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Guidelines on the management of valvular heart disease (version 2012)

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

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Abbreviations and acronyms

ACE	angiotensin-converting enzyme
AF	atrial fibrillation
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blockers
AS	aortic stenosis
AVR	aortic valve replacement
BNP	B-type natriuretic peptide
BSA	body surface area
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CMR	cardiac magnetic resonance
CPG	Committee for Practice Guidelines
CRT	cardiac resynchronization therapy
CT	computed tomography
EACTS	European Association for Cardio-Thoracic Surgery
ECG	electrocardiogram
EF	ejection fraction
EROA	effective regurgitant orifice area
ESC	European Society of Cardiology
EVEREST	(Endovascular Valve Edge-to-Edge REpair STudy)
HF	heart failure
INR	international normalized ratio
LA	left atrial
LMWH	low molecular weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
LVEDD	left ventricular end-diastolic diameter
LVESD	left ventricular end-systolic diameter
MR	mitral regurgitation
MS	mitral stenosis
MSCT	multi-slice computed tomography
NYHA	New York Heart Association
PISA	proximal isovelocity surface area
PMC	percutaneous mitral commissurotomy
PVL	paravalvular leak
RV	right ventricular
rtPA	recombinant tissue plasminogen activator
SVD	structural valve deterioration
STS	Society of Thoracic Surgeons
TAPSE	tricuspid annular plane systolic excursion
TAVI	transcatheter aortic valve implantation
TOE	transoesophageal echocardiography
TR	tricuspid regurgitation
TS	tricuspid stenosis
TTE	transthoracic echocardiography
UFH	unfractionated heparin
VHD	valvular heart disease
3DE	three-dimensional echocardiography

1. PREAMBLE

Guidelines summarize and evaluate all evidence available, at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk-benefit-ratio of particular diagnostic or therapeutic means. Guidelines are not substitutes for, but complements to, textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organisations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established, in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC web site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC and European Association for Cardio-Thoracic Surgery (EACTS) to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management and/or prevention of a given condition, according to ESC Committee for Practice Guidelines (CPG) and EACTS policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The levels of evidence and the strengths of recommendation of particular treatment options were weighed and graded according to predefined scales, as outlined in Tables 1 and 2.

The experts of the writing and reviewing panels filled in Declarations of Interest forms dealing with activities which might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC web site (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EACTS and updated. The Task Force received its entire financial support from the ESC and EACTS, without any involvement from the healthcare industry.

The ESC CPG, in collaboration with the Clinical Guidelines Committee of EACTS, supervises and co-ordinates the preparation of these new Guidelines. The Committees are also responsible for the endorsement process of these Guidelines. The ESC/EACTS Guidelines undergo extensive review by the CPG, the Clinical Guidelines Committee of EACTS and external experts. After appropriate revisions, it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal* and the *European Journal of Cardio-Thoracic Surgery*.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA) downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC and EACTS and directed towards their member National Societies and key opinion-leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC and EACTS member

Table 1: Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2: Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

societies and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus the task of writing these Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines and implementing them into clinical practice can only then be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient and—where appropriate and necessary—the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. INTRODUCTION

2.1 Why do we need new guidelines on valvular heart disease?

Although valvular heart disease (VHD) is less common in industrialized countries than coronary artery disease (CAD), heart failure (HF), or hypertension, guidelines are of interest in this field because VHD is frequent and often requires intervention [1, 2]. Decision-making for intervention is complex, since VHD is often seen at an older age and, as a consequence, there is a higher frequency of comorbidity, contributing to increased risk of intervention [1, 2]. Another important aspect of contemporary VHD is the growing proportion of previously-operated patients who present with further problems [1]. Conversely, rheumatic valve disease still remains a major public health problem in developing countries, where it predominantly affects young adults [3].

When compared with other heart diseases, there are few trials in the field of VHD and randomized clinical trials are particularly scarce.

Finally, data from the Euro Heart Survey on VHD [4, 5], confirmed by other clinical trials, show that there is a real gap between the existing guidelines and their effective application [6–9].

We felt that an update of the existing ESC guidelines [8], published in 2007, was necessary for two main reasons:

- Firstly, new evidence was accumulated, particularly on risk stratification; in addition, diagnostic methods—in particular echocardiography—and therapeutic options have changed due

to further development of surgical valve repair and the introduction of percutaneous interventional techniques, mainly transcatheter aortic valve implantation (TAVI) and percutaneous edge-to-edge valve repair. These changes are mainly related to patients with aortic stenosis (AS) and mitral regurgitation (MR).
- Secondly, the importance of a collaborative approach between cardiologists and cardiac surgeons in the management of patients with VHD—in particular when they are at increased perioperative risk—has led to the production of a joint document by the ESC and EACTS. It is expected that this joint effort will provide a more global view and thereafter facilitate implementation of these guidelines in both communities.

2.2 Contents of these guidelines

These guidelines focus on acquired VHD, are oriented towards management, and do not deal with endocarditis or congenital valve disease, including pulmonary valve disease, since recent guidelines have been produced by the ESC on these topics [10, 11]. Finally, these guidelines are not intended to include detailed information covered in ESC Guidelines on other topics, the ESC Association/Working Group's recommendations, position statements and expert consensus papers and the specific sections of the *ESC Textbook of Cardiovascular Medicine* [12].

2.3 How to use these guidelines

The Committee emphasizes that many factors ultimately determine the most appropriate treatment in individual patients within a given community. These factors include availability of diagnostic equipment, the expertise of cardiologists and surgeons—especially in the field of valve repair and percutaneous intervention—and, notably, the wishes of well-informed patients. Furthermore, due to the lack of evidence-based data in the field of VHD, most recommendations are largely the result of expert consensus opinion. Therefore, deviations from these guidelines may be appropriate in certain clinical circumstances.

3. GENERAL COMMENTS

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 ideally be made by a 'heart team' with a particular expertise in VHD, including cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, or intensive care specialists. This '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 repairability is a key component in decision-making.

Decision-making can be summarized according to the approach described in Table 3.

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 comorbidities.

Table 3: Essential questions in the evaluation of a patient for valvular intervention

• Is valvular heart disease severe?
• Does the patient have symptoms?
• Are symptoms related to valvular disease?
• What are patient life expectancy[a] and expected quality of life?
• Do the expected benefits of intervention (vs spontaneous outcome) outweigh its risks?
• What are the patient's wishes?
• Are local resources optimal for planned intervention?

[a]Life expectancy should be estimated according to age, gender, comorbidities and country-specific life expectancy.

3.1 Patient evaluation

3.1.1 Clinical evaluation. The aim of obtaining a case history is to assess symptoms and to evaluate for associated comorbidity. 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: this also needs to be taken into consideration. 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. The reason for—and degree of—functional limitation should be documented in the records. In the presence of comorbidities it is important to consider the cause of the symptoms.

Questioning the patient is also important in checking the quality of follow-up, as well as the effectiveness of prophylaxis for endocarditis and, where appropriate, rheumatic fever. In patients receiving chronic anticoagulant therapy, it is necessary to assess the compliance with treatment and look for evidence of thromboembolism or bleeding.

Clinical examination 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 co-exist 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.

An electrocardiogram (ECG) and a chest X-ray are usually carried out in conjunction with a clinical examination. Besides cardiac enlargement, analysis of pulmonary vascularization on the chest X-ray is essential when interpreting dyspnoea or clinical signs of HF [13].

3.1.2 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 [14]. It is indicated in any patient with a murmur, unless no suspicion of valve disease is raised after the clinical evaluation.

Table 4: Echocardiographic criteria for the definition of severe valve stenosis: an integrative approach

	Aortic stenosis	Mitral stenosis	Tricuspid stenosis
Valve area (cm^2)	<1.0	<1.0	–
Indexed valve area (cm^2/m^2 BSA)	<0.6	–	–
Mean gradient (mmHg)	>40[a]	>10[b]	≥5
Maximum jet velocity (m/s)	>4.0[a]	–	–
Velocity ratio	<0.25	–	–

BSA: body surface area.
[a]In patients with normal cardiac output/transvalvular flow.
[b]Useful in patients in sinus rhythm, to be interpreted according to heart rate.
Adapted from Baumgartner *et al.* [15].

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 (Table 4) [15]. 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 is less dependent on flow conditions than colour Doppler jet size (Table 5) [16, 17]. However, all quantitative evaluations have limitations. In particular, they combine a number of measurements and 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.

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.

Table 5: 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[a]	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[a]
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[a]		–
Semiquantitative				
Vena contracta width (mm)	>6	≥7 (>8 for biplane)[b]		≥7[a]
Upstream vein flow[c]	–	Systolic pulmonary vein flow reversal		Systolic hepatic vein flow reversal
Inflow	–	E-wave dominant ≥1.5 m/s[d]		E-wave dominant ≥1 m/s[e]
Other	Pressure half-time <200 ms[f]	TVI mitral/TVI aortic >1.4		PISA radius >9 mm[g]
Quantitative		Primary	Secondary[h]	
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

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.
[a]At a Nyquist limit of 50–60 cm/s.
[b]For average between apical four- and two-chamber views.
[c]Unless other reasons for systolic blunting (atrial fibrillation, elevated atrial pressure).
[d]In the absence of other causes of elevated left atrial pressure and of mitral stenosis.
[e]In the absence of other causes of elevated right atrial pressure.
[f]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.
[g]Baseline Nyquist limit shift of 28 cm/s.
[h]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.
Adapted from Lancellotti *et al.* [16, 17].

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. 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 (BSA). 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.

Finally, the pulmonary pressures should be evaluated, as well as right ventricular (RV) function [18].

Three-dimensional echocardiography (3DE) is useful for assessing anatomical features which may have an impact on the type of intervention chosen, particularly on the mitral valve [19].

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 enables us to monitor the results of surgical valve repair or percutaneous procedures. High-quality intraoperative TOE is mandatory when performing valve repair. 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 or for monitoring surgery and percutaneous intervention.

3.1.3 Other non-invasive investigations

3.1.3.1 Stress testing. Stress testing is considered here for the evaluation of VHD and/or its consequences, but not for the diagnosis of associated CAD. Predictive values of functional tests used for the diagnosis of CAD may not apply in the presence of VHD and are generally not used in this setting [20].

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 has an additional value for risk stratification in AS [21]. Exercise testing will also determine the level of authorised 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. 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. However, this technique is not widely accessible, could be technically demanding, and requires specific expertise.

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 [22].

3.1.3.2 Cardiac magnetic resonance. In patients with inadequate echocardiographic quality or discrepant results, cardiac magnetic resonance (CMR) should be used to assess the severity of valvular lesions—particularly regurgitant lesions—and to assess ventricular volumes and systolic function, as CMR assesses these parameters with higher reproducibility than echocardiography [23].

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). In practice, the routine use of CMR is limited because of its limited availability, compared with echocardiography.

3.1.3.3 Computed tomography. Multi-slice computed tomography (MSCT) may contribute to the evaluation of the severity of valve disease, particularly in AS, either indirectly by quantifying valvular calcification, or directly through the measurement of valve planimetry [24, 25]. It is widely used to assess the severity and location of an aneurysm of the ascending aorta. Due to its high negative predictive value, MSCT may be useful in excluding CAD in patients who are at low risk of atherosclerosis [25]. MSCT plays an important role in the work-up of high-risk patients with AS considered for TAVI [26, 27]. 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 [28].

3.1.3.4 Fluoroscopy. Fluoroscopy is more specific than echocardiography for assessing valvular or annular calcification. It is also useful for assessing the kinetics of the occluders of a mechanical prosthesis.

3.1.3.5 Radionuclide angiography. Radionuclide angiography provides a reliable and reproducible evaluation of LV ejection fraction (LVEF) in patients in sinus rhythm. It could be performed when LVEF plays an important role in decision-making, particularly in asymptomatic patients with valvular regurgitation.

3.1.3.6 Biomarkers. B-type natriuretic peptide (BNP) serum level has been shown to be related to functional class and prognosis, particularly in AS and MR [29]. Evidence regarding its incremental value in risk stratification remains limited so far.

3.1.4 Invasive investigations

Coronary angiography. Coronary angiography is widely indicated for the detection of associated CAD when surgery is planned (Table 6) [20]. Knowledge of coronary anatomy contributes to risk stratification and determines if concomitant coronary revascularization is indicated.

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 leading to an unstable haemodynamic condition.

Cardiac catheterization. The measurement of pressures and cardiac output or the performance of ventricular angiography or aortography are restricted to situations where non-invasive evaluation is inconclusive or discordant with clinical findings. Given its potential risks, cardiac catheterization to assess haemodynamics should not be done routinely with coronary angiography.

3.1.5 Assessment of comorbidity. The choice of specific examinations to assess comorbidity is directed by the clinical evaluation. The most frequently encountered comorbidities 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 6: Management of coronary artery disease in patients with valvular heart disease

	Class [a]	Level [b]
Diagnosis of coronary artery disease		
Coronary angiography[c] is recommended before valve surgery in patients with severe valvular heart disease and any of the following: • history of coronary artery disease • suspected myocardial ischaemia[d] • left ventricular systolic dysfunction • in men aged over 40 years and postmenopausal women • ≥1 cardiovascular risk factor.	I	C
Coronary angiography is recommended in the evaluation of secondary mitral regurgitation.	I	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%.[e]	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

CABG: coronary artery bypass grafting.
[a]Class of recommendation.
[b]Level of evidence.
[c]Multi-slice computed tomography may be used to exclude coronary artery disease in patients who are at low risk of atherosclerosis.
[d]Chest pain, abnormal non-invasive testing.
[e]≥50% can be considered for left main stenosis.
Adapted from Wijns *et al.* [20].

3.2 Endocarditis prophylaxis

The indication for antibiotic prophylaxis has been significantly reduced in the recent ESC guidelines [10]. Antibiotic prophylaxis should be considered for high-risk procedures in high-risk patients, such as patients with prosthetic heart valves or prosthetic material used for valve repair, or in patients with previous endocarditis or congenital heart disease according to current ESC guidelines. However, the general role of prevention of endocarditis is still very important in all patients with VHD, including good oral hygiene and aseptic measures during catheter manipulation or any invasive procedure, in order to reduce the rate of healthcare-associated infective endocarditis.

3.3 Prophylaxis for rheumatic fever

In patients with rheumatic heart disease, long-term prophylaxis against rheumatic fever is recommended, using penicillin 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 streptococcus [30].

3.4 Risk stratification

Several registries worldwide have consistently shown that, in current practice, therapeutic intervention for VHD is underused in high-risk patients with symptoms, for reasons which are often unjustified. This stresses the importance of the widespread use of careful risk stratification [31].

In the absence of evidence from randomized clinical trials, 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 7) and its potential late consequences, particularly prosthesis-related complications [32–35].

