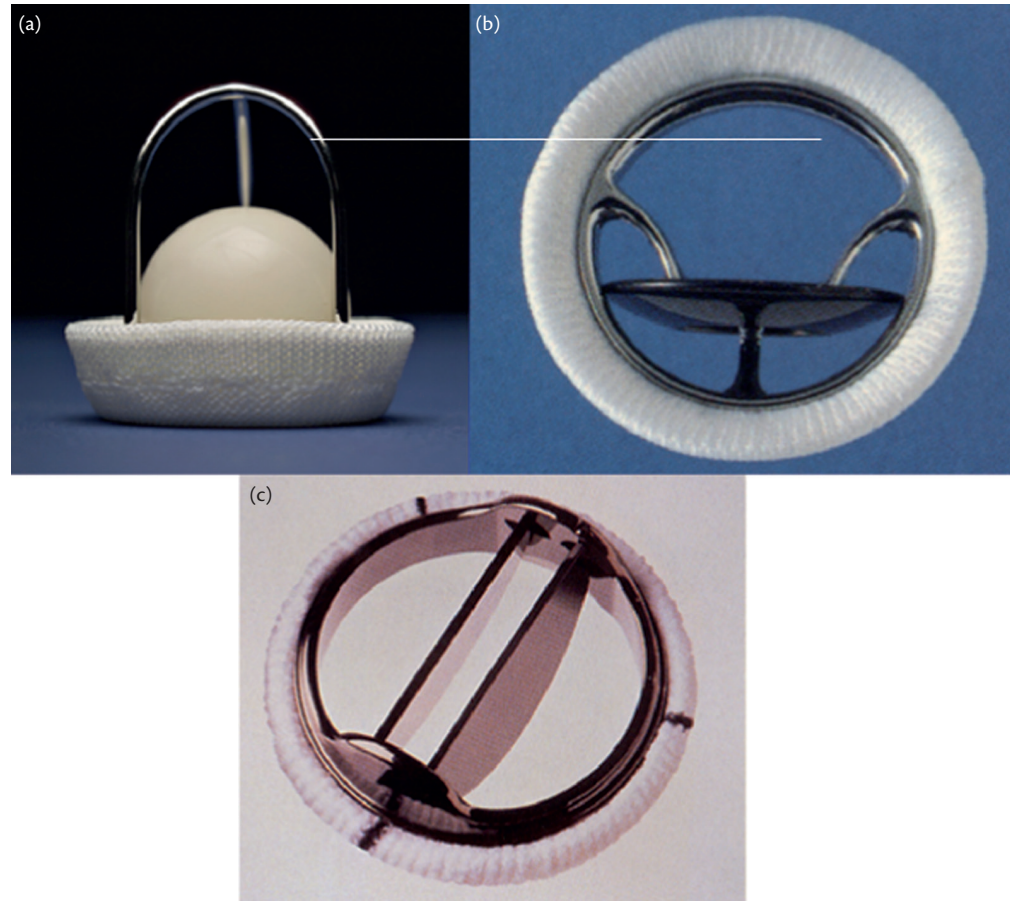


Figure 35.9.1 Main designs of mechanical valves. (a) Caged-ball prosthesis. (b) Tilting-disk prosthesis. (c) Bileaflet prosthesis.

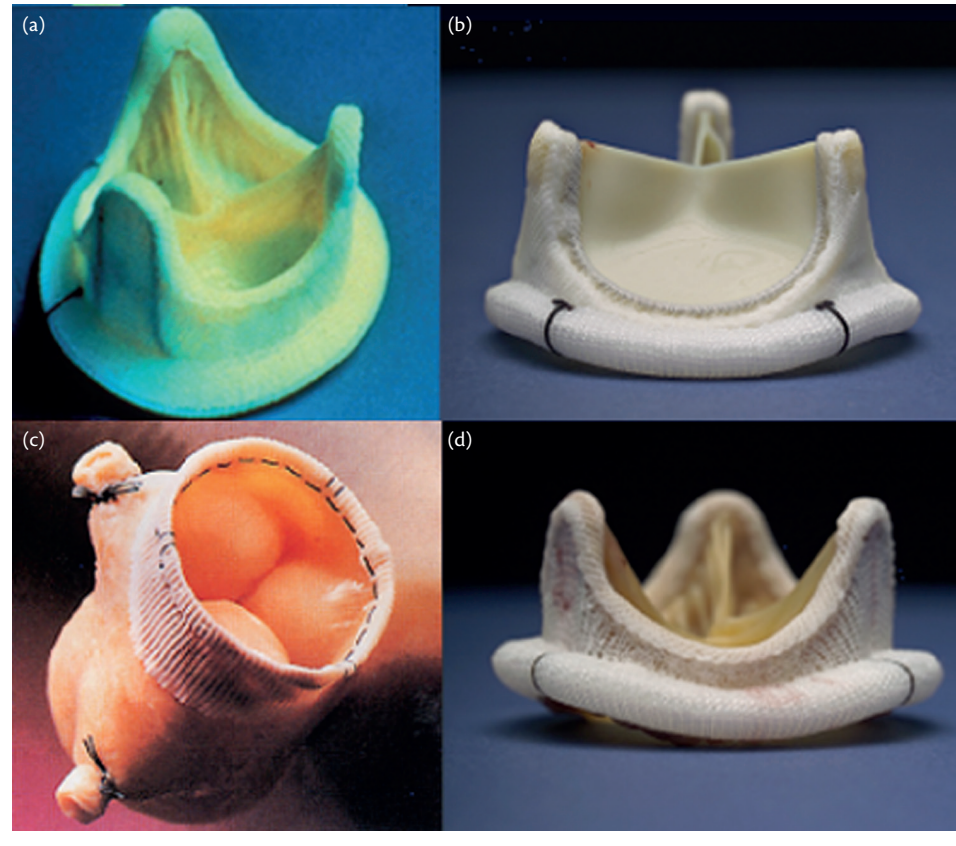


Figure 35.9.2 Main designs of bioprosthetic valves. (a) Porcine intra-annular valve. (b) Pericardial intra-annular valve. (c) Stentless porcine valve. (d) Supra-annular porcine valve.

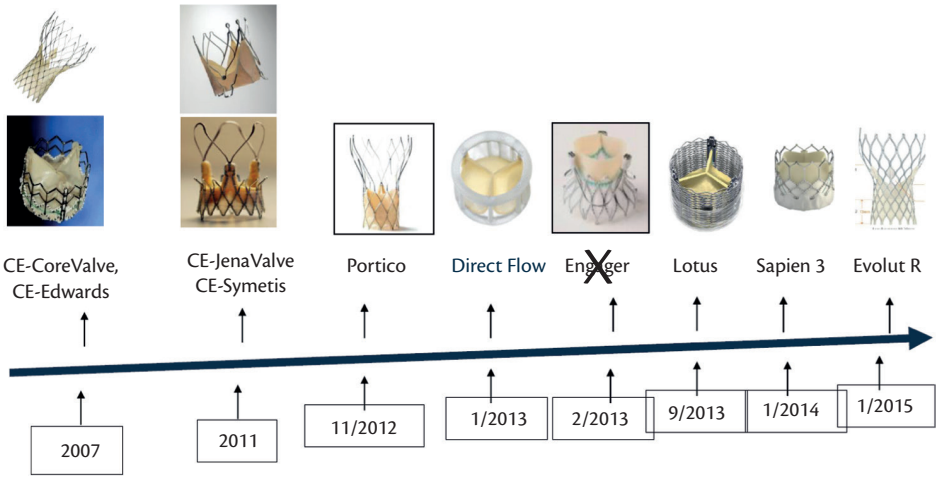


Figure 35.9.3 CE marked TAVI prostheses in Europe with dates of CE-mark registration. Balloon-expanding: Edwards, Sapien 3. Mechanically expanding: Lotus. Inflatable: Direct Flow. Self-expanding: CoreValve, Jena Valve, Symetis Acurate, Portico, Engager, Evolut R. The Engager valve was withdrawn from the market. Reproduced with permission from Figulla et al. Eur Heart J 2016; 37:2226–39.

