



# Guidelines on the management of valvular heart disease

## The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology

**Authors/Task Force Members, Alec Vahanian (Chairperson) Paris (France)\*, Helmut Baumgartner, Vienna (Austria), Jeroen Bax, Leiden (The Netherlands), Eric Butchart, Cardiff (UK), Robert Dion, Leiden (The Netherlands), Gerasimos Filippatos, Athens (Greece), Frank Flachskampf, Erlangen (Germany), Roger Hall, Norwich (UK), Bernard Jung, Paris (France), Jaroslaw Kasprzak, Lodz (Poland), Patrick Nataf, Paris (France), Pilar Tornos, Barcelona (Spain), Lucia Torracca, Milan (Italy), Arnold Wenink, Leiden (The Netherlands)**

**ESC Committee for Practice Guidelines (CPG), Silvia G. Priori (Chairperson) (Italy), Jean-Jacques Blanc (France), Andrzej Budaj (Poland), John Camm (UK), Veronica Dean (France), Jaap Deckers (The Netherlands), Kenneth Dickstein (Norway), John Lekakis (Greece), Keith McGregor (France), Marco Metra (Italy), João Morais (Portugal), Ady Osterspey (Germany), Juan Tamargo (Spain), José Luis Zamorano (Spain)**

**Document Reviewers, José Luis Zamorano (CPG Review Coordinator) (Spain), Annalisa Angelini (Italy), Manuel Antunes (Portugal), Miguel Angel Garcia Fernandez (Spain), Christa Gohlke-Baerwolf (Germany), Gilbert Habib (France), John McMurray (UK), Catherine Otto (USA), Luc Pierard (Belgium), José L. Pomar (Spain), Bernard Prendergast (UK), Raphael Rosenhek (Austria), Miguel Sousa Uva (Portugal), Juan Tamargo (Spain)**

### Table of Contents

Preamble . . . . .	231	Other non-invasive imaging techniques . . . . .	235
Introduction . . . . .	232	Biomarkers . . . . .	235
Why do we need guidelines on valvular heart disease? . . . . .	232	Coronary angiography . . . . .	235
Contents of these guidelines . . . . .	232	Cardiac catheterization . . . . .	235
How to use these guidelines . . . . .	233	Assessment of comorbidity . . . . .	235
Method of review . . . . .	233	Endocarditis prophylaxis . . . . .	235
Definition of levels of recommendation . . . . .	233	Risk stratification . . . . .	235
General comments . . . . .	233	Aortic regurgitation . . . . .	236
Patient evaluation . . . . .	233	Introduction . . . . .	236
Clinical evaluation . . . . .	233	Evaluation . . . . .	236
Echocardiography . . . . .	233	Natural history . . . . .	237
Fluoroscopy . . . . .	234	Results of surgery . . . . .	237
Radionuclide angiography . . . . .	234	Indications for surgery . . . . .	237
Stress testing . . . . .	234	Medical therapy . . . . .	238
		Serial testing . . . . .	238

\* Corresponding author. Chairperson: Alec Vahanian, Service de Cardiologie, Hôpital Bichat AP-HP, 46 rue Henri Huchard, 75018 Paris, France. Tel: + 33 1 40 25 67 60; fax: + 33 1 40 25 67 32.  
E-mail address: alec.vahanian@bch.aphp.fr

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC.

**Disclaimer.** The ESC Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgement. The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, 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.

Special patient populations . . . . .	238	Preoperative clinical evaluation . . . . .	259
Aortic stenosis . . . . .	239	Specific valve lesions . . . . .	259
Introduction . . . . .	239	Aortic stenosis . . . . .	259
Evaluation . . . . .	239	Mitral stenosis . . . . .	260
Natural history . . . . .	240	Aortic regurgitation and mitral regurgitation . . . . .	260
Results of intervention . . . . .	240	Prosthetic valves . . . . .	260
Indications for surgery . . . . .	241	Endocarditis prophylaxis . . . . .	260
Indications for balloon valvuloplasty . . . . .	241	Perioperative monitoring . . . . .	260
Medical therapy . . . . .	241	Management during pregnancy . . . . .	260
Serial testing . . . . .	242	Cardiac risk of pregnancy . . . . .	260
Special patient populations . . . . .	242	Evaluation of the pregnant patient with heart	
Mitral regurgitation . . . . .	243	valve disease . . . . .	260
Organic mitral regurgitation . . . . .	243	Specific risks related to pregnancy . . . . .	261
Evaluation . . . . .	243	Native valve disease . . . . .	261
Natural history . . . . .	243	Patients with prosthetic valves . . . . .	261
Results of surgery . . . . .	244	Treatment . . . . .	261
Indications for intervention . . . . .	244	Aims . . . . .	262
Medical therapy . . . . .	245	Methods . . . . .	262
Serial testing . . . . .	245	Management strategy . . . . .	262
Ischaemic mitral regurgitation . . . . .	246	Delivery . . . . .	262
Evaluation . . . . .	246	References . . . . .	263
Natural history . . . . .	246		
Results of surgery . . . . .	246		
Indications for surgery . . . . .	246		
Functional mitral regurgitation . . . . .	247		
Mitral stenosis . . . . .	247		
Introduction . . . . .	247		
Evaluation . . . . .	247		
Natural history . . . . .	248		
Results of intervention . . . . .	248		
Percutaneous balloon commissurotomy . . . . .	248		
Surgery . . . . .	248		
Indications for intervention . . . . .	248		
Medical therapy . . . . .	250		
Serial testing . . . . .	250		
Special patient populations . . . . .	250		
Tricuspid disease . . . . .	250		
Tricuspid stenosis . . . . .	250		
Evaluation . . . . .	251		
Surgery . . . . .	251		
Percutaneous intervention . . . . .	251		
Indications for intervention . . . . .	251		
Medical therapy . . . . .	251		
Tricuspid regurgitation . . . . .	251		
Evaluation . . . . .	251		
Natural history . . . . .	252		
Results of surgery . . . . .	252		
Indications for surgery . . . . .	252		
Medical therapy . . . . .	252		
Combined and multiple valve diseases . . . . .	252		
Prosthetic valves . . . . .	253		
Choice of prosthetic valve . . . . .	253		
Management after valve replacement . . . . .	254		
Baseline assessment and modalities of follow-up . . . . .	254		
Antithrombotic management . . . . .	254		
Management of valve thrombosis . . . . .	256		
Management of thrombo-embolism . . . . .	258		
Management of haemolysis and paravalvular leak . . . . .	258		
Management of bioprosthetic failure . . . . .	258		
Heart failure . . . . .	258		
Management during non-cardiac surgery . . . . .	258		
Clinical predictors of increased perioperative			
cardiovascular risk . . . . .	258		