Operative mortality can be estimated by various multivariable scoring systems using combinations of risk factors [36]. The two most widely used scores are the EuroSCORE (European System

Table 7: Operative mortality after surgery for valvular heart disease

	EACTS (2010)	STS (2010)	UK (2004–2008)	Germany (2009)
Aortic valve replacement, no CABG (%)	2.9 (40 662)	3.7 (25 515)	2.8 (17 636)	2.9 (11 981)
Aortic valve replacement + CABG (%)	5.5 (24 890)	4.5 (18 227)	5.3 (12 491)	6.1 (9113)
Mitral valve repair, no CABG (%)	2.1 (3231)	1.6 (7293)	2 (3283)	2 (3335)
Mitral valve replacement, no CABG (%)	4.3 (6838)	6.0 (5448)	6.1 (3614)	7.8 (1855)
Mitral valve repair/replacement + CABG (%)	6.8/11.4 (2515/1612)	4.6/11.1 (4721/2427)	8.3/11.1 (2021/1337)	6.5/14.5 (1785/837)

( ): number of patients; CABG: coronary artery bypass grafting; EACTS: European Association for Cardiothoracic Surgery [32]; STS: Society of Thoracic Surgeons (USA). Mortality for STS includes first and redo interventions [33]; UK: United Kingdom [34]; Germany [35].

for Cardiac Operative Risk Evaluation; www.euroscore.org/ calc.html) and the STS (Society of Thoracic Surgeons) score (http://209.220.160.181/STSWebRiskCalc261/), the latter having the advantage of being specific to VHD but less user-friendly than the EuroSCORE. Other specific scoring systems have also been developed for VHD [37, 38]. Different scores provide relatively good discrimination (difference between high- and low-risk patients) but lack accuracy in estimating operative mortality in individual patients, due to unsatisfactory calibration (difference between expected and observed risk) [39]. Calibration is poor in high-risk patients, with an overestimation of the operative risk, in particular with the Logistic EuroSCORE [40, 41]. This underlines the importance of not relying 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 the following means: repeated recalibration of scores over time, as is the case for STS and EuroSCORE with the EuroSCORE II—addition of variables, in particular indices aimed at assessing functional and cognitive capacities and frailty in the elderly—design of separate risk scores for particular subgroups, like the elderly or patients undergoing combined valvular and coronary surgery [42].

Similarly, specific scoring systems should be developed to predict outcome after transcatheter valve interventions.

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, comorbidities, and indices of cognitive and functional capacity [43]. Expected quality of life should also be considered.

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 [44]. Depending on local expertise, patient transfer to a more specialised centre should be considered for procedures such as complex valve repair [45].

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 [46].

3.5 Management of associated conditions

3.5.1 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 6 and detailed in specific guidelines [20].

3.5.2 Arrhythmias. Oral anticoagulation with a target international normalized ratio (INR) of 2 to 3 is recommended in patients with native VHD and any type of atrial fibrillation (AF), taking the bleeding risk into account [47]. A higher level of anticoagulation may be necessary in specific patients with valve prostheses (see Section 11). The substitution of vitamin K antagonists by new agents is not recommended, because specific trials in patients with VHD are not available. 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, except in long-standing chronic AF.

In patients undergoing valve surgery, surgical ablation should be considered in patients with symptomatic AF and may be considered in patients with asymptomatic AF, if feasible with minimal risk [47]. The decision should be individualized according to clinical variables, such as age, the duration of AF, and left atrial (LA) size.

No evidence supports the systematic surgical closure of the LA appendage, unless as part of AF ablation surgery.

4. AORTIC REGURGITATION

Aortic regurgitation (AR) can be caused by primary disease of the aortic valve leaflets and/or abnormalities of the aortic root geometry. The latter entity is increasingly observed in patients operated on for pure AR in Western countries. Congenital abnormalities, mainly bicuspid morphology, are the second most frequent finding [1, 12, 48]. The analysis of the mechanism of AR influences patient management, particularly when valve repair is considered.

4.1 Evaluation

Initial examination should include a detailed clinical evaluation. AR is diagnosed by the presence of a diastolic murmur with the appropriate characteristics. Exaggerated arterial pulsations and low diastolic pressure represent the first and main clinical signs for quantifying AR. In acute AR, peripheral signs are attenuated, which contrasts with a poor clinical status [12].

The general principles for the use of non-invasive and invasive investigations follow the recommendations made in the *General comments* (Section 3).

The following are specific issues in AR:

- Echocardiography is the key examination in the diagnosis and quantification of AR severity, using colour Doppler (mainly *vena contracta*) and pulsed-wave Doppler (diastolic flow reversal in the descending aorta) [16, 49]. Quantitative Doppler echocardiography, using the analysis of proximal isovelocity surface area, is less sensitive to loading conditions, but is less well established than in MR and not used routinely at this time [50]. The criteria for defining severe AR are described in Table 5.

  Echocardiography is also important to evaluate regurgitation mechanisms, describe valve anatomy, and determine the feasibility of valve repair [16, 49]. The ascending aorta should be measured at four levels: annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta [51]. Indexing aortic diameters for BSA should be performed for individuals of small body size. An ascending aortic aneurysm/dilatation, particularly at the sinotubular level, may cause secondary AR [52]. If valve repair or a valve-sparing intervention is considered, TOE may be performed preoperatively to define the anatomy of the cusps and ascending aorta. Intraoperative TOE is mandatory in aortic valve repair, to assess the functional results and identify patients who are at risk of early recurrence of AR [53].

  Determining LV function and dimensions is essential. Indexing for BSA is recommended, especially in patients of small body size (BSA ≤1.68 m [2]) [54]. New parameters

obtained by 3DE and tissue Doppler and strain rate imaging may be useful in the future [55].
- CMR or MSCT scanning are recommended for evaluation of the aorta in patients with Marfan syndrome, or if an enlarged aorta is detected by echocardiography, particularly in patients with bicuspid aortic valves [56].

4.2 Natural history

Patients with acute severe AR, most frequently caused by infective endocarditis and aortic dissection, have a poor prognosis without intervention 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 [57].

In asymptomatic patients with severe chronic AR and normal LV function, the likelihood of adverse events is low. However, when LV end-systolic diameter (LVESD) is >50 mm, the probability of death, symptoms or LV dysfunction is reported to be 19% per year [57–59].

The natural history of ascending aortic and root aneurysm has been best defined for Marfan syndrome [60]. The strongest predictors of death or aortic complications are the root diameter and a family history of acute cardiovascular events (aortic dissection, sudden death) [61]. Uncertainty exists as to how to deal with patients who have other systemic syndromes associated with ascending aorta dilatation, but it appears reasonable to assume a prognosis similar to Marfan syndrome and treat them accordingly. Generally, patients with bicuspid aortic valves have previously been felt to be at increased risk of dissection. More recent evidence indicates that this hazard may be related to the high prevalence of ascending aortic dilatation [62]. However, despite a higher aortic diameter growth rate, it is currently less clear whether the likelihood of aortic complications is increased, compared with patients with a tricuspid aortic valve of similar aortic size [63, 64].

4.3 Results of surgery

Treatment of isolated AR has traditionally been by valve replacement. In the past 20 years, repair strategies for the regurgitant aortic valve have been developed for tricuspid aortic valves and congenital anomalies [65–67]. When there is an associated aneurysm of the aortic root, conventional surgical therapy has consisted of the combined replacement of the aorta and valve with reimplantation of the coronary arteries. Valve-sparing aortic replacement is increasingly employed in expert centres, especially in young patients, to treat combined aortic root dilatation and valve regurgitation [65–67].

Supra-coronary ascending aortic replacement can be performed with or without valve repair when root size is preserved [67].

Replacement of the aortic valve with a pulmonary autograft is less frequently used and is mostly applied in young patients (<30 years) [68].

In current practice, valve replacement remains the most widely used technique but the proportion of valve repair procedures is increasing in experienced centres. Calcification and cusp retraction appear to be the main adverse factors for repair procedures. Operative mortality is low (1–4%) in isolated aortic valve surgery, both for replacement and repair [32–35, 66]. Mortality increases with advanced age, impaired LV function, and the need for concomitant coronary artery bypass grafting (CABG), where it ranges from 3–7% [32–35]. The strongest predictors of operative mortality are older age, higher preoperative functional class, LVEF <50%, and LVESD >50 mm. Aortic root surgery with reimplantation of coronary arteries has, in general, a slightly higher mortality than isolated valve surgery. In young individuals, combined treatment of aneurysm of the ascending aorta—with either valve preservation or replacement—can be performed in expert centres with a very low mortality rate [66, 67]. Mortality increases in emergency procedures for acute dissection. Both biological and mechanical prostheses are associated with the long-term risk of valve related complications (see Section 11).

4.4 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 diminish symptoms, to prevent the development of HF, and to avoid aortic complications in patients with aortic aneurysm [69].

On the basis of robust observational evidence, recommended surgical indications are as follows (Table 8A, B; Figure 1):

- 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 dilatation after careful exclusion of other possible causes. Although, in these patients, postoperative outcome is worse than in those operated on earlier, an acceptable operative mortality, improvement of symptoms and acceptable longer-term survival can be obtained [48, 70, 71].
- Surgery is indicated in asymptomatic patients with severe AR and impaired LV function (EF <50%) and should be considered if LV end-diastolic diameter (LVEDD) is >70 mm or LVESD is >50 mm (or >25 mm/m^2 BSA in patients with small body size), since the likelihood of developing irreversible myocardial dysfunction is high if intervention is delayed further, and postoperative results are excellent if surgery is performed without delay. Good imaging quality and data confirmation with repeated measurements are recommended before surgery in asymptomatic patients. A rapid worsening of ventricular parameters on serial testing is another reason to consider surgery.
- The rationale for surgery in patients with ascending aortic and root dilatation has been best defined in Marfan patients. In borderline cases, the individual and family history, the patient's age, and the anticipated risk of the procedure should be taken into consideration. In patients with Marfan syndrome, surgery should be performed with a lesser degree of dilatation (≥50 mm). In previous guidelines, surgery was considered when aortic diameter was >45 mm. The rationale for this aggressive approach is not justified by clinical evidence in all patients. However, in the presence of risk factors (family history of dissection, size increase >2 mm/year in repeated examinations using the same technique and confirmed by another technique; severe AR; desire to become pregnant), surgery should be considered for a root diameter ≥45 mm [61]. With an aorta

Table 8: Indications for surgery in (A) severe aortic regurgitation and (B) aortic root disease (whatever the severity of aortic regurgitation)

	Class [a]	Level [b]	Ref [c]
A. Indications for surgery in severe aortic regurgitation			
Surgery is indicated in symptomatic patients.	I	B	59
Surgery is indicated in asymptomatic patients with resting LVEF ≤50%.	I	B	71
Surgery is indicated in patients undergoing CABG or surgery of ascending aorta, or on another valve.	I	C	
Surgery should be considered in asymptomatic patients with resting EF >50% with severe LV dilatation: LVEDD >70 mm, or LVESD >50 mm or LVESD >25 mm/m^2 BSA.[d]	IIa	C	
B. Indications for surgery in aortic root disease (whatever the severity of AR)			
Surgery is indicated in patients who have aortic root disease with maximal ascending aortic diameter[e] ≥50 mm for patients with Marfan syndrome.	I	C	
Surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter: ≥45 mm for patients with Marfan syndrome with risk factors[f] ≥50 mm for patients with bicuspid valve with risk factors[g] ≥55 mm for other patients	IIa	C	

AR: aortic regurgitation; BSA: body surface area; CABG: coronary artery bypass grafting; EF: ejection fraction; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d]Changes in sequential measurements should be taken into account.
[e]Decision should also take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.
[f]Family history of aortic dissection and/or aortic size increase >2 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level with side-by-side comparison and confirmed by another technique), severe AR or mitral regurgitation, desire of pregnancy.
[g]Coarctation of the aorta, systemic hypertension, family history of dissection or increase in aortic diameter >2 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level with side-by-side comparison and confirmed by another technique).

diameter of 40–45 mm, previous aortic growth and family history of dissection are important factors which would indicate advising against pregnancy [72]. 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, the decision to consider surgery in aortic diameters ≥50 mm should be based on patient age, body size, comorbidities, type of surgery, and the presence of additional risk factors (family history, systemic hypertension, coarctation of the aorta, or increase in aortic diameter >2 mm/year in repeated examinations, using the same technique and confirmed by another technique). In other circumstances, aortic root dilatation ≥55 mm indicates that surgery should be performed, irrespective of the degree of AR [73].

- For patients who have an indication for surgery on the aortic valve, lower thresholds can be used for concomitant aortic 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 [74].
- Lower thresholds of aortic diameters may also be considered in low-risk patients, if valve repair is likely and performed in an experienced centre with high repair rates.

The choice of the surgical procedure is adapted to the experience of the team, the presence of a root aneurysm, characteristics of the leaflets, life expectancy, and desired anticoagulation status.

4.5 Medical therapy

Vasodilators and inotropic agents may be used for short-term therapy to improve the condition of patients with severe HF before proceeding with aortic valve surgery. In individuals with chronic severe AR and HF, vasodilators (angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)) are useful in the presence of hypertension, when surgery is contraindicated, or LV dysfunction persists postoperatively. A positive effect of these agents, or dihydropyridine calcium channel blockers, in asymptomatic patients without hypertension in order to delay surgery is unproven [75].

In patients with Marfan syndrome, beta-blockers may slow aortic root dilatation and reduce the risk of aortic complications and should be considered before and after surgery [61]. Preliminary findings suggest that selective ARBs have an intrinsic effect on the aortic wall by preserving elastin fibres. Their clinical benefit remains to be proven by ongoing trials.

Patients with Marfan syndrome, or others with borderline aortic root diameters approaching the threshold for intervention, should be advised to avoid strenuous physical exercise, competitive, contact and isometric sports.

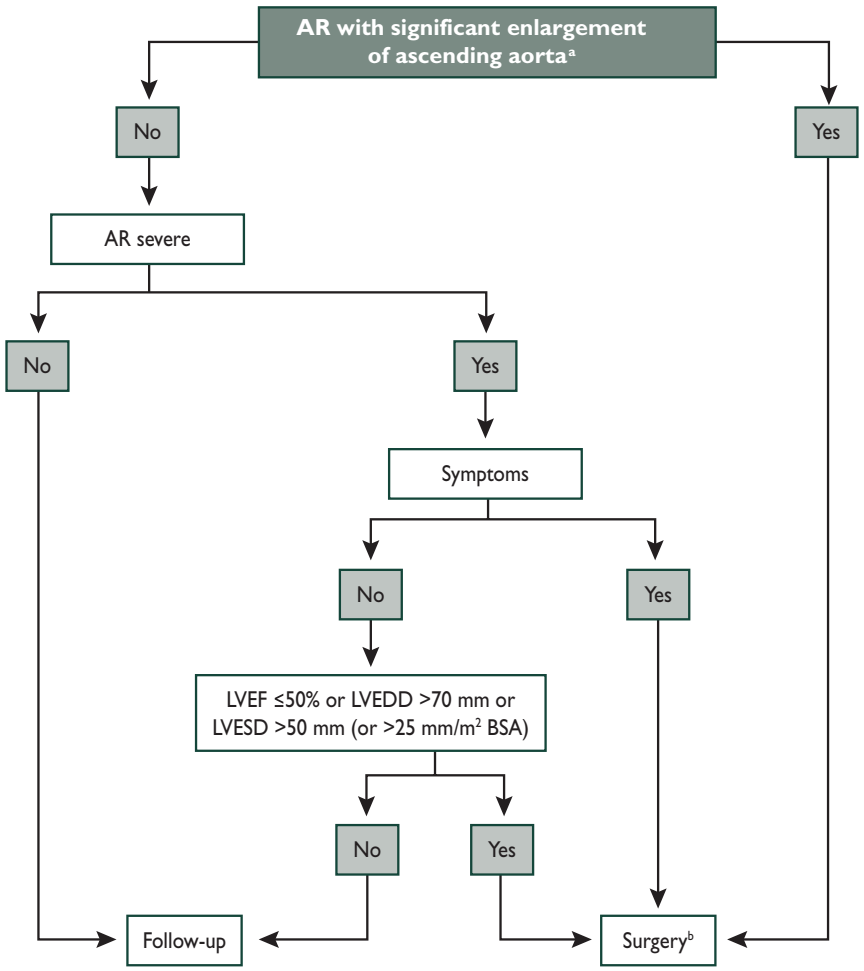

Figure 1: Management of aortic regurgitation. AR: aortic regurgitation; BSA: body surface area; LVEDD: left ventricul ar end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter. [a]See Table 8 for definition. [b]Surgery must also be considered if significant changes in LV or aortic size occur during follow-up.