Three randomized trials comparing mechanical and biological valves consistently found very close survival rates, no significant difference in rates of valve thrombosis and thromboembolism, higher rates of bleeding with mechanical prosthesis and higher rates of reinterventions with bioprostheses.[13–15] Two recent retrospective series analysed 15-year follow-up in patients aged between 50 and 69 years undergoing aortic valve replacement according to the type of prosthesis.[16, 17] The analysis of two propensity-matched subgroups of more than 1000 patients found the same differences in major bleeding and reinterventions but led to contrasting findings with regards to survival (Table 35.9.1). One study reported similar survival[16] while the other one found higher 15-year survival rates in patients who received a mechanical prosthesis; the difference was, however, significant in patients aged between 50 and 59 years but not in those aged between 60 and 69.[17]

Choice of the prosthetic valve

The choice between a mechanical and a biological valve in adults is mainly determined by estimating the risk of anticoagulation-related bleeding and thromboembolism with a mechanical valve versus the risk of SVD with a bioprosthesis, and by considering the patient's lifestyle and preferences. Bleeding risk is determined mainly by the target international normalized ratio (INR), the quality of anticoagulation control, the concomitant use of aspirin, and the patient's risk factors

Table 35.9.1 Studies comparing mechanical prostheses and bioprostheses for aortic valve replacement

	Veterans trial[13]		**Edinburgh trial[14]**		**Stassano et al.[15]**		**Chiang et al.[16]**		**Glaser et al.[17]**	
Method	Randomized		Randomized		Randomized		Propensity-matched		Propensity-matched	
Data	15-year rates		20-year rates		Linearized rates per 100 patient-years		15-year rates		15-year rates for survival. Crude rates for events.	
Prosthesis	Mec	Bio	Mec	Bio	Mec	Bio	Mec	Bio	Mec	Bio
n	198	196	109	102	149	147	1001	1001	1099	1099
Mean age (years)	–	–	–	–	64±8	64±4	62±5	62±6	62±5	62±5
Survival	34±3	21±3*	28±4	31±5	–	–	62 (58–66)	61 (56–65)	59	50*
Embolic events	18±4	18±4	24±6	39±9	0.54 (0.14–0.94)	0.24 (0.03–0.51)	8.6 (6.2–11.0)	7.7 (5.7–9.7)	5.8	6.1
Prosthetic thrombosis	2±1	1±1	–	–	0.23 (0.03–0.49)	0	–	–	–	–
Major bleeding	51±4	30±4*	38±7	32±13*	1.47 (0.81–2.13)	0.72 (0.25–1.19)	13.0 (9.9–16.1)	6.6 (4.8–8.4)*	9.6	4.9*
Reoperation	10±3	29±5*	7±3	56±8*	0.62 (0.19–1.05)	2.32 (1.48–3.18)*	6.9 (4.2–9.6)	12.1 (8.8–15.4)*	2.2	5.2*

Values are presented as percentages ± standard error or (95% confidence intervals).
Bio, bioprosthesis; Mec, mechanical prosthesis.
* Statistically significant differences with mechanical prosthesis (p <0.05).

Table 35.9.2 Choice of the aortic/mitral prosthesis—in favour of a mechanical prosthesis; the decision is based on the integration of several of the listed factors

	Class[a]	Level[b]
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications for long-term anticoagulation*	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration†	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position	IIa	C
A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and <65 years for prostheses in the mitral position‡	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy§, for whom future redo valve surgery would be at high risk	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to high risk for thromboembolism¶	IIb	C

[a] Class of recommendation.
[b] Level of evidence.
* Increased bleeding risk because of co-morbidities, compliance concerns, geographic, lifestyle, and occupational conditions.
† Young age (<40 years), hyperparathyroidism.
‡ In patients aged 60–65 years who should receive an aortic prosthesis, and those aged 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of other factors than age.
§ Life expectancy should be estimated >10 years, according to age, gender, co-morbidities, and country-specific life expectancy.
¶ Risk factors for thromboembolism are atrial fibrillation, previous thromboembolism, hypercoagulable state, severe left ventricular systolic dysfunction.

for bleeding. The risk linked to SVD must take into account the rate of SVD, which decreases with age and is higher in the mitral than the aortic position, and the risk of reoperation, which is only slightly higher than for a first operation.[18] Transcatheter implantation of a prosthesis in a degenerated bioprosthesis (valve-in-valve) may lower the risk of reintervention and be an incentive to favour the use of bioprostheses. However, the feasibility and quality of the results of this strategy depend on the size of aortic bioprostheses implanted at the index procedure and experience is so far limited in the mitral position. In valve sizes 21 or smaller, the valve-in-valve concept will lead to residual gradients and is associated with a higher failure rate.

More importantly, rather than setting arbitrary age limits, prosthesis choice should be discussed in detail between the informed patient, cardiologists, and surgeons, taking into account the factors detailed in Table 35.9.2 and Table 35.9.3. In patients aged 60–65 years who are to receive an aortic prosthesis, and those aged 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of additional factors. The following considerations should be taken into account:

- Bioprostheses should be considered in patients whose life expectancy is lower than the presumed durability of the bioprosthesis, particularly if co-morbidities may necessitate further surgical procedures, and in those with increased bleeding

Table 35.9.3 Choice of the aortic/mitral prosthesis—in favour of a bioprosthesis; the decision is based on the integration of several of the listed factors

	Class[a]	Level[b]
A bioprosthesis is recommended according to the desire of the informed patient	I	C
A bioprosthesis is recommended when good quality anticoagulation is unlikely (compliance problems, not readily available) or contraindicated because of high bleeding risk (prior major bleed, co-morbidities, unwillingness, compliance problems, lifestyle, occupation)	I	C
A bioprosthesis is recommended for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control	I	C
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy	IIa	C
A bioprosthesis should be considered in patients aged >65 years for prosthesis in aortic position or >70 years in mitral position, or those with life expectancy* lower than the presumed durability of the bioprosthesis†	IIa	C

[a] Class of recommendation.
[b] Level of evidence.
* Life expectancy should be estimated according to age, gender, co-morbidities, and country-specific life expectancy.
† In patients aged 60–65 years who should receive an aortic prosthesis and those aged 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.

risk. Although SVD is accelerated in chronic renal failure, poor long-term survival with either type of prosthesis and an increased risk of complications with mechanical valves may favour the choice of a bioprosthesis.[19]

- In women who wish to become pregnant, the high risk of thromboembolic complications with a mechanical prosthesis during pregnancy, whatever the anticoagulant regimen used, and the low risk of elective reoperation are incentives to consider a bioprosthesis, despite the rapid occurrence of SVD in this age group.[20]
- Quality of life issues and informed patient preferences must also be taken into account. The inconvenience of oral anticoagulation can be minimized by self-management of anticoagulation. Although bioprosthetic recipients can avoid long-term anticoagulation, they face the possibility of deterioration in functional status due to SVD and the prospect of reoperation if they live long enough.
- During mid-term follow-up, certain patients receiving a bioprosthetic valve may develop another condition requiring oral anticoagulation, in particular atrial fibrillation.