## Preamble

Guidelines and Expert Consensus Documents aim to present management recommendations based on all of the relevant evidence on a particular subject in order to help physicians select the best possible management strategies for the individual patient suffering from a specific condition, taking into account the impact on outcome and also the risk-benefit ratio of a particular diagnostic or therapeutic procedure. Numerous studies have demonstrated that patient outcomes improve when guideline recommendations, based on the rigorous assessment of evidence-based research, are applied in clinical practice.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and also by other organizations or related societies. The profusion of documents can put at stake the authority and credibility of guidelines, particularly if discrepancies appear between different documents on the same issue, as this can lead to confusion in the minds of physicians. In order to avoid these pitfalls, the ESC and other organizations have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents. The ESC recommendations for guidelines production can be found on the ESC website.<sup>1</sup> It is beyond the scope of this preamble to recall all but the basic rules.

In brief, the ESC appoints experts in the field to carry out a comprehensive review of the literature, with a view to making a critical evaluation of the use of diagnostic and therapeutic procedures and assessing the risk-benefit ratio of the therapies recommended for management and/or prevention of a given condition. Estimates of expected health outcomes are included, where data exist. The strength of evidence for or against particular procedures or treatments is weighed according to predefined scales for grading recommendations and levels of evidence, as outlined in what follows.

The Task Force members of the writing panels, as well as the document reviewers, are asked to provide disclosure statements of all relationships they may have which might

be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC, and can be made available by written request to the ESC President. Any changes in conflict of interest that arise during the writing period must be notified to the ESC.

Guidelines and recommendations are presented in formats that are easy to interpret. They should help physicians make clinical decisions in their daily routine practice by describing the range of generally acceptable approaches to diagnosis and treatment. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of the patient's care.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. In some cases, the document can be presented to a panel of key opinion leaders in Europe, specialists in the relevant condition in question, for discussion and critical review. If necessary, the document is revised once more and finally approved by the CPG and selected members of the Board of the ESC and subsequently published.

After publication, dissemination of the message is of paramount importance. Publication of executive summaries and the production of pocket-sized and PDA-downloadable versions of the recommendations are helpful. However, surveys have shown that the intended end-users are often not aware of the existence of guidelines or simply do not put them into practice. Implementation programmes are thus necessary and form an important component of the dissemination of knowledge. Meetings are organized by the ESC and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at a national level, once the guidelines have been endorsed by the ESC member societies, and translated into the local language, when necessary.

All in all, the task of writing Guidelines or Expert Consensus Document 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 then only be completed if surveys and registries are organized to verify that actual clinical practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to check the impact of strict implementation of the guidelines on patient outcome.

## Introduction

### Why do we need guidelines on valvular heart disease?

Although valvular heart disease (VHD) is less common in industrialized countries than coronary disease, heart

failure, or hypertension, guidelines are of interest in this field for several reasons:

- VHD is common and often requires intervention.
- Substantial advances have been made in the understanding of its pathophysiology.
- In recent years, the patient population has changed. The continuous decline of acute rheumatic fever owing to better prophylaxis of streptococcus infections explains the decrease in the incidence of rheumatic valve disease, whereas increased life expectancy partially accounts for the increase in the incidence of degenerative valvular diseases in industrialized countries. The incidence of endocarditis remains stable and other causes of valve disease are rare.<sup>2,3</sup> Because of the predominance of degenerative valve disease, the two most frequent valve diseases are now calcific aortic stenosis (AS) and mitral regurgitation (MR), whereas aortic regurgitation (AR) and mitral stenosis (MS) have become less common.<sup>3</sup> Older age is associated with a higher frequency of comorbidity, which contributes to increased operative risk and renders decision-making for intervention more complex. Another important aspect of contemporary heart valve disease is the growing proportion of previously operated patients who present with further problems.<sup>3</sup> Conversely, rheumatic valve disease still remains a major public health problem in developing countries, where it predominantly affects young adults.<sup>4</sup> However, rheumatic heart disease is still present in industrialized countries owing to immigration and sequelae of rheumatic fever in older patients.
- Diagnosis is now dominated by echocardiography, which has become the standard to evaluate valve structure and function.
- Treatment has not only developed through the continuing progress in prosthetic valve technology, but has also been reoriented by the development of conservative surgical approaches and the introduction of percutaneous interventional techniques.

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

The same is true with guidelines: there is only one set of guidelines in the field of VHD in the USA<sup>5</sup> and four national guidelines in Europe.<sup>6-9</sup> Moreover, published guidelines are not always consistent due to the lack of randomized clinical trials as well as the constant evolution of practice. Finally, data from the recent Euro Heart Survey on VHD show that there is a real gap between the existing guidelines and their effective application.<sup>3</sup>

It is for this reason that the ESC has produced these guidelines, which are the first European guidelines on this topic.