Given the family risk of thoracic aortic aneurysms, screening the proband's first-degree relatives with appropriate imaging studies is indicated in Marfan patients and should be considered in bicuspid patients with aortic root disease.

4.6 Serial testing

Patients with mild-to-moderate AR can be reviewed on a yearly basis and echocardiography performed every 2 years. All patients with severe AR and normal LV function should be seen for follow-up at 6 months after their initial examination. If LV diameter and/or EF show significant changes, or become close to the threshold for intervention, follow-up should be continued at 6-monthly intervals. Patients with stable parameters should be followed annually. In patients with a dilated aorta—and especially in patients with Marfan syndrome or with a bicuspid valve—echocardiography should be performed on a yearly basis. MSCT or preferably CMR are advisable when the distal ascending aorta is not well visualized and/or when the surgical indication may be based on aortic enlargement, rather than LV size or function.

4.7 Special patient populations

If AR requiring surgery is associated with severe MR, both should be operated on.

In patients with moderate AR, who undergo CABG or mitral valve surgery, the decision to treat the aortic valve should be based on the aetiology of the AR, age, worsening of LV function, and the possibility of valve repair.

More detailed information about patients with Marfan syndrome can be found in the ESC Guidelines on grown-up congenital heart disease [11].

5. AORTIC STENOSIS

AS has become the most frequent type of VHD in Europe and North America. It primarily presents as calcific AS in adults of advanced age (2–7% of the population >65 years) [1, 2]. The second most frequent aetiology, which dominates in the younger age group, is congenital, whereas rheumatic AS has become rare. Treatment of high surgical risk patients has been modified with the introduction of TAVI.

5.1 Evaluation

Careful questioning, in order to check for the presence of symptoms (exertional shortness of breath, angina, dizziness, or syncope), is critical for proper patient management and must take into account the possibility that patients may deny symptoms as they subconsciously reduce their activities.

The characteristic systolic murmur draws attention and guides further diagnostic work-up. The murmur may occasionally be faint, however, and primary presentation may be HF of unknown cause. The disappearance of the second aortic sound is specific to severe AS, although not a sensitive sign [12].

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the *General comments* (Section 3).

Specific issues in AS are as follows:

- 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 (Table 4) [15].

  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 <1.0 cm^2 is considered severe, critical AS is most likely with a valve area <0.8 cm^2 [76]. Indexing to BSA, with a cut-off value of <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 <40 mmHg. 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. So far, this has mainly been recognized in patients with poor systolic LV function. However, when the mean gradient is <40 mmHg, a small valve area does not definitely confirm severe AS, since mild-to-moderately diseased valves may not open fully, resulting in a 'functionally small valve area' (pseudo-severe AS) [77]. Low dose dobutamine echocardiography may be helpful in this setting, to distinguish truly severe AS from pseudo-severe AS. 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 [22, 78].

  More recently, the possible presence of severe AS in patients with valve area <1.0 cm^2 and mean gradient <40 mmHg, despite preserved LVEF, has been suggested, introducing the new entity of 'paradoxical low flow (stroke volume index <35 ml/m^2), low gradient (mean gradient <40 mmHg) AS with preserved LVEF' [76]. This appears to be typically encountered in the elderly and is associated with small ventricular size, marked LV hypertrophy, and a history of hypertension. This subset of AS patients remains challenging. It has also been demonstrated that patients presenting with small valve area—but low gradients despite normal LVEF—may indeed frequently have moderate AS [79]. It must be recognized that there may frequently be reasons other than an underlying severe AS for this combination of measurements: firstly, Doppler measurements tend to underestimate flow, resulting in eventual underestimation of valve area and erroneous assumption of 'low flow conditions' [15]; secondly, small body size may be present [15]; and thirdly, the cut-offs for gradients are not entirely consistent. It has been demonstrated that the generation of a mean gradient of 40 mmHg requires a valve area closer to 0.8 cm^2 than 1.0 cm^2 [76]. 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. In addition to more detailed echocardiographic measurements, this may require CMR and catheterization. Since such patients are typically elderly, with hypertension and other comorbidities, the evaluation remains difficult even after confirmation of haemodynamic data. LV hypertrophy and fibrosis, as well as symptoms or elevation of neurohormones, may be partially due to hypertensive heart disease and not help to reassure severe AS patients. Furthermore, it remains unclear how to exclude pseudo-severe AS in this setting. Evaluation of the degree of calcification by MSCT may also be helpful [24].

  When hypertension is present, the severity should be reassessed when the patient is normotensive [15].

  Exercise stress echocardiography may provide prognostic information in asymptomatic severe AS by assessing the increase in mean pressure gradient and change in LV function with exercise [21, 80, 81].

  TOE is rarely helpful for the quantification of AS, as valve area planimetry becomes difficult in calcified valves [15]. TOE may, however, provide additional evaluation of mitral valve abnormalities and has gained importance in assessing annulus diameter before TAVI and in guiding the procedure [26, 27, 82].
- Exercise testing is contraindicated in symptomatic patients with AS. On the other hand, it is recommended in physically active patients for unmasking symptoms and in the risk stratification of asymptomatic patients with severe AS [21, 83]. Then again, breathlessness on exercise may be difficult to interpret and is non-specific in patients with low physical activity levels, particularly the elderly. 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, and/or ECG changes [21, 83].
- MSCT and CMR provide additional information on the assessment of the ascending aorta when it is enlarged. MSCT may be useful in quantifying the valve area and coronary calcification, which aids in assessing prognosis. MSCT has become an important diagnostic tool for evaluation of the aortic root, the distribution of calcium, the number of leaflets, the ascending aorta, and peripheral artery pathology and dimensions before undertaking TAVI [26, 27].

  Measurements of the aortic annulus obtained by multimodality imaging differ between techniques and, hence, should be interpreted with caution before TAVI [26]. Thus, an

integrative approach is recommended.

CMR may also be useful for the detection and quantification of myocardial fibrosis, providing additional prognostic information in symptomatic patients without CAD [84].

- Natriuretic peptides have been shown to predict symptom-free survival and outcome in normal- and low-flow severe AS and may be useful in asymptomatic patients [85–87].
- Retrograde LV catheterization to assess the severity of AS is seldom needed and should only be used when non-invasive evaluation remains inconclusive.

Finally, the search for comorbidities is essential in this patient population.

5.2 Natural history

Calcific AS is a chronic, progressive disease. During a long latent period, patients remain asymptomatic [88–91]. 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), even in very severe AS [88-91]. In asymptomatic patients with severe AS, reported average event-free survival at 2 years ranged from 20% to more than 50% [88–91]. The lower estimates of event-free survival 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. Then again, 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 [88–91], LVEF [90], rate of haemodynamic progression [89], increase in gradient with exercise [80, 81], excessive LV hypertrophy [92], and abnormal tissue Doppler parameters of systolic and diastolic LV function [87].
- Exercise testing: discovery 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 [93].
- Biomarkers: elevated plasma levels of natriuretic peptides, although the precise values are not well defined [85–87].

As soon as symptoms occur, the prognosis of severe AS is dismal, with survival rates of only 15–50% at 5 years. The data on the spontaneous outcome of patients with low gradient and normal EF are still controversial [79].

5.3 Results of intervention

Aortic valve replacement (AVR) is the definitive therapy for severe AS. In contemporary series, operative mortality of isolated AVR for AS is 1–3% in patients younger than 70 years and 4–8% in selected older adults (Table 7) [1, 12, 32–35, 40, 41, 94–97]. The following factors have been shown to increase the risk of operative mortality: older age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, co-existing CAD, and previous bypass or valve surgery. After successful AVR, symptoms and quality of life are in general greatly improved. Long-term survival may be close to the age-matched general population in older patients. In younger patients, there is substantial improvement compared to conservative medical therapy: nevertheless, compared to age-matched controls, a lower survival may be expected. Risk factors for late death include age, comorbidities, severe symptoms, LV dysfunction, ventricular arrhythmias, and untreated co-existing CAD. In addition, poor postoperative outcome may result from prosthesis-related complications and suboptimal prosthetic valve haemodynamic performance.

Surgery has been shown to prolong and improve quality of life, even in selected patients over 80 years of age [94–97]. Age, *per se*, should therefore not be considered a contraindication for surgery. Nevertheless, a large percentage of suitable candidates are currently not referred for surgery [4, 6].

Balloon valvuloplasty 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, the complication rate is high (>10%), 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 [98].

In patients with high surgical risk, TAVI has been shown to be feasible (procedural success rates >90%) using transfemoral, transapical or, less commonly, subclavian or direct transaortic access [97, 99–107]. In the absence of anatomical contraindications, a transfemoral approach is the preferred technique in most centres, although no direct comparisons are available between transfemoral, transapical or other approaches. Similarly, there is no direct comparison between the available devices. Reported 30-day mortality rates range from 5–15% [99–101, 103–106]. The main procedure-related complications include: stroke (1–5%); need for new pacemaker (up to 7% for the balloon-expanded system and up to 40% for the self-expanding); [99, 103] and vascular complications (up to 20%) [97, 99]. Paravalvular regurgitation is common, although reported to be trace or mild in the majority of patients and rarely clinically relevant whereas more than mild AR may have an impact on long-term survival [103, 105]. This remains a concern and requires further careful follow-up and critical evaluation. Approximately 1–2% of TAVI patients require immediate cardiac surgery for life-threatening complications [100].

TAVI provides haemodynamic results, in terms of gradient and valve area, that are slightly superior to conventional bioprostheses [97].

Reported 1-year survival for TAVI ranges from 60–80%, largely depending on the severity of comorbidities [97, 99, 102, 103, 105, 107, 108]. Most survivors experience significant improvement of health status and quality of life. However, the matter of long-term durability of these valves still has to be addressed, although 3–5 year results are promising [108].

The recent Valve Academic Research Consortium statement provides a standardized definition for end points after TAVI, which will enable a more accurate comparison between devices and approaches [109].

Patients considered not suitable for AVR after surgical consultation clearly benefit from TAVI, compared with conservative

treatment including balloon valvuloplasty, as demonstrated by a randomized trial (1-year mortality 31% vs 51% and significantly better symptomatic improvement, with fewer repeat hospitalizations) [99]. The first randomized trial comparing TAVI and surgical AVR in high-risk but operable patients showed TAVI to be non-inferior for all-cause mortality at 1 year (24.2% vs 26.8%), with marked functional improvement in both groups [97]. The analysis of secondary end points showed that TAVI carried a higher risk of cerebrovascular events and vascular complications and a higher incidence of paravalvular leaks, although mostly trace and mild. Conversely, bleeding and postoperative AF were more frequent after surgery. The interpretation of the results of the PARTNER trials should take into account the specific indications and contraindications for TAVI and the surgical and interventional expertise of the centres involved [97, 99].

5.4 Indications for intervention

5.4.1 Indications for aortic valve replacement. The indications for AVR are shown in Table 9 and Figure 2.

Early valve replacement should be strongly recommended in all symptomatic patients with severe AS who are otherwise candidates for surgery. As long as the mean gradient remains >40 mmHg, there is virtually no lower EF limit for surgery.

The management of patients with classical low-flow, low-gradient AS (valve area <1 cm^2, EF <40%, mean gradient <40 mmHg) is more difficult. If depressed EF is predominantly caused by excessive afterload (afterload mismatch), LV function usually improves after surgery [22, 79, 110]. Conversely, improvement in LV function after AVR is uncertain if the primary cause is scarring due to extensive myocardial infarction or cardiomyopathy. In

Table 9: Indications for aortic valve replacement in aortic stenosis

	Class[a]	Level[b]	Ref[c]
AVR is indicated in patients with severe AS and any symptoms related to AS.	I	B	12, 89, 94
AVR is indicated in patients with severe AS undergoing CABG, surgery of the ascending aorta or another valve.	I	C	
AVR is indicated in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) not due to another cause.	I	C	
AVR is indicated in asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise clearly related to AS.	I	C	
AVR should be considered in high risk patients with severe symptomatic AS who are suitable for TAVI, but in whom surgery is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	B	97
AVR should be considered in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline.	IIa	C	
AVR should be considered in patients with moderate AS[d] undergoing CABG, surgery of the ascending aorta or another valve.	IIa	C	
AVR should be considered in symptomatic patients with low flow, low gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS.[e]	IIa	C	
AVR should be considered in symptomatic patients with severe AS, low flow, low gradient with reduced EF, and evidence of flow reserve.[f]	IIa	C	
AVR 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 or more of the following findings is present: • Very severe AS defined by a peak transvalvular velocity >5.5 m/s or, • Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year.	IIa	C	
AVR may be considered in symptomatic patients with severe AS low flow, low gradient, and LV dysfunction without flow reserve.[f]	IIb	C	
AVR may be considered in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: • Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations • Increase of mean pressure gradient with exercise by >20 mmHg • Excessive LV hypertrophy in the absence of hypertension.	IIb	C	

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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d]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.
[e]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).
[f]Also termed contractile reserve.

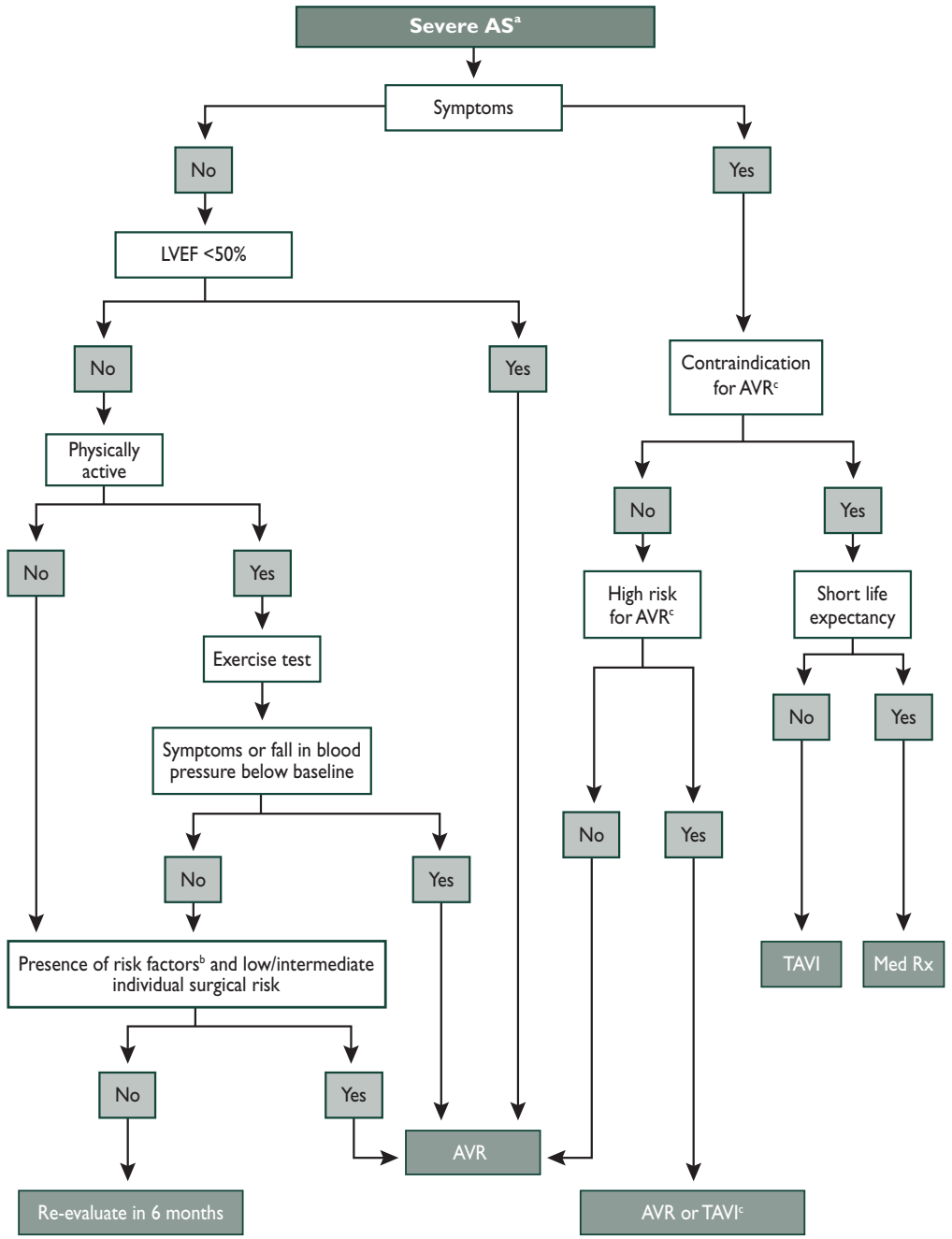

Figure 2: Management of severe aortic stenosis. The management of patients with low gradient and low ejection fraction is detailed in the text. AS: aortic stenosis; AVR: aortic valve replacement; BSA: body surface area; LVEF: left ventricular ejection fraction; Med Rx: medical therapy; TAVI: transcatheter aortic valve implantation. [a]See Table 4 for definition of severe AS. [b]Surgery should be considered (IIaC) if one of the following is present: peak velocity >5.5 m/s; severe valve calcification + peak velocity progression ≥0.3 m/s/year. Surgery may be considered (IIbC) if one of the following is present: markedly elevated natriuretic peptide levels; mean gradient increase with exercise >20 mmHg; excessive LV hypertrophy. [c]The decision should be made by the 'heart team' according to individual clinical characteristics and anatomy.