The impact of valve prosthesis–patient mismatch in the aortic position supports the use of a prosthesis with the largest possible effective orifice area, although the use of *in vitro* data and the geometric orifice area lacks reliability.[21] If the valve prosthesis:patient ratio is expected to be less than 0.65 cm^2/m^2 body surface area, enlargement of the annulus to allow placement of a larger prosthesis may be considered.

Management after valve replacement

Thromboembolism and anticoagulant-related bleeding represent the majority of complications experienced by prosthetic valve recipients. Endocarditis prophylaxis and management of prosthetic valve endocarditis are detailed in separate European Society of Cardiology Guidelines.[10]

Baseline assessment and modalities of follow-up

A complete baseline assessment should, ideally, be performed 6–12 weeks after surgery or transcatheter aortic valve implantation (TAVI). This includes clinical assessment, chest X-ray, electrocardiogram, transthoracic echocardiogram (TTE), and blood testing (haemoglobin, platelet count, creatinine, lactic dehydrogenase, and INR). This assessment is of the utmost importance to interpret changes in murmur and prosthetic sounds, as well as ventricular function, transprosthetic gradients, and absence of paravalvular regurgitation. This postoperative visit is also useful to improve patient education on endocarditis prophylaxis and, if needed, on anticoagulant therapy and to emphasize that new symptoms should be reported as soon as they occur.

All patients who have undergone valve surgery require lifelong follow-up by a cardiologist in order to detect early deterioration in prosthetic function or ventricular function or progressive disease of another heart valve. Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. TTE should be performed if any new symptoms occur after valve replacement or if complications are suspected. After transcatheter as well as surgical implantation of a bioprosthetic valve, echocardiography including the measurement of transprosthetic gradients should be performed within 30 days (preferably around 30 days for surgery) after valve implantation (i.e. baseline imaging), at 1 year after implantation, and annually thereafter.[22] Transprosthetic gradients are best interpreted in comparison with the baseline values, rather than in comparison with theoretical values for a given prosthesis, which lack reliability. Transoesophageal echocardiography (TOE) should be considered if TTE is of poor quality and in all cases of suspected prosthetic dysfunction or endocarditis.[23, 25] Cinefluoroscopy for mechanical valves and multislice computed tomography (CT) scanning provide useful additional information if valve thrombus or pannus are suspected to impair valve function.[24, 25]

Antithrombotic management

General management

Antithrombotic management should address effective control of modifiable risk factors for thromboembolism in addition to the prescription of antithrombotic drugs.[18] Indications for antithrombotic therapy after valve repair or replacement are summarized in Table 35.9.4.

In patients with surgical aortic bioprostheses, the use of low-dose aspirin is now favoured as an alternative to postoperative anticoagulant therapy.[28] This relies, however, on a low level of evidence and retrospective analyses of large databases led to contrasting results.[29–31]

When postoperative anticoagulant therapy is indicated, oral anticoagulation should be started during the first postoperative days. Intravenous unfractionated heparin (UFH), monitored to an activated partial thromboplastin time of 1.5–2.0 times control value enables rapid anticoagulation to be obtained before the INR rises.[31] Low-molecular-weight heparin (LMWH) seems to offer effective and stable anticoagulation and has been used in small observational series mostly using enoxaparin.[32, 33] This is off-label use. The limiting factors for the use of LMWH early after mechanical valve replacement are the lack of randomized controlled trials, concerns about pharmacokinetics in obese patients and target anti-Xa activity, contraindication in the presence of severe renal dysfunction, and less effective neutralization. If LMWH is used, anti-Xa monitoring is recommended.

The first postoperative month is a high-risk period for thromboembolism and anticoagulation should not be lower than the target value during this time, particularly in patients with mechanical mitral prostheses.[34, 35] Anticoagulation is subject to increased variability and should be monitored more frequently. The addition of aspirin to anticoagulant therapy decreases postoperative thromboembolic risk but increases bleeding risk and cannot be recommended routinely.[36]

When long-term anticoagulant therapy is needed in patients with a bioprosthesis, most often because of atrial fibrillation, VKAs are favoured. Despite the absence of data from clinical

Table 35.9.4 Indications for antithrombotic therapy in patients with a prosthetic heart valve or valve repair

	Class[a]	Level[b]	Ref.[c]
Mechanical prosthesis			
Oral anticoagulation using VKA is recommended lifelong for all patients	I	B	26, 27
Bridging using therapeutic doses of UFH or LMWH is recommended when VKA should be interrupted	I	C	
The addition of low-dose aspirin (75–100 mg/day) to VKA should be considered after thromboembolism despite adequate INR	IIa	C	
The addition of low-dose aspirin (75–100 mg/day) to VKA may be considered in case of concomitant atherosclerotic disease	IIb	C	
INR self-management is recommended, provided appropriate training and quality control are performed	I	B	47
In patients treated with coronary stent implantation, triple therapy with aspirin (75–100 mg/day), clopidogrel (75 mg/day), and VKA should be considered for 1 month, irrespective of the type of stent used and clinical presentation (i.e. ACS or stable CAD)	IIa	B	55
Triple therapy comprising aspirin (75–100 mg/day), clopidogrel (75 mg/day), and VKA for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, that outweigh the bleeding risk	IIa	B	55
Dual therapy comprising VKA and clopidogrel (75 mg/day) should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk	IIa	A	56, 57
In patients with PCI, discontinuation of antiplatelet treatment should be considered at 12 months	IIa	B	58
In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%	IIa	B	55, 56
The use of NOACs is contraindicated	III	B	39
Bioprostheses			
Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprostheses who have other indications for anticoagulation*	I	C	
Oral anticoagulation using VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid bioprosthesis	IIa	C	
Oral anticoagulation using VKA should be considered for the first 3 months after surgical mitral or tricuspid valve repair	IIa	C	
Low-dose aspirin (75–100 mg/day) should be considered for the first 3 months after surgical implantation of an aortic bioprosthesis or valve-sparing aortic surgery	IIa	C	
Dual antiplatelet therapy should be considered for the first 3-6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other reasons	IIa	C	
Single antiplatelet therapy may be considered after TAVI in case of high bleeding risk	IIb	C	
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis	IIb	C	

CAD, coronary artery disease; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting recommendations.
* Atrial fibrillation, venous thromboembolism, hypercoagulable state, or with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction <35%).

trials, non-vitamin K antagonist oral anticoagulants can be used in patients who have atrial fibrillation associated with a bioprosthesis after the third postoperative month.[40] There is no evidence to support the use of antiplatelet agents beyond 3 months in patients with surgical bioprostheses who do not have an indication other than the presence of the bioprosthesis itself.

Despite the lack of evidence, a combination of low-dose aspirin and a thienopyridine is used early after TAVI and percutaneous edge-to-edge repair, followed by aspirin or a thienopyridine alone in patients who have no other indication for oral anticoagulation. In patients in atrial fibrillation, a combination of a VKA and aspirin or thienopyridine is generally used, but should be weighed against increased bleeding risk. Triple antithrombotic therapy should be avoided given the bleeding risk.[31] Recent data suggest that single antiplatelet therapy may have a better safety profile with the same efficacy than dual antiplatelet therapy after TAVI.[37] Observational findings suggest that anticoagulant therapy reduces the incidence of subclinical thrombosis as compared with double antiplatelet therapy.[38] The results of ongoing large-scale dedicated trials are needed to improve evidence in this field.