### Contents of these guidelines

The guidelines focus on VHD in adults and adolescents, are oriented towards management, and will not deal with endocarditis and congenital valve diseases in adults and adolescents, since recent guidelines have been produced by the ESC on these topics.<sup>10,11</sup> Finally, these guidelines are not intended to include detailed information covered in ESC Guidelines on other topics, ESC Expert Consensus Documents, recommendations from the working group on VHD, and the specific sections of the ESC Textbook on Cardiology.<sup>12-15</sup>

## How to use these guidelines

The committee emphasizes the fact 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 interventional cardiologists and surgeons, especially in the field of conservative techniques, and, notably, the wishes of well-informed patients. Furthermore, owing 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.

## Method of review

A literature review was performed using Medline (PubMed) for peer-reviewed published literature focusing on the studies published within the last 10 years. The use of abstracts was avoided in these guidelines.

## Definition of levels of recommendation

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedures and/or treatments and the level of evidence as indicated in *Table 1*. The levels of recommendation were graded on the basis of the ESC recommendations.<sup>1</sup> Unlike in the ACC/AHA levels of recommendation, class III ('conditions for which there is evidence and/or general agreement that the procedure is not useful/effective and in some cases may be harmful') is usually not used in the ESC guidelines.

## 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 investigations and clinical findings should be checked at each step. Indications for interventions rely mainly on the comparative assessment of spontaneous prognosis and the results of intervention according to the characteristics of VHD and comorbidities.

**Table 1** Recommendation classes and levels of evidence

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
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

## Patient evaluation

Diagnosis and evaluation of the severity of VHD should be based on the combined analysis of clinical findings and the results of investigations.

### Clinical evaluation

The aim of analysing case history is to assess present and past symptoms, as well as looking for associated comorbidity. The patient is questioned on her/his lifestyle to detect progressive changes in the daily activity in order to limit the subjectivity of symptom analysis, in particular, in the elderly.<sup>13</sup> Questioning the patient is also important to check the quality of follow-up, the effectiveness of prophylaxis of endocarditis and, where applicable, of rheumatic fever. In patients receiving chronic anticoagulant therapy, it is necessary to assess the stability of anticoagulation and look for thrombo-embolism or bleeding.

Clinical examination plays a major role in the detection of VHD in asymptomatic patients. It is the first step in the diagnosis of VHD and the assessment of its severity. In patients with a heart valve prosthesis, it is necessary to be aware of any change in murmur or prosthetic sounds.

An electrocardiogram (ECG) and chest X-ray are usually carried out alongside clinical examination. Besides cardiac enlargement, analysis of pulmonary vascularization on the chest X-ray is useful when interpreting dyspnoea or clinical signs of heart failure.<sup>16</sup>

### Echocardiography

In addition to clinical findings, echocardiography is the key technique to confirm the diagnosis of VHD, as well as to assess its severity and prognosis. It is indicated in any patient with a murmur when valve disease is suspected, the only possible exception being young patients who only have a trivial (grade 1/6) mid-systolic murmur.

The evaluation of the severity of stenotic VHD should combine the assessment of valve area and flow-dependent indices such as mean gradient and/or maximal flow velocity.<sup>17</sup> Flow-dependent indices such as mean gradient or maximal flow velocity add further information and have a prognostic value.<sup>18</sup>

The assessment of valvular regurgitation should combine different indices including quantitative Doppler echocardiography, such as the effective regurgitant orifice area (ERO), which is less dependent on flow conditions than colour Doppler jet size.<sup>19</sup> However, all quantitative evaluations, such as the continuity equation or flow convergence, have limitations. In particular, they combine a number of measurements and are highly sensitive to errors of measurement; therefore, their use requires experience.

Thus, when assessing the severity of VHD, it is necessary to check consistency between the different echocardiographic measurements as well as with the anatomy and mechanisms of VHD. It is also necessary to check their consistency with clinical assessment. In *Table 2*, this is illustrated as it applies to the quantification of severe regurgitation.

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

Indices of left ventricular (LV) enlargement and function are strong prognostic factors in AR and MR and, thus,

**Table 2** Criteria for the definition of severe valve regurgitation—an integrative approach

	AR	MR	TR
Specific signs of severe regurgitation	Central jet, width $\geq 65\%$ of LVOT <sup>a</sup> Vena contracta $> 0.6 \text{ cm}^a$	Vena contracta width $\geq 0.7 \text{ cm}$ with large central MR jet (area $> 40\%$ of LA) or with a wall impinging jet of any size, swirling in LA <sup>a</sup> Large flow convergence <sup>b</sup> Systolic reversal in pulmonary veins Prominent flail MV or ruptured papillary muscle	Vena contracta width $> 0.7 \text{ cm}$ in echo Large flow convergence <sup>b</sup> Systolic reversal in the hepatic veins
Supportive signs	Pressure half-time $< 200 \text{ ms}$ Holodiastolic aortic flow reversal in descending aorta Moderate or greater LV enlargement <sup>d</sup>	Dense, triangular CW, Doppler MR jet E-wave dominant mitral inflow ( $E > 1.2 \text{ m/s}$ ) <sup>c</sup> Enlarged LV and LA size <sup>e</sup> (particularly when normal LV function is present)	Dense, triangular CW TR signal with early peak Inferior cava dilatation and respiratory diameter variation $\ll 50\%$ Prominent transtricuspid E-wave, especially if $> 1 \text{ m/s}$ RA, RV dilatation
Quantitative parameters			
R Vol, mL/beat	$\geq 60$	$\geq 60$	
RF, %	$\geq 50$	$\geq 50$	
ERO, $\text{cm}^2$	$\geq 0.30$	$\geq 0.40$	

AR = aortic regurgitation, CW = continuous wave, ERO = effective regurgitant orifice area, LA = left atrium, LV = left ventricle, LVOT = LV outflow tract, MR = mitral regurgitation, MS = mitral stenosis, MV = mitral valve, R Vol = regurgitant volume, RA = right atrium, RF = regurgitant fraction, RV = right ventricle, TR = tricuspid regurgitation.