patients with low gradients and evidence of flow reserve, surgery is advised since it carries an acceptable risk and improves long-term outcome in most patients [22]. Although the outcome of patients without flow reserve is compromised by a higher operative mortality, AVR has been shown to improve EF and clinical status in such patients [22, 78, 110]. Final decision-making should take into account the patient's clinical condition (in particular, the presence and extent of comorbidities), the degree of valve calcification, the extent of coronary disease, and the feasibility of revascularization. The newly recognized entity of paradoxical low flow, low gradient AS with normal EF requires special attention because of the limited amount of data on the natural history and outcome after surgery [76, 79]. In such cases, surgery should be performed only when symptoms are present and if comprehensive evaluation suggests significant valve obstruction.

Management of asymptomatic severe AS remains a matter of controversy. Recent studies do not provide convincing data to support the general recommendation of early AVR, even in

patients with asymptomatic, very severe AS [88–91, 111, 112]. The decision to operate on asymptomatic patients requires careful weighing of the benefits against the risks.

Early elective surgery is indicated in the very rare asymptomatic patients with depressed LV function that is not due to other causes or in those with an abnormal exercise test, particularly with symptom development. It should also be considered in the patients presenting a fall in blood pressure below baseline [21, 83, 90, 93].

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

- very severe AS defined by a peak velocity >5.5 m/s [91, 112], or
- combination of severe valve calcification with a rapid increase in peak transvalvular velocity of ≥0.3 m/s per year [89].

Surgery may also be considered in patients at low operative risk with normal exercise performance but one of the following:

- markedly elevated natriuretic peptide levels confirmed by repeated measurements without other explanations [85–87],
- increase of mean pressure gradient with exercise by >20 mmHg [80, 81], or
- excessive LV hypertrophy without history of hypertension [92].

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

5.4.2 Indications for balloon valvuloplasty. Balloon valvuloplasty may be considered as a bridge to surgery or TAVI in haemodynamically unstable patients who are at high risk for surgery, or in patients with symptomatic severe AS who require urgent major non-cardiac surgery (recommendation class IIb, level of evidence C). Balloon valvuloplasty may also be considered as a palliative measure in selected individual cases when surgery is contraindicated because of severe comorbidities and TAVI is not an option.

5.4.3 Indications for transcatheter aortic valve implantation. TAVI should only be performed in hospitals with cardiac surgery on-site. A 'heart team' that assesses individual patient's risks, as well as the technical suitability of TAVI and access issues, should be best able to make decisions in this patient population [113].

Contraindications, both clinical and anatomical, should be identified (Table 10). Eligible patients should have a life expectancy of more than 1 year and should also be likely to gain improvement in their quality of life, taking into account their comorbidities.

Based on current data, TAVI is recommended in patients with severe symptomatic AS who are, according to the 'heart team', considered unsuitable for conventional surgery because of severe comorbidities (Table 11; Figure 2).

Among high-risk patients who are still candidates for surgery, the decision should be individualized. TAVI should be considered as an alternative to surgery in those patients for whom the 'heart team' favours TAVI, taking into consideration the respective advantages/disadvantages of both techniques. A logistic EuroSCORE ≥20% has been suggested as an indication for TAVI therapy but EuroSCORE is known to markedly overestimate operative mortality [113]. Use of the STS scoring system >10% may result in a more realistic assessment of operative risk [40]. On the

Table 10: Contraindications for transcatheter aortic valve implantation

Absolute contraindications
Absence of a 'heart team' and no cardiac surgery on the site
Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical
Estimated life expectancy <1 year Improvement of quality of life by TAVI unlikely because of comorbidities Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical
Inadequate annulus size (<18 mm, >29 mm[a])
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF <20%
For transapical approach: severe pulmonary disease, LV apex not accessible

AVR: aortic valve replacement; LV: left ventricle; LVEF: left ventricular ejection fraction; TAVI: transcatheter aortic valve implantation.
[a]Contraindication when using the current devices.

Table 11: Recommendations for the use of transcatheter aortic valve implantation

Recommendations	Class [a]	Level [b]	Ref [c]
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary.	I	C	
TAVI should only be performed in hospitals with cardiac surgery on-site.	I	C	
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.	I	B	99
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	B	97

AS: aortic stenosis; AVR: aortic valve replacement; TAVI: transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

other hand, frailty and conditions such as porcelain aorta, history of chest radiation or patent coronary bypass grafts may make patients less suitable for AVR despite a logistic EuroSCORE <20%/STS score <10%. In the absence of a perfect quantitative score, the risk assessment should mostly rely on the clinical judgement of the 'heart team', in addition to the combination of scores [113].

At the present stage, TAVI should not be performed in patients at intermediate risk for surgery and trials are required in this population.

5.5 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 ACE inhibitors, randomized trials have consistently shown that statins do not affect the progression of AS [114, 115]. Statin therapy should therefore not be used in AS patients where their 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 [116].

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, ACE inhibitors, or ARBs if they experience HF symptoms. Co-existing hypertension should be treated.

However, treatment should be carefully titrated to avoid hypotension and patients should be re-evaluated frequently.

Maintenance of sinus rhythm is important.

5.6 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 may 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 to 3 years.

5.7 Special patient populations

Combined AVR and CABG carries a higher risk than isolated AVR [32–35]. 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 <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 [117]. Individual judgement is recommended, taking into consideration BSA, haemodynamic data, leaflet calcification, progression rate of AS, patient life expectancy and associated comorbidities, 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 AVR, 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. The question of 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 (see *General comments*, Section 3). 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 usually improves after the aortic valve is treated.

Concomitant aneurysm/dilatation of the ascending aorta requires the same treatment as in AR (see section 4).

For congenital AS, see the ESC Guidelines on grown-up congenital heart disease [11].

6. MITRAL REGURGITATION

In Europe, MR is the second most frequent valve disease requiring surgery [1]. Treatment has been redefined as a result of the good results of valve repair. This section deals separately with primary and secondary MR, according to the mechanism of MR [118]. In the rare cases where both mechanisms are present, one of them is usually predominant and will guide the management.

6.1 Primary mitral regurgitation

Primary MR covers all aetiologies in which intrinsic lesions affect one or several components of the mitral valve apparatus. Reduced incidence of rheumatic fever and increased lifespan in industrialized countries have progressively changed the distribution of aetiologies, with degenerative MR now being the most common [1, 2, 12]. Endocarditis is dealt with in separate, specific ESC Guidelines [10].

6.1.1 Evaluation

Acute mitral regurgitation. Acute MR due to papillary muscle rupture should be considered 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 function in the presence of acute HF, underpinning the importance of urgent echocardiography in this setting [12, 119].

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 [12].

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the *General comments* (Section 3).

Specific issues in MR are as follows:

- Echocardiography is the principal investigation and must include an assessment of severity, mechanisms, repairability, and consequences [17].

  The criteria for defining severe primary MR are described in Table 5. Several methods can be used to determine the severity of MR. Planimetry of the regurgitant jet should be abandoned, as this measurement is poorly reproducible and depends on numerous factors. Measurement of the width of the *vena contracta*, the narrowest part of the jet, is more accurate. When feasible—and bearing in mind its limitations—the proximal isovelocity surface area (PISA) method is the recommended approach for the assessment of the regurgitant volume and EROA. The final assessment of severity requires integration of Doppler and morphological information and careful cross-checking of the validity of such data against the effects on the LV, LA, and pulmonary pressures (Table 5) [17].

  TTE can provide precise anatomical definition 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. TTE also assesses mitral annular dimensions [17].

  TOE is frequently undertaken when planning surgery for this purpose, although when images are of sufficiently high quality, TTE—in experienced hands—can be sufficient [120]. Overall, it should be stressed that the preoperative assessment of valve repairability requires experience [17].

  The results of mitral valve repair must be assessed intraoperatively by TOE to enable immediate further surgical correction if necessary.

  3DE TOE may provide more information [121]. The consequences of MR on the heart are assessed using echocardiography by measuring LA volume, LV size and EF, systolic pulmonary arterial pressure, and RV function.
- Determination of functional capacity, assessed by cardiopulmonary exercise testing, may aid the assessment [122]. In experienced hands, exercise echocardiography is useful to quantify exercise-induced changes in MR, in systolic pulmonary artery pressure, and in LV function [21, 123, 124]. New tools, such as cardiopulmonary exercise testing, global longitudinal strain (measured by the speckle tracking method), and exercise-induced changes in LV volumes, EF and global strain may predict postoperative LV dysfunction [124].
- Neurohormonal activation in MR has been evaluated, with several studies suggesting the value of elevated BNP levels and a change in BNP as predictors of outcome. A cut-off BNP value ≥105 pg/ml determined in a derivation cohort was prospectively validated in a separate cohort and helped to identify asymptomatic patients at higher risk of developing HF, LV dysfunction or death on mid-term follow-up [125]. Low-plasma BNP has a high negative predictive value and may be helpful for the follow-up of asymptomatic patients [126].

6.1.2 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, left unoperated, it carries a poor spontaneous 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 AF with medical management) have been reported to be 22 ± 3%, 14 ± 3%, and 33 ± 3%, respectively [118]. In addition to symptoms, the following were all found to be predictors of poor outcome: age, AF, severity of MR (particularly EROA), pulmonary hypertension, LA dilatation, increased LVESD, and low LVEF [118, 127–133].

6.1.3 Results of surgery. Despite the absence of a randomized comparison between the results of valve replacement and repair, it is widely accepted that, when feasible, valve repair is the optimal surgical treatment in patients with severe 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 (Table 7).

Beside symptoms, the most important predictors of postoperative outcome are: age, AF, preoperative LV function, pulmonary hypertension, and repairability of the valve. The best results of surgery are observed in patients with a preoperative EF >60%. While a cut-off of 45 mm has previously been generally accepted, in MR due to flail leaflet, LVESD ≥40 mm (≥22 mm/m^2 BSA) has been shown to be independently associated with increased mortality with medical treatment, as opposed to mitral surgery [131]. 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, but these require further validation [133].

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 not as consistent, even in experienced hands [134]. In current practice, surgical expertise in mitral valve repair is growing and becoming widespread [135].

Patients with predictable complex repair should undergo surgery in experienced repair centres with high repair rates and low operative mortality [32–35, 44, 135].

When repair is not feasible, mitral valve replacement with preservation of the subvalvular apparatus is preferred.

6.1.4 Percutaneous intervention. Catheter-based interventions have been developed to correct MR percutaneously. The only one which has been evaluated in organic MR is the edge-to-edge procedure. Data from the EVEREST (Endovascular Valve Edge-to-Edge REpair STudy) trials [136] and the results of registries in Europe [137] and the USA suggest that the MitraClip procedure has a procedural success rate (i.e. postprocedural MR ≤2+) of around 75%, is relatively safe and generally well-tolerated, even by patients in poor clinical condition. One-year freedom from death, mitral valve surgery or more than moderate MR is 55%. The procedure reduces MR less effectively than mitral valve surgery. The follow-up remains limited to a maximum of 2 years and recurrence—or worsening of MR—is more likely to occur during follow-up since 20% of patients required reintervention within 1 year in EVEREST II. The applicability of the procedure is limited because precise echocardiographic criteria have to be respected to make a patient eligible [136]. Mitral valve repair has been reported after an unsuccessful clip procedure, although valve replacement may be necessary in up to 50% of such patients.

6.1.5 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 haemodynamic status, using an intra-aortic balloon pump, positive inotropic agents and, when possible, vasodilators. Valve surgery consists of valve replacement in most cases [119].

The indications for surgery in severe chronic primary MR are shown in Table 12 and Figure 3.

The decision of whether to replace or repair depends mostly on valve anatomy, surgical expertise available, and the patient's condition.

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

When LVEF is <30%, a durable surgical repair can still improve symptoms, although the effect on survival is largely unknown. In this situation, the decision on whether to operate will take into account the response to medical therapy, comorbidity, 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 a 'heart team', and have a life expectancy greater than 1 year (recommendation class IIb, level of evidence C).

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 asymptomatic patients with severe MR, in particular when repair is likely [138, 139].

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 new onset AF or pulmonary hypertension (systolic pulmonary arterial pressure >50 mmHg at rest) [47].

Recent prospective studies have suggested the following indications for surgery in patients at low operative risk, where there is a high likelihood of durable valve repair on the basis of valve lesion and experience of the surgeon:

- Surgery should be considered if there is flail leaflet and LVESD ≥40 mm (≥22 mm/m^2 BSA in patients of small stature) [131].
- Surgery may be considered when one or more of the following conditions are present: systolic pulmonary pressure >60 mmHg at exercise [21, 123], patient in sinus rhythm with severe LA dilatation (volume index ≥60 ml/m^2 BSA) [132].

In other asymptomatic patients, it has been shown that severe MR can be safely followed up until symptoms supervene or previously recommended cut-off values are reached. Such management requires careful and regular follow-up [138].

Close clinical follow-up is recommended when there is doubt about the feasibility of valve repair. In this latter group, operative risk and/or prosthetic valve complications 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 (i.e. within 2 months) is associated with better outcomes, since the development of even mild symptoms by the time of

Table 12: Indications for surgery in severe primary mitral regurgitation

	Class [a]	Level [b]	Ref [c]
Mitral valve repair should be the preferred technique when it is expected to be durable.	I	C	
Surgery is indicated in symptomatic patients with LVEF >30% and LVESD <55 mm.	I	B	127, 128
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60%).	I	C	
Surgery should be considered in asymptomatic patients with preserved LV function and new onset of atrial fibrillation or pulmonary hypertension (systolic pulmonary pressure at rest >50 mmHg).	IIa	C	
Surgery should be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk and flail leaflet and LVESD ≥40 mm.	IIa	C	
Surgery should be considered in patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy with high likelihood of durable repair and low comorbidity.	IIa	C	
Surgery may be considered in patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy with low likelihood of durable repair and low comorbidity.	IIb	C	
Surgery may be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk, and: • left atrial dilatation (volume index ≥60 ml/m² BSA) and sinus rhythm, or • pulmonary hypertension on exercise (SPAP ≥60 mmHg at exercise).	IIb	C	

BSA: body surface area; LV: left ventricle; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; SPAP: systolic pulmonary artery pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

surgery is associated with deleterious changes in cardiac function after surgery [139, 140].