The substitution of VKAs by direct oral inhibitors of factor IIa is contraindicated in patients with mechanical prosthesis due to a higher risk of both thromboembolism and bleeding.[39] In the absence of specific trials, this contraindication expands to oral anti-Xa.

Table 35.9.5 Target international normalized ratio for mechanical prostheses

Prosthesis thrombogenicity*	Patient-related risk factors†	
	No risk factor	≥1 risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

* Prosthesis thrombogenicity: Low = Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon; Medium = other bileaflet valves with insufficient data; High = Lillehei–Kaster, Omniscience, Starr–Edwards (ball–cage), Bjork–Shiley and other tilting-disc valves.
† Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction <35%.

Target INR

In choosing an optimum target INR one should consider patient risk factors and the thrombogenicity of the prosthesis, as determined by reported valve thrombosis rates for that prosthesis in relation to specific INR levels (Table 35.9.5).[18] Currently available randomized trials comparing different INR values cannot be used to determine target INR in all situations and varied methodologies make them unsuitable for meta-analysis.[41–43]

In selecting the optimum INR certain caveats apply:

- Prostheses cannot be conveniently categorized by basic design (e.g. bileaflet, tilting disc, etc.) or date of introduction for the purpose of determining thrombogenicity.
- For many currently available prostheses, particularly newly introduced prostheses, sufficient data on valve thrombosis rates at different levels of INR, which would allow for categorization, do not exist. Until further data become available they should be placed in the 'medium thrombogenicity' category.
- INR recommendations in individual patients may need to be revised downwards if recurrent bleeding occurs, or upwards in case of embolism, despite an acceptable INR level.

Recent randomized trials supported lower target INRs for aortic prostheses.[44–46] However, limited statistical power, certain methodological concerns, and the restriction to certain prostheses and/or to the use of INR self-management led the Task Force not to change recommendations for target INR.

We recommend a median INR value rather than a range to avoid considering extreme values in the target range as a valid target INR, since values at either end of a range are not as safe and effective as median values.

High variability of the INR is a strong independent predictor of reduced survival after valve replacement. There is now evidence that INR self-management reduces INR variability and clinical events, including patients with heart valve prosthesis;[47] however, appropriate training and regular quality control are required. Monitoring by an anticoagulant clinic should, however, be considered for patients with unstable INR or anticoagulant-related complications. Systematic genotyping of patients under a VKA is not recommended in the absence of convincing clinical benefit and concerns on cost-effectiveness.[48]

Management of overdose of VKAs and bleeding

The risk of major bleeding rises considerably when the INR exceeds 4.5 and increases exponentially above an INR of 6.0. An INR of 6.0 or higher therefore requires rapid reversal of anticoagulation because of the risk of subsequent bleeding.

In the absence of bleeding the management depends on the target INR, the actual INR, and the half-life of the VKA used. It is possible to stop oral anticoagulation and to allow the INR to fall gradually or to give oral vitamin K in increments of 1 or 2 mg.[49] If the INR is higher than 10, higher doses of oral vitamin K (5 mg) should be considered. The oral route should be favoured over the intravenous route.[49]

Immediate reversal of anticoagulation is required only for severe bleeding, defined as not amenable to local control, threatening life or important organ function (e.g. intracranial bleeding), causing haemodynamic instability, or requiring an emergency surgical procedure or transfusion. Intravenous prothrombin complex concentrate has a short half-life and therefore if used should be combined with oral vitamin K, whatever the INR.[49] When available, the use of intravenous prothrombin complex concentrate is preferred over fresh frozen plasma. There are no data suggesting that the risk of thromboembolism due to transient reversal of anticoagulation outweighs the consequences of severe bleeding in patients with mechanical prostheses. The optimal time to re-start anticoagulant therapy should be discussed in relation to the location of the bleeding event, its evolution, and interventions performed to stop bleeding and/or to treat an underlying cause.[50] Bleeding while in the therapeutic INR range is often related to an underlying pathological cause and it is important that it is identified and treated.

Combination of oral anticoagulants with antiplatelet drugs

In determining whether an antiplatelet agent should be added to anticoagulation in patients with prosthetic valves, it is important to distinguish between the possible benefits in coronary and vascular disease and those specific to prosthetic valves. Trials showing a benefit from antiplatelet drugs in patients with prosthetic valves and vascular disease[51] should not be taken as evidence that patients with prosthetic valves and no vascular disease will also benefit. The addition of aspirin has not been studied in patients without vascular disease with contemporary target INRs.[31] Underlying uncertainties on the risk:benefit ratio of the combination of VKAs with aspirin account for discrepancies between different recommendations.[52, 53] When added to anticoagulation, antiplatelet agents decrease the thromboembolic risk, but increase the risk of major bleeding.[54] They should, therefore, not be prescribed to all patients with prosthetic valves, but be reserved for specific indications, according to the analysis of benefit and increased risk of major bleeding. If used, the lower recommended dose should be prescribed (e.g. aspirin 75–100 mg/day).

Indications for the addition of an antiplatelet agent are detailed in Table 35.9.4. The addition of antiplatelet agents should be