<sup>a</sup>At a Nyquist limit of 50–60 cm/s.

<sup>b</sup>Large flow convergence defined as flow convergence radius  $\geq 0.9 \text{ cm}$  for central jets, with a baseline shift at a Nyquist of 40 cm/s; cut-offs for eccentric jets are higher and should be angled correctly.

<sup>c</sup>Usually above 50 years of age or in conditions of impaired relaxation, in the absence of MS or other causes of elevated LA pressure.

<sup>d</sup>In the absence of other aetiologies of LV dilatation.

<sup>e</sup>In the absence of other aetiologies of LV and LA dilatation and acute MR.

Adapted from Zoghbi *et al.*<sup>19</sup>

play an important role in decision-making. It is also important to index LV dimensions to body surface area (BSA) to take into account patient's body size. However, the validity of indexed values is uncertain for extreme body size.

Transoesophageal echocardiography (TEE) should be considered when transthoracic examination is of suboptimal quality or when thrombosis, prosthetic dysfunction, or endocarditis is suspected. It should be performed intraoperatively to monitor the results of valve repair or complex procedures.

Three-dimensional echocardiography is a promising technique, particularly for the evaluation of valve anatomy. However, its incremental usefulness in decision-making has not been validated so far.

### Fluoroscopy

Fluoroscopy can be used to assess annular or valvular calcification, as it enables calcification to be distinguished from fibrosis with a higher specificity than echocardiography. Fluoroscopy is also useful to assess the kinetics of the mobile part of a mechanical prosthesis.

### Radionuclide angiography

Radionuclide angiography provides a reproducible evaluation of LV ejection fraction (EF) in patients in sinus rhythm. This aids decision-making in asymptomatic patients

with valvular regurgitation, in particular, when echocardiographic examination is of suboptimal quality.<sup>20</sup>

### Stress testing

#### Exercise electrocardiogram

The primary purpose of exercise testing is to unmask the objective occurrence of symptoms in patients who claim to be asymptomatic. In truly asymptomatic patients, it has an additional value for risk stratification in AS.<sup>21,22</sup> Exercise testing will also determine the level of authorized physical activity, including participation in sports.<sup>23</sup>

#### Exercise echocardiography

Promising recent reports suggest that the estimation of the prognosis of VHD and indications for intervention may be refined by measuring changes in gradients or degree of regurgitation on exercise.<sup>24,25</sup> Echocardiography performed immediately after exercise has shown to be useful to assess the prognosis of degenerative MR.<sup>26</sup> However, these preliminary findings need to be confirmed before this can be recommended in practice.

#### Other stress tests

Low-dose dobutamine stress echocardiography is useful in AS with impaired LV function.<sup>27</sup> The use of stress tests to detect coronary artery disease associated with severe VHD is discouraged because of their low diagnostic value.

## Other non-invasive imaging techniques

### Computed tomography

Preliminary data show that computed tomography (CT) scanning enables valve calcification to be accurately quantified with good reproducibility. Valve calcification is linked to the severity of VHD and provides additional prognostic information.<sup>28</sup> In expert centres, multislice CT can be useful to exclude coronary artery disease in patients who are at low risk of atherosclerosis.

### Magnetic resonance imaging

At present, magnetic resonance imaging (MRI) is not indicated in VHD in routine clinical practice; however, most measurements usually acquired by Doppler echocardiography can also be acquired with MRI and thus MRI can be used as an alternative technique when echocardiography is not feasible. In particular, quantification of cardiac function, dimensions, and regurgitant volume is very accurate with MRI.<sup>29</sup>

### Biomarkers

Natriuretic peptide serum level, in particular, of the B-type, has been shown to be related to functional class and prognosis, particularly in AS and MR.<sup>30,31</sup> However, data regarding their incremental value in risk-stratification so far remain limited.

### Coronary angiography

Coronary angiography is widely indicated to detect associated coronary artery disease when surgery is planned (Table 3). Knowledge of coronary anatomy improves risk-stratification and determines whether coronary revascularization is indicated in association with valvular surgery.

Coronary angiography can be omitted in young patients with no risk factors and in rare circumstances when its risk outweighs benefit, e.g. in acute aortic dissection, a large aortic vegetation in front of 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, is 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 systematically associated with coronary angiography, although this remains common in current practice.<sup>3,32</sup>

### Assessment of comorbidity

The choice of specific examinations to assess comorbidity is directed by the clinical evaluation. The most frequently encountered are peripheral atherosclerosis, renal failure, and chronic obstructive pulmonary disease.<sup>3</sup>

### Endocarditis prophylaxis

Endocarditis prophylaxis should be considered in any patient with VHD and adapted to the individual patient risk.<sup>10</sup>

### Risk stratification

The Euro Heart Survey has shown that, in current practice, there is general agreement between the decision to operate and the existing guidelines in asymptomatic patients. However, in patients with severe symptoms, intervention is underused for reasons that are often unjustified.<sup>3,33</sup> This stresses the importance of the widespread use of careful risk stratification.

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 compared with natural history outweighs the risk of intervention and its potential late consequences, in particular, prosthesis-related complications.