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.

6.1.6 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 intra-aortic balloon pump should be added in case of hypotension.

There is no evidence to support the use of vasodilators, including ACE inhibitors, in chronic MR without HF and they are therefore not recommended in this group of patients. However, when HF has developed, ACE inhibitors are beneficial and should be considered in patients with advanced MR and severe symptoms, who are not suitable for surgery or when there are still residual symptoms following surgery. Beta-blockers and spironolactone should also be considered as appropriate [13].

6.1.7 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 2 years. Asymptomatic patients with severe MR and preserved LV function should be seen every 6 months and echocardiography performed annually. The follow-up is 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.

6.2 Secondary mitral regurgitation

In secondary MR or, as it is also termed, '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 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 a primary valve disease but results from tethering (apical and lateral papillary muscle displacement, annular dilatation) and reduced closing forces, due to LV dysfunction (reduced contractility and/or LV dysynchrony) [12, 17].

6.2.1 Evaluation. 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 [141].

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

After myocardial infarction and in HF patients, secondary MR should be routinely sought and Doppler assessment of severity performed. As in primary MR, planimetry of the regurgitant jet overestimates the severity of ischaemic MR and is poorly reproducible: the *vena contracta* width is more accurate. In secondary MR, because of their prognostic value, lower thresholds of severity, using quantitative methods, have been proposed (20 mm^2

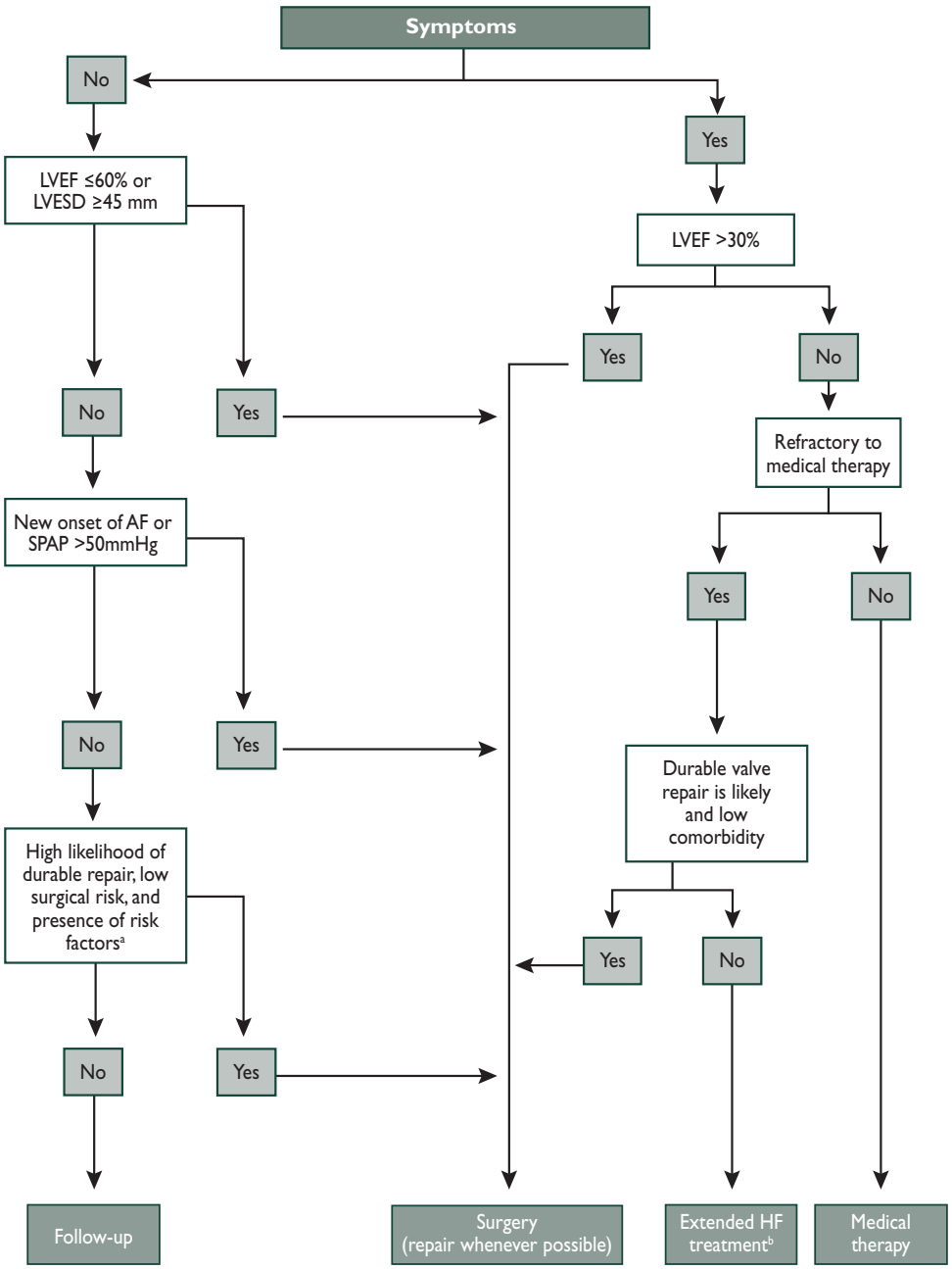

Figure 3: Management of severe chronic primary mitral regurgitation. AF: atrial fibrillation; BSA: body surface area; HF: heart failure; FU: follow-up; LA: left atrium; LV: left ventricle; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; SPAP: systolic pulmonary arterial pressure. [a]When there is a high likelihood of durable valve repair at a low risk, valve repair should be considered (IIaC) in patients with flail leaflet and LVESD ≥40 mm; valve repair may be considered (IIbC) if one of the following is present: LA volume ≥60 ml/m2 BSA and sinus rhythm or pulmonary hypertension on exercise (SPAP ≥60 mmHg). [b]Extended HF management includes the following: cardiac resynchronization therapy; ventricular assist devices; cardiac restraint devices; heart transplantation.

for EROA and 30 ml for regurgitant volume: Table 5) [17, 118, 142]. Assessment of LV systolic function is complicated by MR.

As ischaemic MR is a dynamic condition: stress testing may play a role in its evaluation. Echocardiographic quantification of MR during exercise is feasible, provides a good demonstration of dynamic characteristics and has prognostic importance. An exercise-induced increase of ≥13 mm^2 of the EROA has been shown to be associated with a large increase in the relative risk of death and hospitalization for cardiac decompensation [143]. The prognostic value of exercise tests to predict the results of surgery has, however, to be evaluated. The prognostic importance of dynamic MR is not necessarily applicable to secondary MR due to idiopathic cardiomyopathy.

The assessment of coronary status is necessary to complete the diagnosis and allows evaluation of revascularization options.

In patients with low LVEF, it is also mandatory to assess the absence, or presence and extent, of myocardial viability by one of the available imaging techniques (dobutamine echocardiography, single photon emission CT, positron emission tomography or CMR).

In patients with CAD undergoing revascularization, the decision on whether or not to treat ischaemic MR should be made

before surgery, as general anaesthesia may significantly reduce the severity of regurgitation. When necessary, a preload and/or afterload challenge provides an additional estimation of the severity of MR in the operating room [144].

6.2.2 Natural history. Patients with chronic ischaemic MR have a poor prognosis [118, 142]. The presence of severe CAD and LV dysfunction have prognostic importance. The causative role of MR in the poor prognosis remains uncertain. However, increasing severity is associated with worse outcome [142].

In patients with secondary MR due to non-ischaemic aetiology, the data regarding the natural history are more limited than in ischaemic MR [145]. A precise analysis is difficult because of the limited number of series made up of small patient numbers with many confounding factors. Some studies have shown an independent association between significant MR and a poor prognosis.

6.2.3 Results of surgery. Surgery for secondary MR remains a challenge. Operative mortality is higher than in primary MR and the long-term prognosis is worse due—at least in part—to the more severe comorbidities (Table 7). In ischaemic MR patients, indications and the preferred surgical procedure remain controversial, mainly because of the persistence and high recurrence rate of MR after valve repair and the absence of evidence that surgery prolongs life [146]. 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. The impact of valve surgery on survival remains unclear, since there are no randomized trials and the few observational studies addressing this issue have too many limitations to draw definite conclusions [147]. Regarding prognosis, most studies failed to demonstrate improved long-term clinical outcome following surgical correction of secondary MR [148, 149]. The sole randomized trial, comparing CABG vs CABG + valve repair in patients with moderate MR, was not designed to analyse the effect on survival of the addition of repair to CABG. It showed that the performance of valve repair improved functional class, EF, and LV diameter in the short-term [150].

When surgery is indicated, there is a trend favouring valve repair using only an undersized, rigid ring annuloplasty, which confers a low operative risk although it carries a high risk of MR recurrence [151, 152]. This surgical technique is also applicable in MR secondary to cardiomyopathy [153].

Numerous preoperative predictors of recurrent secondary MR after undersized annuloplasty have been identified and are indicative of severe tethering, and associated with a worse prognosis [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] [152]. The prognostic value of these parameters should, however, be further validated. After surgery, localized alteration of geometry and function in the vicinity of papillary muscles is associated with recurrent MR.

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 [154].

Whether a restrictive annuloplasty might create clinically relevant mitral stenosis (MS) remains unclear.

No randomized study has been performed, comparing repair against replacement. In the most complex high-risk settings, survival after repair and replacement is similar. A recent meta-analysis of retrospective studies suggests better short-term and long-term survival after repair than after replacement [155]. In patients with preoperative predictors of increased MR recurrence, as detailed above, several techniques have been proposed to address subvalvular tethering and may be considered in addition to annuloplasty [156]. A recent randomized trial reports improved survival and a significant decrease in major adverse outcomes in patients requiring revascularization treated with ventricular reshaping [157]. In secondary non-ischaemic MR, surgical modalities aimed at LV reverse remodelling, such as LV reconstruction techniques, have been disappointing and cannot be recommended.

6.2.4 Percutaneous intervention. Experience from a limited number of patients in the EVEREST trials and from observational studies suggests that percutaneous edge-to-edge mitral valve repair is feasible—at low procedural risk—in patients with secondary MR in the absence of severe tethering and may provide short-term improvement in functional condition and LV function [136, 137]. These findings have to be confirmed in larger series with longer follow-up and with a randomized design. Data on coronary sinus annuloplasty are limited and most initial devices have been withdrawn [158].

6.2.5 Indications for intervention. The heterogeneous data regarding secondary MR result in less evidence-based management than in primary MR (Table 13).

Severe MR should be corrected at the time of bypass surgery.

Table 13: Indications for mitral valve surgery in chronic secondary mitral regurgitation

	Class [a]	Level [b]
Surgery is indicated in patients with severe MR[c] undergoing CABG, and LVEF >30%.	I	C
Surgery should be considered in patients with moderate MR undergoing CABG.[d]	IIa	C
Surgery should be considered in symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence of viability.	IIa	C
Surgery may be considered in patients with severe MR, LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated.	IIb	C

CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; SPAP: systolic pulmonary artery pressure.
[a]Class of recommendation.
[b]Level of evidence.
[c]The thresholds for severity (EROA ≥20 mm^2; R Vol >30 ml) differ from that of primary MR and are based on the prognostic value of these thresholds to predict poor outcome: see Table 5 [17].
[d]When exercise echocardiography is feasible, the development of dyspnoea and increased severity of MR associated with pulmonary hypertension are further incentives to surgery.

The indications for isolated mitral valve surgery in symptomatic patients with severe secondary MR and severely depressed systolic LV function, who cannot be revascularized or who present with cardiomyopathy, are questionable. Repair may be considered in selected patients if comorbidity is low, in order to avoid or postpone transplantation. In the other patients, optimal medical treatment is currently the best option, followed, in the event of failure, by extended HF treatment [cardiac resynchronization therapy (CRT); ventricular assist devices; cardiac restraint devices; heart transplantation].

The percutaneous mitral clip procedure may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy (including CRT if indicated), who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year (recommendation class IIb, level of evidence C).

There is continuing debate regarding the management of moderate ischaemic MR in patients undergoing CABG. In such cases, valve repair is preferable. In patients with 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.

There are no data to support surgical correction of mild MR.

6.2.6 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 guidelines on the management of HF [13]. This includes ACE inhibitors and beta-blockers, with the addition of an aldosterone antagonist in the presence of HF. A diuretic is required in the presence of fluid overload. Nitrates may be useful for treating acute dyspnoea, secondary to a large dynamic component.

The indications for resynchronization therapy should be in accordance with related guidelines [13]. In responders, CRT may immediately reduce MR severity through increased closing force and resynchronisation of papillary muscles [159]. A further reduction in MR and its dynamic component can occur through a reduction in tethering force in relation to LV reverse remodelling.

7. MITRAL STENOSIS

Rheumatic fever, which is the predominant aetiology of MS, has greatly decreased in industrialized countries; nevertheless, MS still results in significant morbidity and mortality worldwide [1, 3]. Percutaneous mitral commissurotomy (PMC) has had a significant impact upon the management of rheumatic MS.

7.1 Evaluation

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 the *General comments* (Section 3) [12].

Specific issues in MS are as follows:

- Echocardiography is the main method used to assess the severity and consequences of MS, as well as the extent of anatomic 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 valve area is >1.5 cm^2 (Table 4) [15].

  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 [15, 160, 161].

  Echocardiography also evaluates pulmonary artery pressures, associated MR, concomitant valve disease, and LA size. Due to the frequent association of MS with other valve diseases, a comprehensive evaluation of the tricuspid and aortic valves is mandatory. TTE usually provides sufficient information for routine management.

  TEE should be performed to exclude LA thrombus before PMC or after an embolic episode, if TTE provides suboptimal information on anatomy or, in selected cases, to guide the procedure.

  3DE improves the evaluation of valve morphology (especially visualization of commissures) [162], optimizes accuracy and reproducibility of planimetry, and could be useful for guiding (TOE) and monitoring (TTE) PMC in difficult cases.

  Echocardiography also plays an important role in monitoring the results of PMC during the procedure.
- Stress testing is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of MS. Dobutamine or, preferably, exercise echocardiography may provide additional information by assessing changes in mitral gradient and pulmonary pressures [21].

7.2 Natural history

Survival in asymptomatic patients is usually good up to 10 years, progression being highly variable with sudden deterioration, which is usually precipitated by pregnancy or complications such as AF or embolism [163]. Symptomatic patients have a poor prognosis without intervention [12].

7.3 Results of intervention

7.3.1 Percutaneous mitral commissurotomy. Technical success and complications are related to patient selection and the operator's experience [164]. Good initial results, defined as valve area >1.5 cm^2 with no MR >2/4, are achieved in over 80% of cases.

Major complications include procedural mortality 0.5–4%, haemopericardium 0.5–10%, embolism 0.5–5%, and severe regurgitation 2–10%. Emergency surgery is seldom needed (<1%) [165].