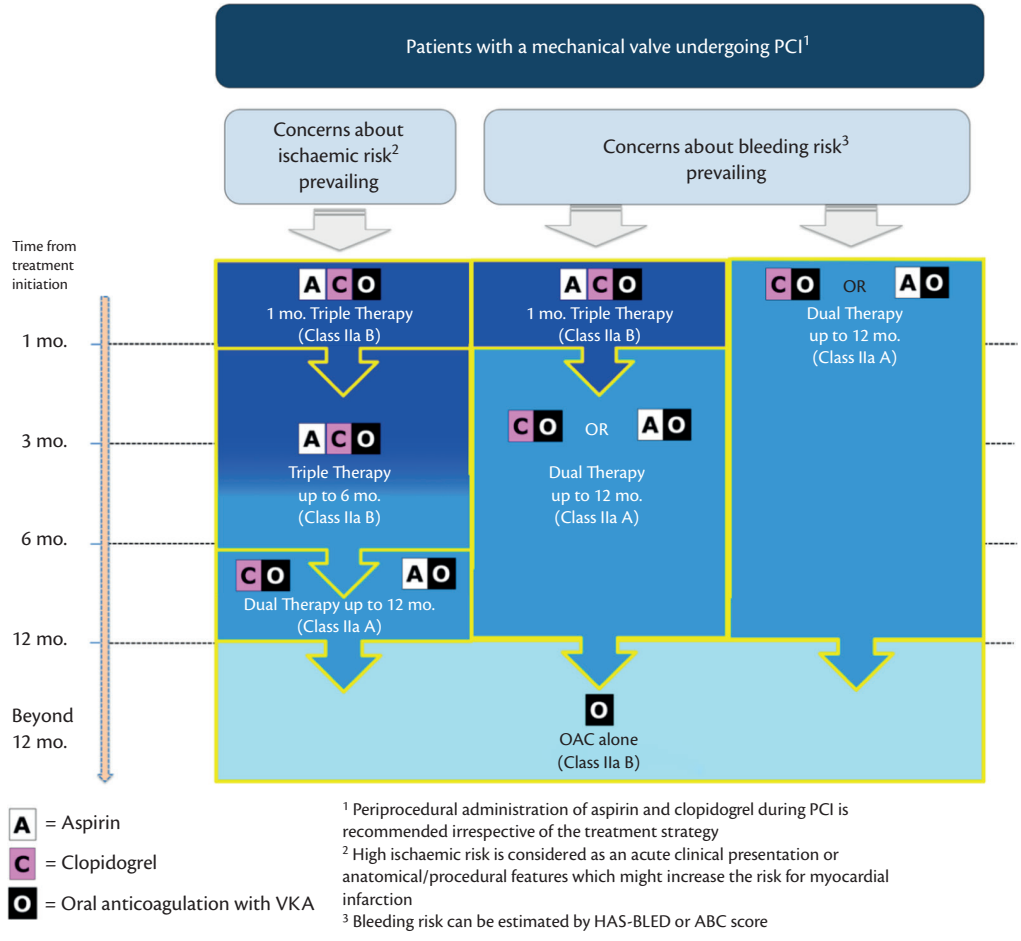


Figure 35.9.4 Antithrombotic therapy in patients with mechanical valve prosthesis undergoing PCI. VKA, vitamin K antagonist. For more details regarding estimation of bleeding risk (HAS-BLED and ABC score) see 2017 ESC focused update on dual antiplatelet therapy.[59]
Adapted from the 2017 ESC Focused Update on dual antiplatelet therapy.

considered only after full investigation and treatment of identified risk factors and optimization of anticoagulation management.

Addition of aspirin and a $P2Y_{12}$ receptor blocker is necessary following intracoronary stenting or acute coronary syndrome (ACS), but increases bleeding risk. Aspirin, clopidogrel, and VKA should be associated at least 1 month after stent implantation. If bleeding risk is high, triple antithrombotic therapy may be limited to 1 month or replaced by a combination of VKA and clopidogrel.[56–59] The use of prasugrel or ticagrelor as part of triple therapy should be avoided.[60] During triple antithrombotic therapy, close monitoring of the INR is advised and the INR should be kept in the low target range. Recommendations on antithrombotic strategies after ACS in patients under oral anticoagulant therapy are detailed in Table 35.9.4 and Figure 35.9.4.

Interruption of anticoagulant therapy for planned invasive procedures

Anticoagulation during non-cardiac surgery requires careful management based on risk assessment.[61] Besides prosthesis and patient-related prothrombotic factors (Table 35.9.5), surgery for malignant disease or an infective process carries a particular risk due to the hypercoagulability.

It is recommended not to interrupt oral anticoagulation for most minor surgical procedures (including dental extraction and cataract removal) and those procedures where bleeding is easily controlled. Appropriate techniques of haemostasis should be used and the INR should be measured on the day of the procedure.[62]

Major surgical procedures require an INR lower than 1.5. In patients with a mechanical prosthesis, oral anticoagulant therapy should be stopped before surgery and bridging using heparin is recommended.[61] Recent data supporting interruption of VKA without bridging do not apply to patients with mechanical prosthesis, who were excluded from this randomized trial.[63] UFH remains the only approved heparin treatment in patients with mechanical prostheses; intravenous administration should be favoured over the subcutaneous route. The use of subcutaneous LMWH is as an alternative to UFH for bridging. However, despite their widespread use and the positive results of observational studies,[64] LMWHs are not approved in patients with mechanical prostheses due to the lack of controlled comparative studies with UFH. When LMWHs are used, they should be administered twice a day using therapeutic doses, adapted to body weight and renal function, and, if possible, with monitoring of anti-Xa activity with a target of 0.5–1.0 U/mL. LMWHs are contraindicated in cases of severe renal failure. The last dose of LMWH should be administered more than 12 h before the procedure, whereas UFH should be discontinued 4 h before surgery. Effective anticoagulation should be resumed as soon as possible after the surgical

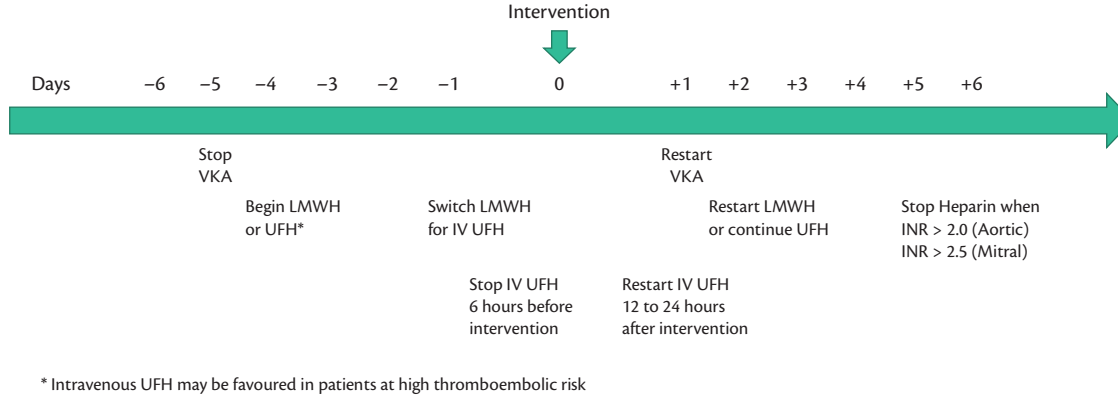


Figure 35.9.5 Main bridging steps for an intervention requiring interruption of oral anticoagulation in a patient with a mechanical prosthesis. Timing should be individualized according to patient characteristics, actual INR, and the type of intervention. INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.
Reproduced with permission from Iung B and Rodes-Cabau J. Eur Heart J 2014;35:2942–2949.

procedure according to bleeding risk and maintained until the INR returns to the therapeutic range.[31, 61] Fondaparinux should not be used for bridging in patients with mechanical prosthesis. Practical modalities of anticoagulation bridging are detailed in Figure 35.9.5.

If required, after a careful risk:benefit assessment, combined aspirin therapy should be discontinued 1 week before a non-cardiac procedure.

Oral anticoagulation can be continued at modified doses in the majority of patients who undergo cardiac catheterization, in particular using the radial approach. In patients who require transseptal catheterization for valvular interventions, direct left ventricular puncture, or pericardial drainage, oral anticoagulants should be stopped with bridging anticoagulation.[18]

In patients who have a sub-therapeutic INR during routine monitoring, bridging with UFH or, preferably, LMWH in an outpatient setting is indicated until a therapeutic INR value is reached.

Management of valve thrombosis

Obstructive valve thrombosis should be suspected promptly in any patient with any type of prosthetic valve who presents with recent dyspnoea or an embolic event. Suspicion should be higher after recent inadequate anticoagulation or a cause for increased coagulability (e.g. dehydration or infection). The diagnosis should be confirmed by TTE and TOE or cinefluoroscopy or CT scan if promptly available.[23–25]

The management of mechanical prosthetic valve thrombosis is high risk whatever the option taken. Surgery is high risk because it is most often performed under emergency conditions and is a reintervention. On the other hand, fibrinolysis carries risks of bleeding, systemic embolism and recurrent thrombosis, which are higher than after surgery.[65]

The analysis of the risks and benefits of fibrinolysis should be adapted to patient characteristics and local resources.

Emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without contraindication to surgery (Table 35.9.6 and Figure 35.9.6). If thrombogenicity of the prosthesis is an important factor it should be replaced with a less thrombogenic prosthesis.