The evaluation of the prognosis of VHD depends on the type of VHD and is derived from studies on natural history, which are frequently old and not always applicable to current presentations of VHD. Only a few contemporary studies enable spontaneous prognosis to be assessed according to patient characteristics.<sup>34</sup>

Factors predicting operative mortality have been identified from large series of patients undergoing cardiac surgery or, more specifically, heart valve surgery.<sup>35-39</sup> They are related to heart disease, the patient's age, comorbidity, and the type of surgery. The easiest way to integrate the weight of the different predictable factors is to combine them in multivariate scores, enabling operative mortality to be estimated. The Euroscore (Table 4) is widely used in this setting. Although it has been elaborated for cardiac surgery in general, it has been validated in valvular surgery.<sup>35,39</sup> One recent analysis of a database from the UK led to a simple scoring system, which has been specifically elaborated and validated in patients operated on for VHD.<sup>37</sup> However, no scoring systems enable the spontaneous outcome to be assessed.

Despite limitations and the need for further validation, the use of these scores reduces the subjectivity of the evaluation of the operative risk and, thus, of the risk-benefit ratio. Of course, this is only one of the elements in decision-making, which should also take into account the patient's life expectancy, quality of life, wishes, as well as local resources, in particular, the availability of valve repair and surgical outcome in the specified centre. Finally, very importantly, the decision to intervene should take into account the decision of the patient and the relatives after they

**Table 3** Indications for coronary angiography in patients with valvular heart disease

	Class
Before valve surgery in patients with severe VHD and any of the following: History of coronary artery disease Suspected myocardial ischaemia <sup>a</sup> LV systolic dysfunction In men aged over 40 and post-menopausal women ≥ 1 Cardiovascular risk factor	IC
When coronary artery disease is suspected to be the cause of severe MR (ischaemic MR)	IC

LV = left ventricle, MR = mitral regurgitation, VHD = valvular heart disease.

<sup>a</sup>Chest pain, abnormal non-invasive testing.

**Table 4** Definitions of risk factors in the EuroSCORE

Risk factor	EuroSCORE definition	Points
Age	<60 years	0
	60–64	1
	65–69	2
	70–74	3
	75–79	4
	80–84	5
	85–89	6
	90–94	7
	≥95	8
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	Claudication, carotid occlusion or stenosis >50%, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	3
Serum creatinine	>200 µM/L preoperatively	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Ventricular tachycardia, fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation, preoperative inotropic support, intra-aortic balloon counterpulsation, or preoperative acute renal failure (anuria or oliguria <10 mL/h)	3
Unstable angina	Rest angina requiring intravenous nitrates until arrival in the anaesthetic room	2
LV dysfunction	Moderate (LVEF 30–50%)	1
	Poor (LVEF <30%)	3
	Recent MI	<90 days
Pulmonary hypertension	Systolic pulmonary artery pressure >60 mmHg	2
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch, or descending aorta	3
Post-infarct septal rupture		4

CABG = coronary artery bypass grafting, LV = left ventricular, EF = ejection fraction, MI = myocardial infarction.

The estimation of the operative mortality for a given patient can be obtained using a calculator accessible at <http://www.euroscore.org/calc.html>.

From Roques *et al.*<sup>35</sup>

have been thoroughly informed of the risks and benefits of the different therapeutic possibilities.

## Aortic regurgitation

### Introduction

AR may be the consequence of diverse aetiologies, the distribution of which has changed over time. The most frequent causes of AR are now those related to aortic root disease and bicuspid aortic valve. The inherent consequence is the frequent involvement of the ascending aorta,<sup>2,3</sup> which may need surgical treatment.

### Evaluation

Initial examination should include a detailed clinical evaluation. AR is diagnosed by the presence of a diastolic murmur. Exaggerated arterial pulsations and low diastolic pressure represent the first and main clinical signs for quantifying AR.<sup>15</sup> Peripheral signs are attenuated in acute AR, which contrasts with a poor functional tolerance.

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the General comments section.

Specific issues in AR are as follows:

Echocardiography is the key examination, its aim being to:

- Diagnose and quantify the severity of AR, using colour Doppler (extension or, better, width of regurgitant jet) and continuous-wave Doppler (rate of decline of aortic regurgitant flow and holodiastolic flow reversal in the descending aorta). All these indices are influenced by loading conditions and the compliance of the ascending aorta and the LV. Quantitative Doppler echocardiography, using the continuity equation or analysis of proximal isovelocity surface area, is less sensitive to loading conditions. The criteria for defining severe AR are described in *Table 2*.<sup>19</sup> The evaluation of severity, using quantitative measurements, is less well established than in MR, and consequently, the results of quantitative measurements should be integrated with other data to come to a final conclusion as regards severity.
- Assess the mechanisms of regurgitation, describe the valve anatomy, and determine the feasibility of valve repair.
- Image the aorta at four different levels: annulus, sinuses of Valsalva, sino-tubular junction, and ascending aorta.<sup>40</sup> Indexing for BSA could be recommended, especially in patients of small body size and women.<sup>41</sup>
- Evaluate LV function. LV dimensions should also be indexed as described earlier.<sup>42</sup>

TEE may be performed to better define the anatomy of the valve and ascending aorta, especially when valve-sparing intervention is considered.

At the present time, clinical decisions should not be based on changes in EF on exercise, nor on data from stress echocardiography because these indices, although potentially interesting, have not been adequately validated.

When available, MRI can be used to assess the severity of regurgitation and LV function, particularly when echocardiographic images are of poor quality.

MRI or CT scanning, according to availability and expertise, is recommended for the evaluation of the aorta in patients with an enlarged aorta as detected by echocardiography, especially in cases of bicuspid valves or Marfan's syndrome.