Clinical follow-up data confirm the late efficacy of PMC: event-free survival ranges from 30–70% after 10–20 years, depending on patient characteristics [160, 166–168]. When the immediate results are unsatisfactory, surgery is usually required shortly thereafter [160, 167, 168]. Conversely, after successful PMC, long-term results are good in the majority of cases and can be predicted by preoperative anatomical and clinical characteristics, and the quality of the immediate results [160, 167, 169]. When functional deterioration occurs, it is late and mainly related to restenosis [170]. Successful PMC also reduces embolic risk [163].

7.3.2 Surgery. Closed mitral commissurotomy is still performed in developing countries, but otherwise has largely been replaced by open mitral commissurotomy using cardiopulmonary bypass, which is also now seldom performed. 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% [171, 172].

In current practice, surgery for MS is mostly valve replacement (95%) as a result of increasingly elderly presentation and unfavourable valve characteristics for valve repair [1, 34]. Operative mortality for valve replacement ranges from 3–10% and correlates with age, functional class, pulmonary hypertension, and presence of CAD. Long-term survival is related to age, functional class, AF, pulmonary hypertension, preoperative LV/RV function, and prosthetic valve complications [12].

7.4 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 and results of PMC), valve anatomy and local expertise.

Indications for intervention are as follows (Table 14; Figure 4):

- Intervention should only be performed in patients with clinically significant MS (valve area ≤1.5 cm^2).
- Intervention should be performed in symptomatic patients. Most patients with favourable valve anatomy currently undergo PMC; however, open commissurotomy may be preferred by experienced surgeons in young patients with mild-to-moderate MR. Decision-making as to the type of intervention in patients with unfavourable anatomy is still a matter of debate and must take into account the multifactorial nature of predicting the results of PMC [160, 170]. PMC should be considered as an initial treatment for selected patients with mild-to-moderate calcification or unfavourable subvalvular apparatus, who have otherwise favourable clinical characteristics, especially in young patients in whom postponing valve replacement is particularly attractive [173].

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

Surgery is preferable in patients who are unsuitable for PMC.

Due to the small but definite risk inherent in PMC, truly asymptomatic patients are not usually candidates for the procedure, except in cases where there is increased risk of thromboembolism or haemodynamic decompensation. In such patients PMC should only be performed if they have favourable characteristics and it is undertaken by experienced operators.

In asymptomatic patients with MS, surgery is limited to those rare patients at high risk of complications and with contraindications to PMC.

Surgery is the only alternative when PMC is contraindicated (Table 15). The most important contraindication to PMC is LA thrombosis. However, when the thrombus is located in the LA 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 2 to 6 months, provided repeat TOE shows the thrombus has disappeared. Surgery is indicated if the thrombus persists.

Table 14: Indications for percutaneous mitral commissurotomy in mitral stenosis with valve area ≤1.5 cm^2

	Class [a]	Level [b]	Ref [c]
PMC is indicated in symptomatic patients with favourable characteristics.[d]	I	B	160, 170
PMC is indicated in symptomatic patients with contraindication or high risk for surgery.	I	C	
PMC should be considered as initial treatment in symptomatic patients with unfavourable anatomy but without unfavourable clinical characteristics.[d]	IIa	C	
PMC should be considered in asymptomatic patients without unfavourable characteristics[d] and • high thromboembolic risk (previous history of embolism, dense spontaneous contrast in the left atrium, recent 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.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d]Unfavourable characteristics for percutaneous mitral commissurotomy 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.

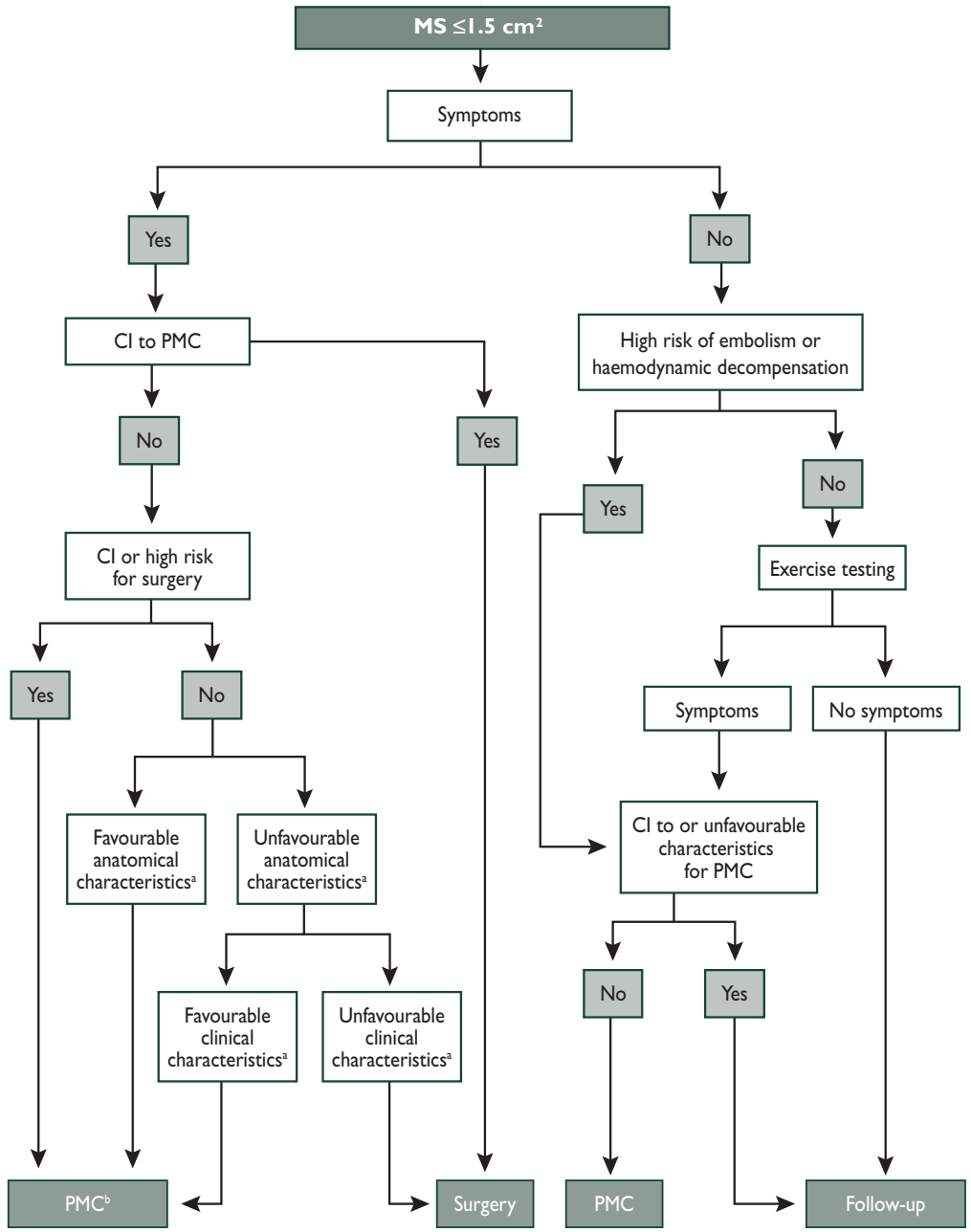

Figure 4: Management of clinically significant mitral stenosis. CI: contraindication; MS: mitral stenosis; PMC: percutaneous mitral commissurotomy. [a]See Table 14. [b]Surgical commissurotomy may be considered by experienced surgical teams or in patients with contraindications to percutaneous mitral commissurotomy.

7.5 Medical therapy

Diuretics or long-acting nitrates transiently ameliorate dyspnoea. Beta-blockers or heart-rate regulating calcium channel blockers can improve exercise tolerance. Anticoagulant therapy with a target INR in the upper half of the range 2 to 3 is indicated in patients with either permanent or paroxysmal AF [47]. In patients with sinus rhythm, anticoagulation is indicated when there has been prior 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 LA volume >60 ml/m^2 (recommendation class IIa, level of evidence C) [174]. Aspirin and other antiplatelet agents are not valid alternatives.

7.6 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 to 3 years) in case of less severe stenosis.

Management of patients after successful PMC is similar to that of asymptomatic patients. It should be more stringent if asymptomatic restenosis occurs. When PMC is not successful and

Table 15: Contraindications to percutaneous mitral commissurotomy

• Mitral valve area >1.5 cm²
• 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
• Concomitant coronary artery disease requiring bypass surgery

symptoms persist, surgery should be considered early unless there are definite contraindications.

7.7 Special patient populations

When restenosis with symptoms occurs after surgical commissurotomy or PMC, reintervention in most cases requires valve replacement. 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. PMC may have a palliative role in patients who present with valve anatomy that is not ideal for PMC, but who are not surgical candidates [175, 176].

For information on MS during pregnancy see Section 13.

In the elderly, 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 anatomic characteristics, PMC can be attempted first, resorting to surgery if results are unsatisfactory. In other patients, surgery is preferable.

In patients with severe MS combined with severe aortic valve disease, surgery is preferable. 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.

In patients with severe TR, PMC can be attempted in patients with sinus rhythm, moderate atrial enlargement, and functional TR secondary to pulmonary hypertension. In other cases surgery on both valves may be preferred [177].

Degenerative mitral annular calcification may be observed in elderly patients, especially with renal failure, but it seldom creates severe MS requiring surgery.

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

8. TRICUSPID REGURGITATION

Trivial TR is frequently detected by echocardiography in normal subjects. Pathological TR is more often secondary, rather than due to a primary valve lesion. Secondary TR is due to annular dilatation and increased tricuspid leaflet tethering in relation to RV pressure and/or volume overload. 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 [12].

8.1 Evaluation

Predominant symptoms are those of associated valve diseases, and even severe TR may be well-tolerated for a long period of time. Although they are load-dependent, clinical signs of right HF are of value in evaluating the severity of TR [12].

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the *General comments* (Section 3).

Specific issues in TR are as follows:

- Echocardiography is the ideal technique to evaluate TR. It provides the following information:

  It is similar to MR in that the presence of structural abnormalities of the valve distinguishes between its primary or secondary forms. In primary TR, the aetiology can usually be identified from specific abnormalities such as vegetations in endocarditis [10], 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 [11]. The degree of dilatation of the annulus should also be measured [17]. Significant tricuspid annular dilatation is defined by a diastolic diameter ≥40 mm or >21 mm/m^2 in the four-chamber transthoracic view [17, 178–180]. In secondary TR, a coaptation distance >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) [181].

  Evaluation of TR severity and pulmonary systolic pressure should be carried out as currently recommended (Table 5) [17].

  Evaluations of the RV dimensions and function should be conducted, despite existing limitations of current indices of RV function. Tricuspid annular plane systolic excursion (TAPSE) (<15 mm), tricuspid annulus systolic velocity (<11 cm/s), and RV end-systolic area (>20 cm^2) could be used to identify patients with RV dysfunction [182].

  The presence of associated lesions (looking carefully at the associated valve lesions, particularly on the left side) and LV function should be assessed.
- When available, CMR is the preferred method for evaluating RV size and function.

8.2 Natural history

The limited data that are available on the natural history of primary TR suggest that severe TR has a poor prognosis, even if it may be well-tolerated functionally for years [12, 183, 184]. As for left-sided valvular regurgitation, prolonged burden of volume overload may result in ventricular dysfunction and irreversible myocardial damage. Flail tricuspid valve (classically associated with severe TR) is associated with decreased survival and increased risk of HF [184]. Secondary TR may diminish or disappear as RV failure improves, following the treatment of its cause. However, TR may persist even after successful correction of left-sided lesions. Predicting the evolution of functional TR

after surgical treatment of mitral valve disease remains difficult. Pulmonary hypertension, increased RV pressure and dimension, reduced RV function, AF, pacemaker leads, and the severity of tricuspid valve deformation (tricuspid annulus diameter, coaptation height) are important risk factors for persistence or late worsening of TR [178, 180, 181].

8.3 Results of surgery

Ring annuloplasty is key to surgery for TR. Better long-term results are observed with prosthetic rings than with the suture annuloplasty, the incidence of residual TR being, respectively, 10% vs 20–35% at 5 years [179, 180, 185, 186]. Current experience favours the use of ring annuloplasty for severe TR related to isolated tricuspid annular dilatation [187]. When the tricuspid valve is significantly deformed, complementary tricuspid valve procedures with the objective of reducing residual postoperative TR (i.e. enlargement of the anterior leaflet) may be useful [188]. 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 [189]. Adding a tricuspid repair, if indicated during left-sided surgery, does not increase operative risks. Ten-year survival ranges from 30–50%, the predictors being preoperative functional class, LV and RV function, and prosthetic complications [185–189]. In the presence of trans-tricuspid pacemaker leads and TR, 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 clinical condition of the patient (including age and the number of previous cardiac interventions) and may well have poor long-term results related to the presence of irreversible RV dysfunction before reoperation, or LV, myocardial or valvular dysfunction.

8.4 Indications for surgery

The timing of surgical intervention remains controversial, mostly due to the limited data available and their heterogeneous nature (Table 16). 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 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 moderate primary TR, as well as in patients with mild or moderate secondary TR and significant dilatation of the annulus (≥40 mm) [178–180].

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 MR) 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 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 Baumgartner *et al.* [11].

Table 16: Indications for tricuspid valve surgery

	Class [a]	Level [b]
Surgery is indicated in symptomatic patients with severe TS.[c]	I	C
Surgery is indicated in patients with severe TS undergoing left-sided valve intervention.[d]	I	C
Surgery is indicated in patients with severe primary or secondary TR undergoing left-sided valve surgery.	I	C
Surgery is indicated in symptomatic patients with severe isolated primary TR without severe right ventricular dysfunction.	I	C
Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery.	IIa	C
Surgery should be considered in patients with mild or moderate secondary TR with dilated annulus (≥40 mm or >21 mm/m²) undergoing left-sided valve surgery.	IIa	C
Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive right ventricular dilatation or deterioration of right ventricular function.	IIa	C
After left-sided valve surgery, surgery should be considered in patients with severe TR who are symptomatic or have progressive right ventricular dilatation/dysfunction, *in the absence* of left-sided valve dysfunction, severe right or left ventricular dysfunction, and severe pulmonary vascular disease.	IIa	C

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

8.5 Medical therapy

Diuretics reduce congestion. Specific therapy of the underlying disease is warranted.

9. TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is mostly of rheumatic origin, is rarely observed in developed countries although it is still seen in developing countries [3, 12]. Detection requires careful

evaluation, as it is almost always associated with left-sided valve lesions that dominate the presentation.

9.1 Evaluation

Clinical signs are often masked by those of the associated valvular lesions, especially MS [12, 190]. Echocardiography provides the most useful information. TS is often overlooked and requires careful evaluation. 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 3DE is used. No generally-accepted grading of TS severity exists. A mean gradient ≥5 mmHg at normal heart rate is considered indicative of clinically significant TS [15]. Echocardiography should also examine the presence of commissural fusion, the anatomy of the valve and its subvalvular apparatus, which are the most important determinants of repairability and the degree of concomitant TR.

9.2 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 [189–191].

9.3 Percutaneous intervention

Percutaneous balloon tricuspid dilatation has been performed in a limited number of cases, either alone or alongside PMC, but this frequently induces significant regurgitation. There is a lack of data on evaluation of long-term results [192].

9.4 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 (Table 16).

9.5 Medical therapy

Diuretics are useful in the presence of HF—but of limited efficacy.

10. 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 [190].

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 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 MR may lead to underestimation of the severity of AS, since decreased stroke volume due to MR 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, i.e. symptoms or presence of LV dilatation or dysfunction. Intervention can be considered for non-severe multiple lesions associated with symptoms or leading to LV 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. Although repair remains the ideal option, the desire to repair one valve may be decreased if prosthetic valve replacement is needed on another.