Fibrinolysis should be considered in:

- Critically ill patients unlikely to survive surgery because of co-morbidities or severely impaired cardiac function before developing valve thrombosis.
- Situations in which surgery is not immediately available and the patient cannot be transferred.
- Thrombosis of tricuspid or pulmonary valve replacements, because of the higher success rate and low risk of systemic embolism.

In case of haemodynamic instability a short protocol is recommended, using either intravenous recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 minutes with UFH, or streptokinase 1,500,000 U in 60 minutes without UFH. Longer durations of infusions can be used in stable patients.[66]

Fibrinolysis is less likely to be successful in mitral prostheses, in chronic thrombosis, or in the presence of pannus, which can be difficult to distinguish from thrombus.[67]

Non-obstructive prosthetic valve thrombosis is diagnosed using TOE performed after an embolic event, or systematically following mitral valve replacement with a mechanical prosthesis. Management depends mainly on the occurrence of a thromboembolic event and the size of the thrombus (Figure 35.9.7). Close monitoring by TOE is mandatory. The prognosis is favourable with medical therapy in most cases of small thrombus (<10 mm). A good response with gradual resolution of the thrombus obviates the need for surgery. Conversely, surgery should be considered for large (≥10 mm) non-obstructive prosthetic thrombus complicated by embolism or which persists despite optimal anticoagulation.[34] Fibrinolysis may be considered if surgery is at high risk. However, it should only be used where absolutely necessary because of the risks of bleeding and thromboembolism.

Valve thrombosis occurs mainly on mechanical prostheses. However, cases of early thrombosis of porcine aortic bioprostheses have been reported.[68] Transcatheter heart valve thrombosis

Table 35.9.6 Management of prosthetic valve dysfunction

	Class[a]	Level[b]
Mechanical prosthetic thrombosis		
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious co-morbidity	I	C
Fibrinolysis (using r-tPA 10 mg bolus + 90 mg in 90 min with UFH, or streptokinase 1,500,000 U in 60 min without UFH) should be considered when surgery is not available or at very high risk, or for thrombosis of right-sided prostheses	IIa	C
Surgery should be considered for large (≥10 mm) non-obstructive prosthetic thrombus complicated by embolism	IIa	C
Bioprosthetic thrombosis		
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention	I	C
Haemolysis and paravalvular leak		
Reoperation is recommended if paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms	I	C
Transcatheter closure may be considered for paravalvular leaks with clinically significant regurgitation in surgical high-risk patients (heart team decision)	IIb	C
Bioprosthetic failure		
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation	I	C
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction, if reoperation is at low risk	IIa	C
Transcatheter valve-in-valve implantation in aortic position should be considered by the heart team depending on the risk of reoperation and the type and size of prosthesis	IIa	C

r-tPA: recombinant tissue plasminogen activator; UFH: unfractionated heparin.
[a] Class of recommendation.
[b] Level of evidence.

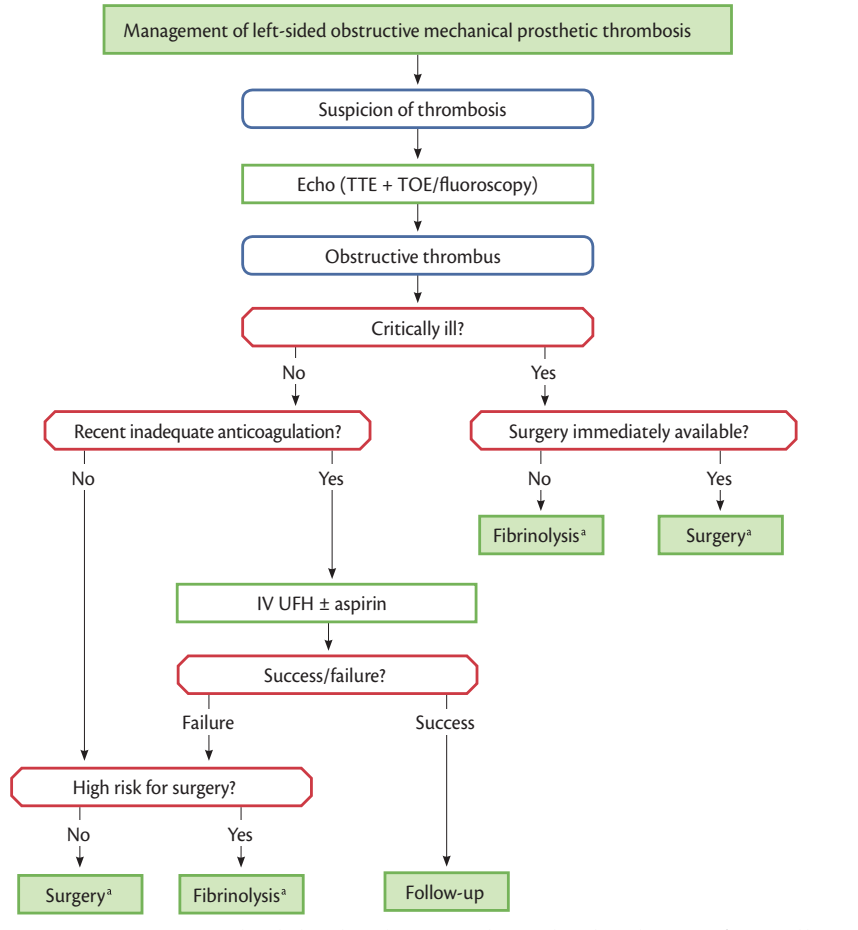
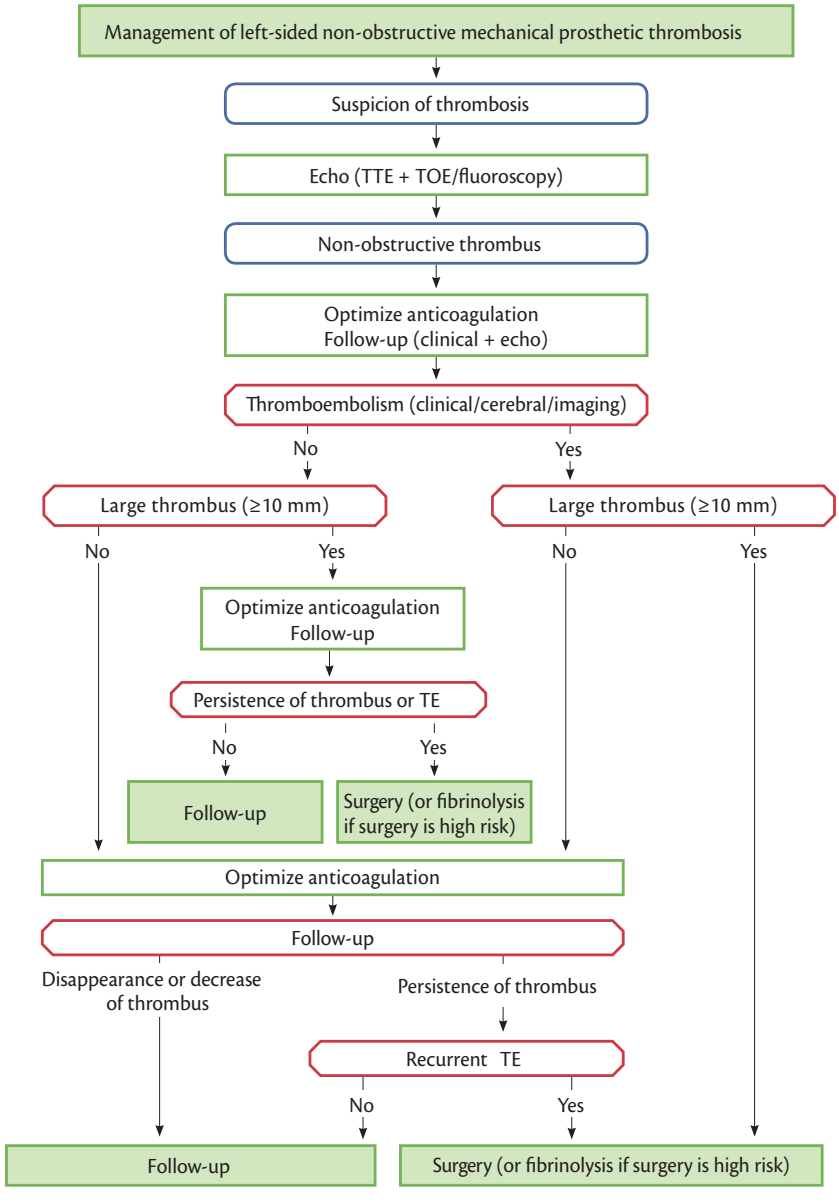