### Natural history

Patients with acute AR have a poor prognosis without intervention owing to the significant increase in diastolic LV pressure, leading to poor haemodynamic tolerance. There is little information in the literature on the progression from mild to severe AR. Patients with severe AR and symptoms have a poor prognosis.<sup>43</sup>

In asymptomatic patients with severe AR and normal LV function, the number of events during follow-up is low: development of asymptomatic LV dysfunction, <1.3% per year; sudden death, <0.2% per year; and symptoms, LV impairment, or death, 4.3% per year. Age, end-systolic diameter or volume, and EF at rest are predictors of outcome. On multivariate analysis, age and end-systolic diameter, when it is >50 mm, predict a poor outcome.<sup>43–46</sup> Recent data suggest that it could be more appropriate to use thresholds related to BSA and the proposed value is an end-systolic diameter >25 mm/m<sup>2</sup> BSA.<sup>42</sup>

The natural history of aortic root aneurysm has been mainly studied in patients with Marfan's syndrome. The strongest predictors of complication are the diameter of the aortic root at the level of the sinuses of Valsalva and the presence of a family history of cardiovascular events (aortic dissection, sudden cardiac death).<sup>40,47–49</sup> When the aorta has reached 6 cm in size, yearly rates of rupture, dissection, and death are, respectively, 3.6, 3.7, and 10.8%. There is a rising incidence of dissection or rupture with the increase in aneurysm size.<sup>47–49</sup> Recent data using indexed values show a 4, 8, and >20% risk of complications, respectively, when the measurements are 2.75, 2.75–4.24, and >4.25 cm/m<sup>2</sup>.<sup>41</sup> Patients with bicuspid valves<sup>50</sup> may also present a rapid progression rate. Less information is available for other aetiologies such as annulo-aortic ectasia.

### Results of surgery

Surgical treatment of AR is aortic valve replacement when there is no associated aortic aneurysm. When an aneurysm of the aortic root is associated, surgery also comprises replacement of the ascending aorta with re-implantation of the coronary arteries, combined with either replacement of the valve or valve-sparing techniques. In current practice, valve replacement remains the standard and the other procedures are performed in only a small percentage of patients. Supra-coronary replacement of ascending aorta can be performed when Valsalva sinuses are preserved.

**Table 5** Operative mortality after surgery for valvular heart disease

	STS (2001)	UKCSR (1999–2000)	EHS (2001)
Aortic valve replacement, no CABG (%)	3.7	3.1	2.7
Aortic valve replacement +CABG (%)	6.3	7	4.3
Mitral valve repair, no CABG (%)	2.2	2.8	0
Mitral valve replacement, no CABG (%)	5.8	6.2	1.7
Mitral valve repair or replacement +CABG (%)	10.1	8.6	8.2

CABG = coronary artery bypass grafting.

STS = Society of Thoracic Surgeons (USA). Mortality for STS includes first and redo interventions.<sup>51</sup> UKCSR = United Kingdom Cardiac Surgical Register. Mortality for UKCSR corresponds to first interventions only.<sup>52</sup> EHS = Euro Heart Survey.<sup>3</sup> CABG = coronary artery bypass grafting.

Operative mortality is low (1–3%)<sup>3,43,51,52</sup> (*Table 5*) in asymptomatic patients submitted to isolated aortic valve surgery. In symptomatic patients, in patients with combined aortic valve and root surgery, and in patients with concomitant coronary artery bypass grafting (CABG), operative mortality ranges from 3 to 7%. The strongest pre-operative predictors of heart failure or death after surgery are age, preoperative functional class, resting EF <50% or shortening fraction <25%, and LV end-systolic diameter >55 mm.<sup>43–45,53–56</sup>

Immediate and late results of the replacement of the ascending aorta, using a composite graft, are excellent in Marfan's syndrome when performed by experienced teams on an elective basis.<sup>40,57</sup> Data on conservative surgery are more limited and come from expert centres. In such settings, recent series have reported an operative mortality of 1.6%, 10 year survival of 88%, freedom from aortic valve replacement of 99%, and freedom from at least moderate AR of 83%.<sup>58,59</sup>

### Indications for surgery

In symptomatic acute AR, urgent intervention is indicated. In chronic AR, the goals of the operation are to improve outcome, to diminish symptoms, to prevent the development of postoperative heart failure and cardiac death, and to avoid aortic complications in patients who present with aortic aneurysm.<sup>46,60</sup>

On the basis of robust observational evidence, recommended surgical indications are as follows (*Table 6, Figure 1*):

Symptom onset is an indication for surgery. Surgery should not be denied in symptomatic 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 patients operated at an earlier stage, acceptable operative mortality, improvement of



**Table 6** Indications for surgery in aortic regurgitation

	Class
<b>Severe AR</b>	
Symptomatic patients (dyspnoea, NYHA class II, III, IV or angina)	IB
Asymptomatic patients with resting LVEF $\leq$ 50%	IB
Patients undergoing CABG or surgery of ascending aorta, or on another valve	IC
<b>Asymptomatic patients with resting LVEF &gt;50% with severe LV dilatation:</b>	
End-diastolic dimension >70 mm or	IlaC
ESD >50 mm (or >25 mm/m <sup>2</sup> BSA) <sup>a</sup>	IlaC
<b>Whatever the severity of AR</b>	
Patients who have aortic root disease with maximal aortic diameter <sup>b</sup>	
$\geq$ 45 mm for patients with Marfan's syndrome	IC
$\geq$ 50 mm for patients with bicuspid valves	IlaC
$\geq$ 55 mm for other patients	IlaC

Severity is defined from clinical and echocardiographic assessment (see text).

In asymptomatic patients, repeated and high-quality measures are necessary before surgery.

AR = aortic regurgitation, BSA = body surface area, CABG = coronary artery bypass grafting, ESD = end-systolic dimension, EF = ejection fraction, LV = left ventricular.

<sup>a</sup>Patient's stature should be considered. Indexing is helpful. Changes in sequential measurements should be taken into account.