The management of specific associations of VHD is detailed in the individual sections.

11. PROSTHETIC VALVES

Patients who have undergone previous valve surgery accounted for 28% of all patients with VHD in the Euro Heart Survey [1]. Optimal choice of valve substitute—as well as subsequent management of patients with prosthetic valves—is essential to reduce prosthesis-related complications.

11.1 Choice of prosthetic valve

There is no perfect valve substitute. All involve some compromise and all introduce new disease processes, whether they are mechanical (single tilting disc and bileaflet valves) or biological. The latter include homografts, pulmonary autografts and porcine, pericardial bovine or equine bioprostheses. Xenograft valves can be further subdivided into stented and stentless. Stentless valves may have better haemodynamics but no improvement in long-term durability has been demonstrated so far [193]. Sutureless bioprostheses are an incoming technology, allowing quick placement of a bioprosthesis without a sewing cuff and also having larger effective orifice areas.

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.

All mechanical valves require lifelong anticoagulation. In biological valves, long-term anticoagulation is not required unless AF or other indications are present, but they are subject to structural valve deterioration (SVD) over time.

Homografts and pulmonary autografts are mainly used in the aortic position in adults, although they account for <1% of AVRs in large databases. Homografts are subject to SVD. A propensity-matched analysis did not find the durability of homografts to be better than that of pericardial bioprostheses and a randomized trial showed superior durability of stentless bioprostheses over homografts [194, 195]. Median time to reoperation for SVD of homografts is age-dependent and varies from an average of 11 years in a 20-year-old patient to 25 years in a 65-year-old patient [194, 195]. Technical concerns, limited availability, and increased complexity of reoperation restrict the use of homografts [196]. Although under debate, the main indication for homografts is acute infective endocarditis with perivalvular lesions [10, 197].

The transfer of the pulmonary autograft in the aortic position (Ross procedure) provides excellent haemodynamics but requires expertise and has several disadvantages: the risk of early stenosis of the pulmonary homograft, the risk of recurrence of AR due to subsequent dilatation of the native aortic root or the pulmonary autograft itself when used as a mini-root repair, and the risk of rheumatic involvement [198]. Although the Ross operation is occasionally carried out in 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 [11].

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

The heterogeneity of VHD and the variability of outcomes following these procedures make the design and execution of prospective randomized comparisons difficult. Two randomized trials comparing older models of mechanical and biological valves found no significant difference in rates of valve thrombosis and thromboembolism, in accordance with numerous individual valve series. Long-term survival was very similar [199, 200]. A more recent trial randomized 310 patients aged 55–70 years to mechanical or biological prostheses [201]. No differences were found in survival, thromboembolism or bleeding rates, but a higher rate of valve failure and reoperation was observed following implantation of bioprostheses. Meta-analyses of observational series do not find differences in survival when patient characteristics are taken into account. Microsimulation models may assist in making individual patient choices by enabling valve-related event-free survival to be assessed according to patient age and type of prosthesis [202].

Apart from haemodynamic considerations, the choice between a mechanical and a biological valve in adults is mainly determined by estimating the risk of anticoagulant-related bleeding and thromboembolism with a mechanical valve, as compared with the risk of SVD with a bioprosthesis, and by considering the patient's goals, values, and life and healthcare preferences [46, 203–205]. The former is determined mainly by the target INR, the quality of anticoagulation control, the concomitant use of aspirin, and the patient's risk factors 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 [203].

Rather than setting arbitrary age limits, prosthesis choice should be individualized and discussed in detail between the informed patient, cardiologists and surgeons, taking into account the factors detailed in Tables 17 and 18. In patients aged 60–65 years, who are to receive an aortic prosthesis, and those 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 comorbidities may necessitate further surgical procedures, and in those with increased bleeding 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 in this situation [206].

Table 17: Choice of the aortic/mitral prosthesis. In favour of a mechanical prosthesis.

	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.[c]	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration.[d]	I	C
A mechanical prosthesis is recommended in patients already on anticoagulation as a result of having a mechanical prosthesis in another valve position.	I	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.[e]	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy,[f] 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 of thromboembolism.[g]	IIb	C

The decision is based on the integration of several of the following factors
[a]Class of recommendation.
[b]Level of evidence.
[c]Increased bleeding risk because of comorbidities, compliance concerns, geographic, lifestyle and occupational conditions.
[d]Young age (<40 years), hyperparathyroidism.
[e]In patients aged 60–65 years who should receive an aortic prosthesis, and those between 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of other factors than age.
[f]Life expectancy should be estimated >10 years, according to age, gender, comorbidities, and country-specific life expectancy.
[g]Risk factors for thromboembolism are atrial fibrillation, previous thromboembolism, hypercoagulable state, severe left ventricular systolic dysfunction.

Table 18: Choice of the aortic/mitral prosthesis. In favour of a bioprosthesis.

	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; comorbidities; 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 future redo valve surgery would be at low risk.	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[c] lower than the presumed durability of the bioprosthesis.[d]	IIa	C

The decision is based on the integration of several of the following factors
[a]Class of recommendation.
[b]Level of evidence.
[c]Life expectancy should be estimated according to age, gender, comorbidities, and country-specific life expectancy.
[d]In patients aged 60–65 years who should receive an aortic prosthesis and those 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.

- 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 [207].
- 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 the therapy. Although bioprosthetic recipients can avoid long-term use of 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 (AF, stroke, peripheral arterial disease and others).

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 [208]. If the valve prosthesis–patient ratio is expected to be <0.65 cm^2/m^2 BSA, enlargement of the annulus to allow placement of a larger prosthesis may be considered [209].

11.2 Management after valve replacement

Thromboembolism and anticoagulant-related bleeding represent the majority of complications experienced by prosthetic valve recipients [12]. Endocarditis prophylaxis and management of prosthetic valve endocarditis are detailed in separate ESC Guidelines [10].

11.2.1 Baseline assessment and modalities of follow-up. A complete baseline assessment should, ideally, be performed 6–12 weeks after surgery. This includes clinical assessment, chest X-ray, ECG, TTE, and blood testing. This assessment is of the utmost importance in interpreting 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. Yearly echocardiographic examination is recommended after the fifth year in patients with a bioprosthesis and earlier in young patients. Trans-prosthetic gradients are best interpreted in comparison with the baseline values, rather than in comparison with theoretical values for a given prosthesis, which lack reliability. TOE should be considered if TTE is of poor quality and in all cases of suspected prosthetic dysfunction or endocarditis [210]. Cinefluoroscopy and MSCT provide useful additional information if valve thrombus or pannus are suspected [211].

11.2.2 Antithrombotic management

11.2.2.1 General management. Antithrombotic management should address effective control of modifiable risk factors for thromboembolism, in addition to the prescription of antithrombotic drugs [203, 212, 213].

Indications for antithrombotic therapy after valve repair or replacement are summarized in Table 19.

The need for a three-month period of postoperative anticoagulant therapy has been challenged in patients with aortic bioprostheses, with the use of low-dose aspirin now favoured as an alternative [214, 215].

The substitution of vitamin K antagonists by direct oral inhibitors of factor IIa or Xa is not recommended in patients with a mechanical prosthesis, because specific clinical trials in such patients are not available at this time.

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 (aPTT) of 1.5–2.0 times control value, enables rapid anticoagulation to be obtained before the INR rises. Low molecular weight heparin (LMWH) seems to offer effective and stable anticoagulation and has been

used in small observational series [216]. 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 our inability to neutralize it. 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 [217, 218]. In addition, during this period, anticoagulation is subject to increased variability and should be monitored more frequently.

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 in AF, a combination of vitamin K antagonist and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding.

11.2.2.2 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 20) [203, 219]. 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 [220–222].

Certain caveats apply in selecting the optimum INR:

- 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 designs—there is insufficient data on valve thrombosis rates at different levels of INR, which would otherwise allow for categorisation. 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.

We recommend a median INR value, rather than a range, to avoid considering extreme values in the 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. Self-management of anticoagulation has been shown to reduce INR variability and clinical events, although appropriate training is required. Monitoring by an anticoagulant clinic should, however, be

Table 19: Indications for antithrombotic therapy after valvular surgery

	Class [a]	Level [b]	Ref [c]
Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B	213
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.[d]	I	C	
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C	
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C	
Oral anticoagulation should be considered for the first three months after implantation of a mitral or tricuspid bioprosthesis.	IIa	C	
Oral anticoagulation should be considered for the first three months after mitral valve repair.	IIa	C	
Low-dose aspirin should be considered for the first three months after implantation of an aortic bioprosthesis.	IIa	C	
Oral anticoagulation may be considered for the first three months after implantation of an aortic bioprosthesis.	IIb	C	

INR: international normalized ratio.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d]Atrial fibrillation, venous thromboembolism, hypercoagulable state, or with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction <35%).

Table 20: Target international normalized ratio (INR) for mechanical prostheses

Prosthesis thrombogenicity [a]	Patient-related risk factors [b]	
	No risk factor	Risk factor ≥1
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

[a]Prosthesis thrombogenicity: Low: Carbomedics, Medtronic Hall, St Jude Medical, ON-X; Medium: other bileaflet valves; High: Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves.
[b]Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction <35%.

considered for patients with unstable INR or anticoagulant-related complications.

11.2.2.3 Management of overdose of vitamin K antagonists and bleeding. The risk of major bleeding increases considerably when the INR exceeds 4.5 and increases exponentially above an INR of 6.0. An INR ≥6.0 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 vitamin K antagonist 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 [223]. If the INR is >10, higher doses of oral vitamin K (5 mg) should be considered. The oral route should be favoured over the intravenous route, which may carry a higher risk of anaphylaxis [223].

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, if used, should therefore be combined with oral vitamin K, whatever the INR [223]. When available, the use of intravenous prothrombin complex concentrate is preferred over fresh frozen plasma. The use of recombinant activated factor VII cannot be recommended, due to insufficient data. 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. Bleeding while in the therapeutic INR range is often related to an underlying pathological cause and it is important that it be identified and treated.

11.2.2.4 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 vascular disease and in patients with prosthetic valves and vascular disease should not be taken as evidence that patients with prosthetic valves and no vascular disease will also benefit [224]. When added to anticoagulation, antiplatelet agents increase the risk of major bleeding [225, 226]. 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 ≤100 mg daily).

Indications for the addition of an antiplatelet agent are detailed in Table 19. The addition of antiplatelet agents should be considered only after full investigation and treatment of identified risk factors and optimisation of anticoagulation management.

Addition of aspirin and a $P2Y_{12}$ receptor blocker is necessary following intracoronary stenting, but increases the risk of bleeding. Bare-metal stents should be preferred over drug-eluting stents in patients with mechanical prostheses, to shorten the use of triple antithrombotic therapy to 1 month [20]. Longer durations (3–6 months) of triple antithrombotic therapy should be considered in selected cases after acute coronary syndrome [47]. During this period, close monitoring of INR is advised and any over-anticoagulation should be avoided [20].

Finally, there is no evidence to support the use of antiplatelet agents beyond 3 months in patients with bioprostheses who do not have an indication, other than the presence of the bioprosthesis itself.

11.2.2.5 Interruption of anticoagulant therapy. Anticoagulation during non-cardiac surgery requires very careful management, based on risk assessment [203, 227]. Besides prosthesis and patient-related prothrombotic factors (Table 20), surgery for malignant disease or an infective process carries a particular risk due to the hypercoagulability associated with these conditions.

It is recommended not to interrupt oral anticoagulation for most minor surgical procedures (including dental extraction, cataract removal) and those procedures where bleeding is easily controlled (recommendation class I, level of evidence C). Appropriate techniques of haemostasis should be used and the INR should be measured on the day of the procedure [228, 229].

Major surgical procedures require an INR <1.5. In patients with a mechanical prosthesis, oral anticoagulant therapy should be stopped before surgery and bridging, using heparin, is recommended (recommendation class I, level of evidence C) [227–229]. UFH remains the only approved heparin treatment in patients with mechanical prostheses; intravenous administration should be favoured over the subcutaneous route (recommendation class IIa, level of evidence C). The use of subcutaneous LMWH should be considered as an alternative to UFH for bridging (recommendation class IIa, level of evidence C). However, despite their widespread use and the positive results of observational studies [230, 231] 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, if possible, with monitoring of anti-Xa activity with a target of 0.5–1.0 U/ml [227]. LMWHs are contraindicated in cases of severe renal failure. The last dose of LMWH should be administered >12 hours before the procedure, whereas UFH should be discontinued 4 hours before surgery. Effective anticoagulation should be resumed as soon as possible after the surgical procedure according to bleeding risk and maintained until the INR returns to the therapeutic range [227].

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 catheterisation, in particular using the radial approach. In patients who require transseptal catheterisation, direct LV puncture or pericardial drainage, oral anticoagulants should be stopped and bridging anticoagulation performed as described above [203].

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

11.2.3 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, infection, etc.). The diagnosis should be confirmed by TTE and/or TOE or cinefluoroscopy [210, 232].

The management of prosthetic 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 [233].

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

Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity (recommendation class I, level of evidence C: Figure 5). 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 comorbidities 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 [234].

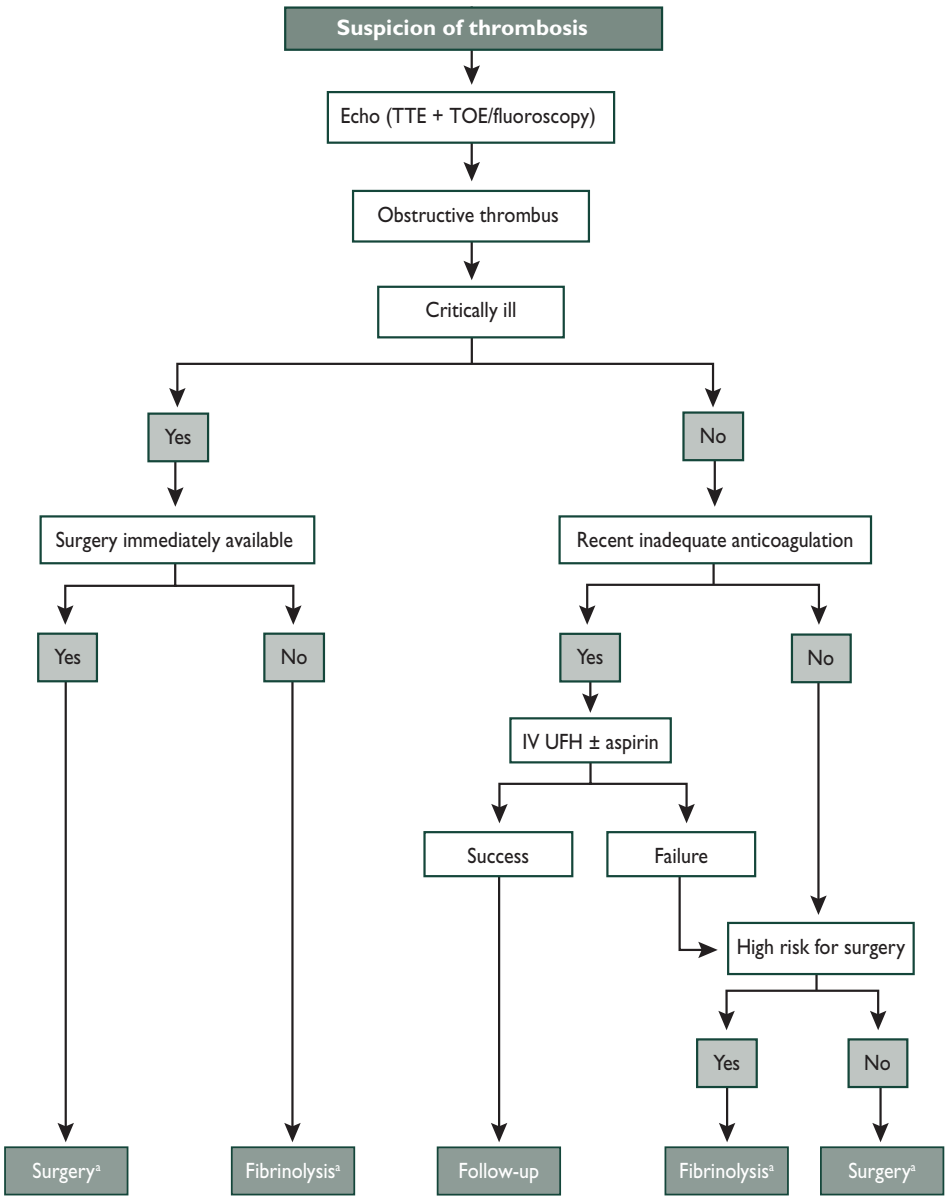

Figure 5: Management of left-sided obstructive prosthetic thrombosis. IV UFH: intravenous unfractionated heparin; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography. [a]Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery.