Figure 35.9.6 Management of left-sided obstructive mechanical prosthetic thrombosis. IV, intravenous; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; UFH, unfractionated heparin.
[a] Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery.

IV = intravenous; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography; UFH = unfractionated heparin.
[a]Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery.



TE = thromboembolism; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

Figure 35.9.7 Management of left-sided non-obstructive mechanical prosthetic thrombosis. TE, thromboembolism; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

has also been reported, mainly during the first year following implantation and was successfully treated by prolonged anticoagulation in three-quarters of cases.[69] Subclinical thrombosis of bioprosthesis are more frequent when assessed by cardiac CT scan showing reduced leaflet motion associates with a small increase in transprosthetic gradients but the clinical consequences are unknown.[70, 71] Anticoagulation using VKA or UFH, or both, is the first-line treatment of bioprosthetic valve thrombosis.

Management of thromboembolism

Thromboembolism after valve surgery is multifactorial in origin.[18] Although thromboembolic events frequently originate from the prosthesis, many others arise from other sources and are part of their background incidence in the general population.

Thorough investigation of each episode of thromboembolism is therefore essential (including cardiac and non-cardiac imaging) (Figure 35.9.7), rather than simply increasing the target INR or adding an antiplatelet agent. Prevention of further thromboembolic events involves the following:

- Treatment or reversal of risk factors such as atrial fibrillation, hypertension, hypercholesterolaemia, diabetes, smoking, and infection.
- Optimization of anticoagulation control, if possible with patient self-management, on the basis that better control is more effective than simply increasing the target INR. This should be discussed with the neurologist in case of recent stroke.
- Low-dose aspirin (75–100 mg daily) should be added, if it was not previously prescribed, after careful analysis of the risk:benefit ratio, avoiding over-anticoagulation.

Management of haemolysis and paravalvular leak

Blood tests for haemolysis should be part of routine follow-up after valve replacement. Haptoglobin measurement is too

sensitive and lactate dehydrogenase, although non-specific, is better related to the severity of haemolysis. The diagnosis of haemolytic anaemia requires TOE to detect a paravalvular leak if TTE is not contributory. Reoperation is recommended if a paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms (Table 35.9.6). Medical therapy, including iron supplementation, beta blockers, and erythropoietin, is indicated in patients with severe haemolytic anaemia when contraindications to surgery are present.[72] Transcatheter closure of paravalvular leaks is feasible, but experience is limited and there is presently no conclusive evidence to show a consistent efficiency.[73] It may be considered in selected patients in whom reintervention is deemed high risk or is contraindicated.

Management of bioprosthetic valve failure

After transcatheter as well as surgical implantation of a bioprosthetic valve, echocardiography including the measurement of transprosthetic gradients should be performed within 30 days (preferably around 30 days for surgery) after valve implantation (i.e. baseline imaging), at 1 year after implantation, and annually thereafter.[22] The definitions of structural valve deterioration and bioprosthetic valve failure have recently been standardized in a consensus publication.[22]

Auscultatory and echocardiographic findings should be carefully compared with previous examinations in the same patient. Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient or severe regurgitation. Reoperation should be considered in asymptomatic patients with any significant prosthetic dysfunction, provided they are at low risk for reoperation (Table 35.9.6).

The decision to reoperate should take into account the risk of reoperation and the emergency situation. This underlines the need for careful follow-up to allow for timely reoperation. Operative mortality of redo surgery is low when performed on an elective basis in stable conditions.[74]

Percutaneous balloon interventions should be avoided in the treatment of stenotic left-sided bioprostheses.

Transcatheter valve-in-valve implantation is now an option for treating degenerated bioprostheses in the aortic or mitral position in patients with increased surgical risk.[75, 76] Valve-in-valve may not be feasible in small aortic bioprostheses and experience remains limited so far, in particular in the mitral position. Multimodality imaging is key for patient selection.[77] Valve-in-ring may be used after failed mitral valve repair, but experience remains limited and its feasibility depends on the type of prosthetic ring and prosthesis sizing may be difficult.[78] Valve-in-valve and valve-in-ring procedures may be reasonable alternatives if the patient is at increased surgical risk, but it is necessary for a multidisciplinary Heart Team discusses every patient and chooses the best individualized approach.

Heart failure

Heart failure after valve surgery should lead to a search for prosthetic dysfunction or prosthesis–patient mismatch deterioration of repair, left ventricular dysfunction, or progression of another valve disease. Non-valvular related causes such as coronary artery disease, hypertension, or sustained arrhythmias should also be considered. The management of patients with heart failure should follow the relevant guidelines.[79]

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Chapter 35.10 Management during non-cardiac surgery

Cardiovascular morbidity and mortality is increased in patients with valvular heart disease (VHD), mainly severe VHD, who undergo non-cardiac surgery. Perioperative management of patients with VHD relies on lower levels of evidence than those used for ischaemic heart disease, as detailed in specific European Society of Cardiology guidelines.[1]

Preoperative evaluation

Clinical assessment should search for symptoms, arrhythmias, and the presence of a murmur. Echocardiography should be performed in any patient with known or suspected VHD.

Cardiovascular risk is also stratified according to the type of non-cardiac surgery, classified according to the risk of cardiac complications.[1]

Determination of functional capacity is a pivotal step in preoperative risk assessment, measured either by an exercise test or ability to perform activities in daily life. Each patient should be discussed with cardiologists, anaesthetists (ideally cardiac anaesthetists), surgeons (both cardiac and the ones undertaking the non-cardiac procedure), and the patient and his or her family.

Specific valve lesions

Aortic stenosis

In patients with severe aortic stenosis needing urgent non-cardiac surgery, this should be performed under careful haemodynamic monitoring.

In patients with severe aortic stenosis needing elective non-cardiac surgery, the management depends mainly on the presence of symptoms and the type of surgery (Figure 35.10.1).[1–3] In symptomatic patients, aortic valve replacement should be considered before non-cardiac surgery. In patients at increased surgical risk, balloon aortic valvuloplasty or transcatheter aortic valve implantation is a therapeutic option.