<sup>b</sup>Decision should take into account the shape and thickness of ascending aorta as well as the shape of the other parts of aorta.

For patients who have an indication for surgery on the aortic valve, lower thresholds can be used for combining surgery on the ascending aorta.

clinical symptoms, and acceptable long-term survival can be obtained.<sup>53,56</sup>

Surgery should also be considered in asymptomatic patients with severe AR and impaired LV function at rest [resting EF  $\leq$ 50% and/or LV end-diastolic diameter >70 mm and/or end-systolic diameter >50 mm (or >25 mm/m<sup>2</sup> BSA)] since the likelihood of early development of symptoms is high, perioperative mortality low, and postoperative results excellent. A rapid increase in ventricular parameters on serial testing is another reason to consider surgery. Good-quality echocardiograms and data confirmation with repeated measurements are strongly recommended before surgery in asymptomatic patients.

The rationale for an aggressive approach in patients with mild AR and aortic dilatation is better defined in patients with Marfan's syndrome than in patients with bicuspid valves, and even more so in annulo-aortic ectasia. In borderline cases, the decision to replace the ascending aorta also relies on perioperative surgical findings as regards the thickness of the aortic wall and the status of the rest of the aorta.

Aortic root dilatation  $\geq$ 55 mm should be a surgical indication, irrespective of the degree of AR. In cases of Marfan's syndrome or bicuspid aortic valves, even lower degrees of root dilatation ( $\geq$ 45 and  $\geq$ 50 mm, respectively) have been proposed as indications for surgery, especially when there is a rapid increase of aortic diameter between serial measurements (5 mm per year) or family history of aortic dissection.<sup>48,49</sup>

For patients who have an indication for surgery on the aortic valve, lower thresholds can be used for combining surgery on the ascending aorta. Lower thresholds of aortic diameters can also be considered for indicating surgery if valve repair can be performed by experienced surgeons.

The choice of the surgical technique is adapted according to the following factors: associated root aneurysm, characteristics of leaflets, underlying pathology, life expectancy, and desired anticoagulation status.

## Medical therapy

Nitroprusside and inotropic agents (dopamine or dobutamine) may be used before surgery in patients with poorly tolerated acute AR to stabilize their clinical condition. In patients with chronic severe AR and heart failure, ACE-inhibitors are the treatment of choice when surgery is contraindicated or in cases with persistent postoperative LV dysfunction.

In asymptomatic patients with high blood pressure, the indication for anti-hypertensive treatment with vasodilators such as ACE-inhibitors or dihydropyridine calcium channel blockers is warranted.

The role of vasodilators in the asymptomatic patients without high blood pressure in order to delay surgery is unproved.<sup>61,62</sup>

In patients with Marfan's syndrome, beta-blockers slow the progression of the aortic dilatation<sup>63</sup> and should also be given after operation. In patients with severe AR, the use of beta-blockers should be very cautious because the lengthening of diastole increases the regurgitant volume. However, they can be used in patients with severe LV dysfunction. Recently, enalapril has also been used to delay aortic dilatation<sup>64</sup> in patients with Marfan's syndrome. Whether the same beneficial effect occurs in patients with bicuspid aortic valves is not known.

Patients with AR should be educated on endocarditis prevention and antibiotic prophylaxis.<sup>10</sup>

In patients with Marfan's syndrome or in young patients with aortic root aneurysm, the family needs to be screened to detect asymptomatic cases.

## Serial testing

Patients with mild-to-moderate AR can be seen 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 they become close to the thresholds for intervention, follow-up should continue at 6 month intervals. When parameters are stable, follow-up can be yearly.

In patients with a dilated aortic root, and especially in patients with Marfan's syndrome or with bicuspid aortic valves, examination of the aorta should be performed on a yearly basis, but with closer intervals if aortic enlargement is detected.

## Special patient populations

In patients with moderate AR who undergo CABG or mitral valve surgery, the decision to replace the aortic valve should be individualized according to aetiology of AR, age, disease progression, and possibility of valve repair.