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 [210, 233].

Non-obstructive prosthetic 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 6). 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 (recommendation class IIa, level of evidence C) or which persists despite optimal anticoagulation [217]. 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.

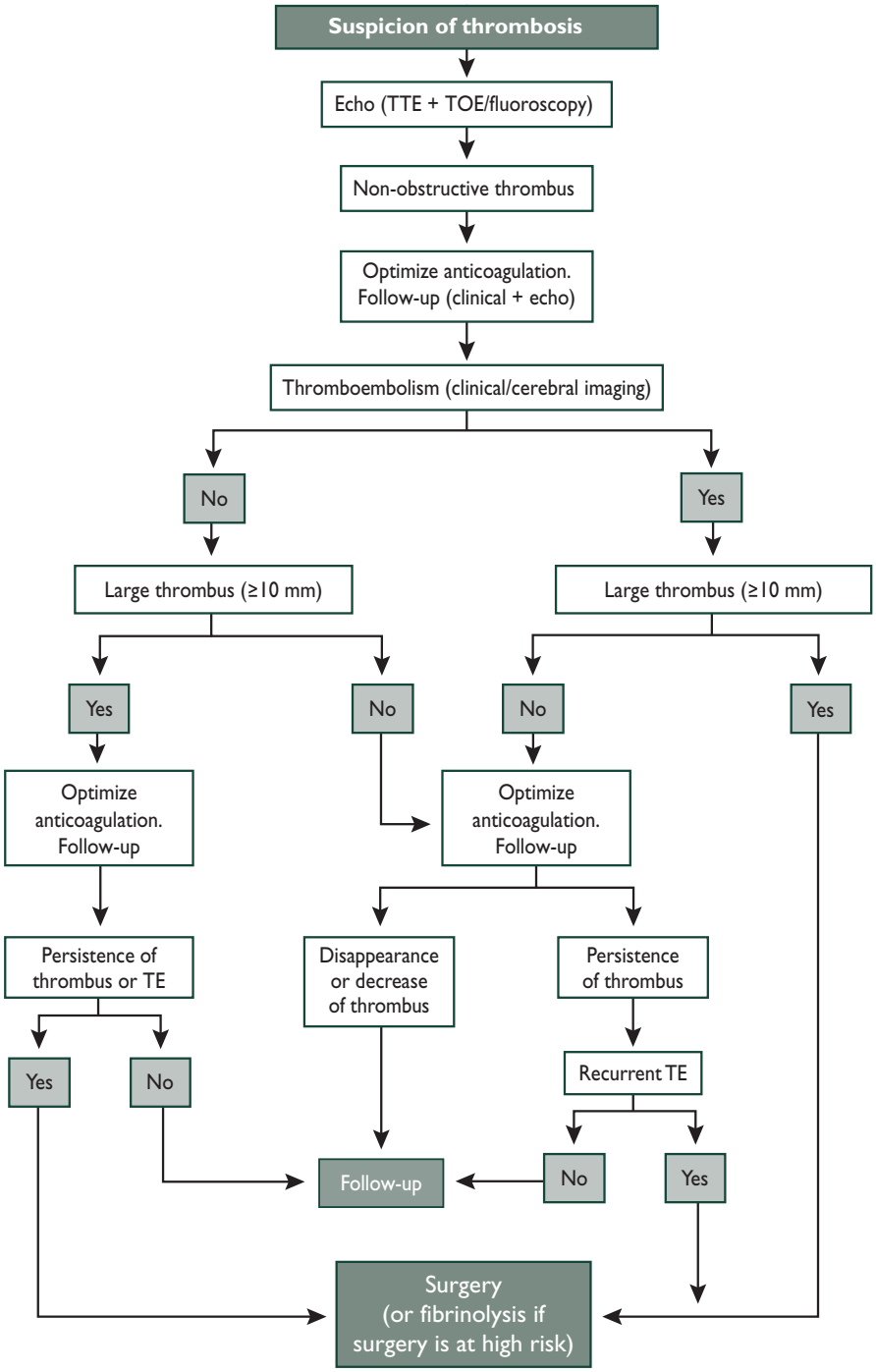

Figure 6: Management of left-sided non-obstructive prosthetic thrombosis. TE: thromboembolism; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

11.2.4 Management of thromboembolism. Thromboembolism after valve surgery is multifactorial in origin [203]. Although thromboembolic events frequently originate from the prosthesis, many others arise from other sources and are part of the background incidence of stroke and transient ischaemic attack in the general population.

Thorough investigation of each episode of thromboembolism is therefore essential (including cardiac and non-cardiac imaging: Figure 6), rather than simply increasing the target INR or adding an antiplatelet agent. Prevention of further thromboembolic events involves:

- Treatment or reversal of risk factors such as AF, hypertension, hypercholesterolaemia, diabetes, smoking, infection, and prothrombotic blood test abnormalities.
- 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 (≤100 mg daily) should be added, if it was not previously prescribed, after careful analysis of the risk-benefit ratio, avoiding excessive anticoagulation.

11.2.5 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 (PVL) if TTE is not contributive. Reoperation is recommended if PVL is related to endocarditis, or if PVL causes haemolysis requiring repeated blood transfusions or leading to severe symptoms (recommendation class I, level of evidence C). Medical therapy, including iron supplementation, beta-blockers and erythropoietin, is indicated in patients with severe haemolytic anaemia and PVL not related to endocarditis, where contraindications to surgery are present, or in those patients unwilling to undergo reoperation [235]. Transcatheter closure of PVL is feasible but experience is limited and there is presently no conclusive evidence to show a consistent efficiency [236]. It may be considered in selected patients in whom reintervention is deemed high-risk or is contraindicated.

11.2.6 Management of bioprosthetic failure. After the first 5 years following implantation—and earlier in young patients—yearly echocardiography is required indefinitely to detect early signs of SVD, leaflet stiffening, calcification, reduced effective orifice area, and/or regurgitation. 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 trans-prosthetic gradient or severe regurgitation (recommendation class I, level of evidence C). Reoperation should be considered in asymptomatic patients with any significant prosthetic dysfunction, provided they are at low risk for reoperation (recommendation class IIa, level of evidence C). Prophylactic replacement of a bioprosthesis implanted >10 years ago, without structural deterioration, may be considered during an intervention on another valve or on the coronary arteries (recommendation class IIb, level of evidence C).

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 [237].

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

Treating bioprosthetic failure by transcatheter valve-in-valve implantation has been shown to be feasible [238, 239]. Current evidence is limited, therefore it cannot be considered as a valid alternative to surgery except in inoperable or high-risk patients as assessed by a 'heart team'.

11.2.7 Heart failure. HF after valve surgery should lead to a search for prosthetic-related complications, deterioration of repair, LV dysfunction or progression of another valve disease. Non-valvular-related causes such as CAD, hypertension or sustained arrhythmias should also be considered. The management of patients with HF should follow the relevant guidelines [13].

12. MANAGEMENT DURING NON-CARDIAC SURGERY

Cardiovascular morbidity and mortality is increased in patients with 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 ESC Guidelines [227].

12.1 Preoperative evaluation

Clinical assessment should search for symptoms, arrhythmias and the presence of a murmur—which justifies echocardiographic examination, particularly in the elderly.

Cardiovascular risk is also stratified according to the type of non-cardiac surgery and classified according to the risk of cardiac complications [227].

Each case should be individualized and discussed with cardiologists, anaesthetists (ideally cardiac anaesthetists), surgeons (both cardiac and the ones undertaking the non-cardiac procedure), and the patient and his/her family.

12.2 Specific valve lesions

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

In patients with severe AS needing elective non-cardiac surgery, the management depends mainly on the presence of symptoms and the type of surgery (Figure 7) [227, 240, 241].

In symptomatic patients, AVR should be considered before non-cardiac surgery. A high risk for valvular surgery should lead to re-evaluation of the need to carry out non-cardiac surgery before considering balloon aortic valvuloplasty or TAVI.

In asymptomatic patients with severe AS, non-cardiac surgery at low- or moderate risk can be performed safely [240]. If non-cardiac surgery is at high risk, the presence of very severe AS, severe valve calcification or abnormal exercise test results are incentives to consider AVR first. In asymptomatic patients who are at high risk for valvular surgery, non-cardiac surgery, if mandatory, should be performed under strict haemodynamic monitoring.

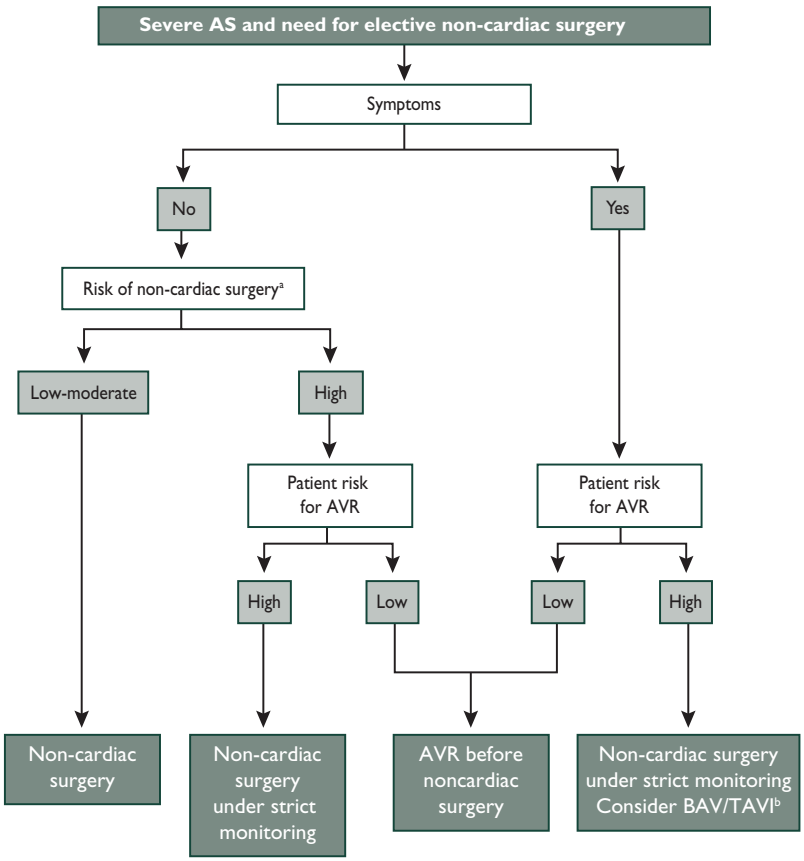

Figure 7: Management of severe aortic stenosis and elective non-cardiac surgery according to patient characteristics and the type of surgery. AS: aortic stenosis; AVR: aortic valve replacement; BAV: balloon aortic valvuloplasty; TAVI: transcatheter aortic valve implantation. [a]Classification into three groups according to the risk of cardiac complications (30-day death and myocardial infarction) for non-cardiac surgery (227) (high risk >5%; intermediate risk 1–5%; low risk <1%). [b]Non-cardiac surgery performed only if strictly needed. The choice between balloon aortic valvuloplasty and transcatheter aortic valve implantation should take into account patient life expectancy.

When valve surgery is needed before non-cardiac surgery, a bioprosthesis is the preferred substitute, in order to avoid anti-coagulation problems during the subsequent non-cardiac surgery.

12.2.2 Mitral stenosis. In asymptomatic patients with significant MS and a systolic pulmonary artery pressure <50 mmHg, non-cardiac surgery can be performed safely.

In symptomatic patients or in patients with systolic pulmonary artery pressure >50 mmHg, correction of MS—by means of PMC whenever possible—should be attempted before non-cardiac surgery if it is high risk. If valve replacement is needed, the decision to proceed before non-cardiac surgery should be taken with caution and individualized.

12.2.3 Aortic and mitral regurgitation. In asymptomatic patients with severe MR or AR and preserved LV function, non-cardiac surgery can be performed safely. The presence of symptoms or LV dysfunction should lead to consideration of valvular surgery, but this is seldom needed before non-cardiac surgery. If LV dysfunction is severe (EF <30%), non-cardiac surgery should only be performed if strictly necessary, after optimization of medical therapy for HF.

12.2.4 Prosthetic valves. The main problem is the adaptation of anticoagulation in patients with mechanical valves, which is detailed in *Interruption of anticoagulant therapy* (Section 11.2.2.5).

12.3 Perioperative monitoring

Perioperative management should be used to control heart rate (particularly in MS), to avoid fluid overload as well as volume depletion and hypotension (particularly in AS) and to optimize anticoagulation if needed [240].

In patients with moderate-to-severe AS or MS, beta-blockers or amiodarone can be used prophylactically to maintain sinus rhythm [241]. The use of beta-blockers and statins should be adapted to the risk of ischaemic heart disease according to guidelines.

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

13. MANAGEMENT DURING PREGNANCY

The management of VHD during pregnancy is detailed in the ESC Guidelines on pregnancy [207]. In brief, management before and during pregnancy—and planning of delivery—should be discussed between obstetricians, cardiologists and the patient and

her family, according to specific guidelines. Ideally, valve disease should be evaluated before pregnancy and treated if necessary. Pregnancy may be discouraged in certain conditions.

13.1 Native valve disease

MS is often poorly tolerated when valve area is <1.5 cm^2, even in previously asymptomatic patients. Symptomatic MS should be treated using bed rest and beta-blockers, possibly associated with diuretics. In the case of persistent dyspnoea or pulmonary artery hypertension despite medical therapy, PMC should be considered after the 20th week in experienced centres. Anticoagulant therapy is indicated in selected cases [207].

Complications of severe AS occur mainly in patients who were symptomatic before pregnancy. The risk of HF is low when mean aortic gradient is <50 mmHg.

Chronic MR and AR are well-tolerated, even when severe, provided LV systolic function is preserved. Surgery under cardiopulmonary bypass is associated with a foetal mortality rate of between 20–30% and should be restricted to the rare conditions that threaten the mother's life.

13.2 Prosthetic valves

Maternal mortality is estimated at between 1–4% in women with mechanical valves. These patients should be informed of the risks and constraints due to anticoagulant therapy if pregnancy occurs. During the first trimester, in choosing between vitamin K antagonists, UFH, and LMWH, the respective maternal- and foetal risks should be weighed up carefully. Vitamin K antagonists are favoured during the second and third trimester until the 36th week, when they should be replaced by heparin [207].

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