In asymptomatic patients with severe aortic stenosis, elective non-cardiac surgery can be performed safely albeit with a risk of worsening heart failure.[2, 3]

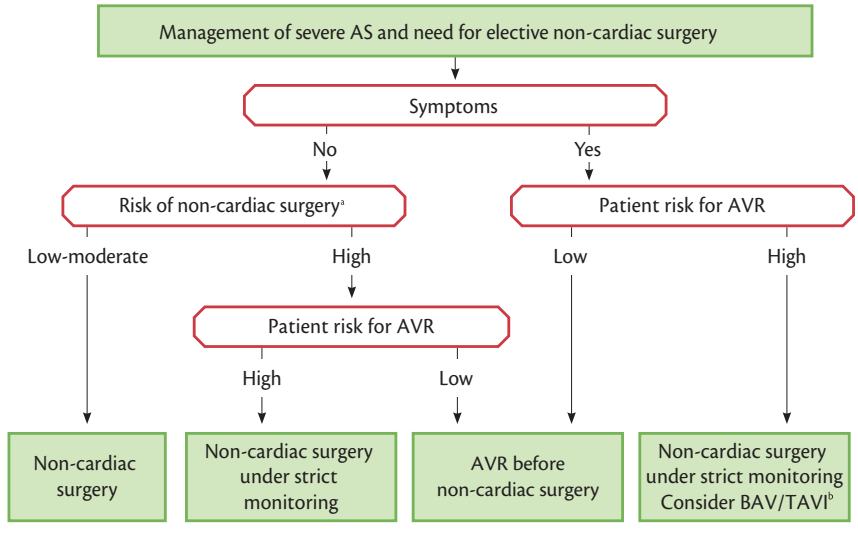
If non-cardiac surgery is haemodynamically challenging with large volume shifts, aortic valve replacement should be considered first. In patients who are at high risk for valvular surgery or transcatheter aortic valve implantation, non-cardiac surgery should be performed under strict haemodynamic monitoring and transoesophageal echocardiography.

When valve surgery is needed before non-cardiac surgery, a bioprosthesis may be considered in order to avoid anticoagulation problems during surgery.

Mitral stenosis

In patients with non-significant mitral stenosis (valve area >1.5 cm^2), and in asymptomatic patients with significant mitral stenosis and a systolic pulmonary artery pressure lower than 50 mmHg, non-cardiac surgery can be performed safely.

In symptomatic patients or in patients with systolic pulmonary artery pressure higher than 50 mmHg, correction of mitral stenosis, by means of percutaneous mitral commissurotomy whenever possible, should be attempted before non-cardiac surgery if it is high risk.



AS = aortic stenosis; AVR = aortic valve replacement; BAV = balloon aortic valvuloplasty; TAVI = transcatheter aortic valve implantation.
[a]Classification into three groups according to the risk of cardiac complications (30-day death and myocardial infarction) for non-cardiac surgery (high risk >5%; intermediate risk 1–5%; low risk <1%).[196]
[b]Non-cardiac surgery performed only if strictly needed. The choice between percutaneous aortic valvuloplasty and TAVI should take into account patient life expectancy

Figure 35.10.1 Management of severe aortic stenosis and elective non-cardiac surgery according to patient characteristics and the type of surgery. AS, aortic stenosis; AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a] Classification into three groups according to the risk of cardiac complications (30-day death and myocardial infarction) for non-cardiac surgery (high risk >5%; intermediate risk 1–5%; low risk <1%).[1]
[b] Non-cardiac surgery performed only if strictly needed. The choice between percutaneous aortic valvuloplasty and transcatheter aortic valve implantation should take into account the patient's life expectancy.

Aortic and mitral regurgitation

In asymptomatic patients with severe aortic or mitral regurgitation and preserved left ventricular function, non-cardiac surgery can be performed safely. The presence of symptoms or left ventricular dysfunction should lead to consideration of valvular surgery, but this is seldom needed before non-cardiac surgery. If left ventricular dysfunction is severe (ejection fraction <30%), non-cardiac surgery should only be performed if strictly necessary, after optimization of medical therapy for heart failure.

Prosthetic valves

The main problem is the adaptation of anticoagulation in patients with mechanical valves, which is detailed in 'Interruption of anticoagulant therapy for planned invasive procedures' in Chapter 35.9.

Perioperative monitoring

Perioperative management should be used to control heart rate (particularly in mitral stenosis), to avoid fluid overload as well as volume depletion and hypotension (particularly in aortic stenosis) and to optimize anticoagulation if needed. Transoesophageal echocardiography monitoring may be considered.

In patients with moderate to severe aortic or mitral stenosis, beta blockers can be used prophylactically to maintain sinus rhythm.[4] The use of beta blockers should be adapted to the risk of ischaemic heart disease.

It is prudent to electively admit patients with severe VHD to intensive care postoperatively.

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Chapter 35.11 Management during pregnancy

Introduction

The management of valvular heart disease during pregnancy is detailed in the European Society of Cardiology guidelines on pregnancy.[1] In brief, management before and during pregnancy and delivery should be discussed between the patient and a dedicated, specialized, multidisciplinary cardiac-obstetric team and a written plan for pregnancy and mode of delivery should be established. Ideally, valve disease should be evaluated before pregnancy and treated if necessary. Pregnancy should be discouraged in certain conditions such as severe mitral stenosis, severe symptomatic aortic stenosis, Marfan syndrome with an aortic diameter larger than 45 mm, or an aortic diameter index greater than 27.5 mm/m^2 in Turner syndrome. If the patient becomes pregnant, caesarean section is recommended for patients with valvular lesions presenting in pre-term labour on oral anticoagulants, in severe mitral or aortic stenosis, ascending aortic diameter larger than 45 mm, or severe pulmonary hypertension.

Native valve disease

Moderate or severe mitral stenosis with a valve area less than 1.5 cm^2 is poorly tolerated even in previously asymptomatic patients. Symptomatic mitral stenosis should be treated using bed rest and beta blockers and diuretics if needed. Percutaneous mitral commissurotomy should be considered in severely symptomatic patients (New York Heart Association class III–IV) and/or those with systolic pulmonary artery pressure greater than 50 mmHg despite optimal therapy. Percutaneous mitral commissurotomy should be performed after the 20th week of pregnancy in experienced centres.[1] Anticoagulant therapy is indicated for atrial fibrillation, left atrial thrombosis, or prior embolism.[1]

Complications of severe aortic stenosis occur mainly in patients who were symptomatic before pregnancy and among those with impaired left ventricular function. Evaluation with exercise testing is recommended prior to pregnancy.

Chronic mitral regurgitation and aortic regurgitation are well tolerated, even when severe, provided left ventricular systolic function is preserved. Surgery under cardiopulmonary bypass is associated with a fetal mortality rate of between 15% and 30%[2] and should be restricted to the rare conditions that threaten the mother's life.

Prosthetic valves

Maternal mortality is estimated at between 1% and 4% and serious events up to 40% in women with mechanical valves.[3] Therapeutic anticoagulation is of utmost importance because of high thrombotic risk during pregnancy. There is no ideal regimen. Oral anticoagulants are safest for the mother (lowest thrombotic risk), but carry potential fetal risks (embryopathy, fetal loss) which, however, are dose dependent. Therefore, in patients requiring 5 mg or less of warfarin, oral anticoagulants throughout pregnancy and a change to unfractionated heparin before delivery is favoured, whereas in patients requiring higher doses, a switch to low-molecular-weight heparin during the first trimester with strict anti-Xa monitoring (therapeutic range 0.8–1.2) and oral anticoagulants afterwards is favoured.[1]

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