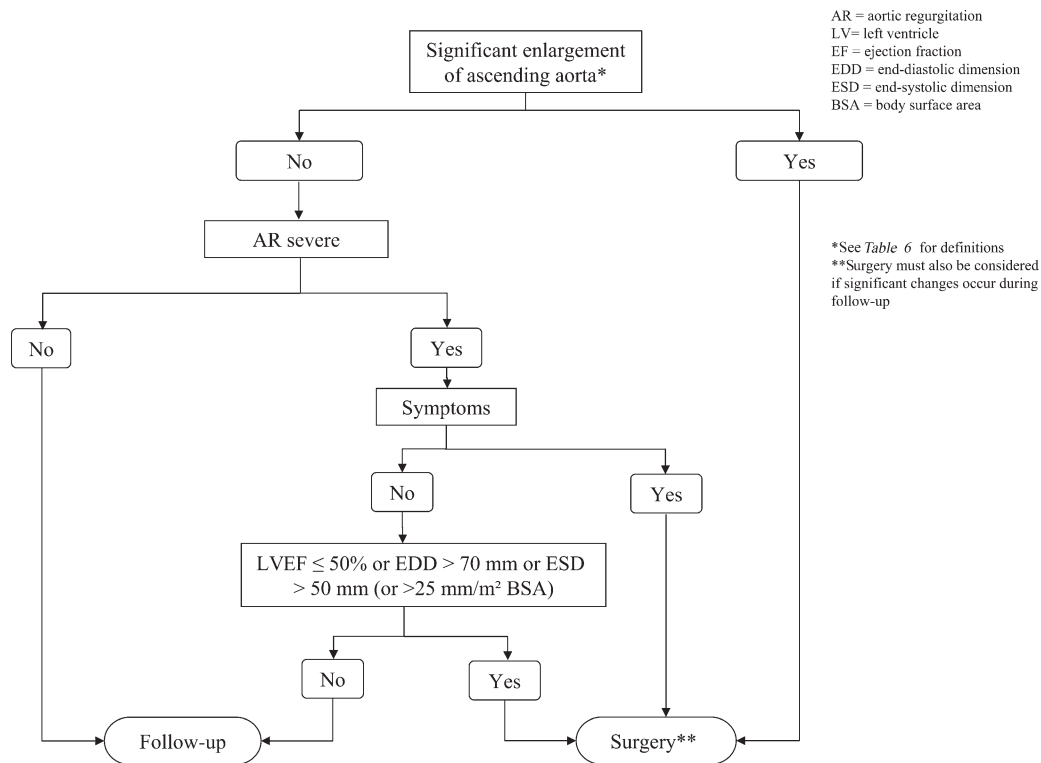


Figure 1 Management of aortic regurgitation.

Concurrent aortic valve replacement is more frequently considered when mitral surgery is prosthetic valve replacement than when it is mitral valve repair.

If AR requiring surgery is associated with severe MR, then both should be operated on. Usually the aortic valve will require replacement and the operation required on the mitral valve will depend on the chances of successful repair. Clearly, if the chances are low and the patient is likely to require anticoagulants because of the aortic surgery, then mitral valve replacement is likely to be preferable. If the associated MR does not demand immediate surgery, the decision is more difficult and needs to be individualized, but if the regurgitation is organic and repair is likely, then concurrent mitral valve surgery is attractive. There will, however, be occasions when the patient's clinical condition mandates the quickest and most simple procedure.

## Aortic stenosis

### Introduction

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).<sup>2,3,65,66</sup> The second most frequent aetiology, which dominates in the younger age group, is congenital, whereas rheumatic AS has become rare.

### Evaluation

Patient history and physical examination remain essential. Careful exploration for the presence of symptoms (exertional shortness of breath, angina, dizziness, or syncope) is

critical for proper patient management and must take into account that patients may deny symptoms because they significantly reduce their activities.

The characteristic systolic murmur draws the attention and guides the further diagnostic work in the right direction. Occasionally, the murmur may, however, be faint and primary presentation may be heart failure of unknown cause. The disappearance of the second aortic sound is specific to severe AS, although not a sensitive sign.<sup>15</sup>

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the General comments section.

Specific issues that need to be addressed in AS are as follows:

Echocardiography has become 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, and finally provides prognostic information.

Doppler echocardiography is the preferred technique to assess severity.<sup>17</sup> 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, it has to be emphasized that valve area measurements also have their potential inaccuracies 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 it should be considered in combination with flow rate, pressure gradient and ventricular function, as well as functional status. AS with a valve area <1.0 cm<sup>2</sup> is considered severe; however, indexing to BSA, with

a cut-off value of  $0.6 \text{ cm}^2/\text{m}^2$  BSA is helpful, in particular in patients with either unusually small or large BSA.

Severe AS is unlikely if cardiac output is normal, and there is a mean pressure gradient  $<50$  mmHg. In the presence of low flow, usually due to depressed LV function, low pressure gradients may be encountered in patients with severe AS. As soon as mean gradient is  $<40$  mmHg, even 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' (pseudosevere AS).<sup>67</sup>

Stress echocardiography using low-dose dobutamine may be helpful in this setting to distinguish truly severe AS from the rare cases of pseudosevere AS.<sup>27</sup> Truly severe AS shows only small changes in valve area (increase  $<0.2 \text{ cm}^2$ ) with increasing flow rate but significant increase in gradients (maximum value of mean gradient  $>50$  mmHg), whereas pseudosevere AS shows marked increase in valve area but only minor changes in gradients.<sup>27,68</sup> In addition, this test may detect the presence of contractile reserve (increase  $>20\%$  of stroke volume during low-dose dobutamine test), which has prognostic implications.<sup>27,68</sup>

Exercise stress echocardiography has been proposed for risk stratification in asymptomatic severe AS<sup>25</sup> but more data are necessary to determine its role.

Echocardiographic evaluation will identify coexistent valvular lesions including mitral annular calcification in degenerative disease and rheumatic mitral valve disease, as well as asymmetric dynamic subvalvular obstruction especially in elderly women.

TEE is rarely needed; however, it may provide images that are good enough to allow valve planimetry and this is useful when transthoracic visualization is poor and leaflets only moderately calcified. TEE will also provide additional evaluation of other mitral valve abnormalities.

Exercise testing is contraindicated in symptomatic patients with AS but is useful for unmasking symptoms and in the risk stratification of asymptomatic patients with severe AS.<sup>21,22</sup> In such cases, it is safe, provided it is performed under the supervision of an experienced physician, with symptoms, changes in blood pressure, and ECG closely monitored. In current practice, stress tests are under-used in patients with asymptomatic AS.<sup>3</sup>

CT and MRI could improve assessment of the ascending aorta, if required. Preliminary data suggest that multislice CT may be useful in quantifying valve calcification, which aids in assessing prognosis,<sup>28</sup> as well as in measuring valve area.<sup>69</sup> However, more data are required to determine the full role of multislice CT.

Natriuretic peptides have been shown in preliminary studies to predict symptom-free survival in AS.<sup>30</sup> However, more data are required before recommending their serial measurement to identify optimal timing of surgery.

Retrograde LV catheterization to assess the severity of AS is seldom needed and should only be used with caution, as it is not without risk.<sup>32</sup>

### Natural history

Calcific AS is a chronic progressive disease. During a long latent period, patients remain asymptomatic.<sup>70-72</sup> However, it should be emphasized that duration of the asymptomatic phase varies widely among individuals.

Sudden cardiac death is a frequent cause of death in symptomatic patients but appears to be rare in the asymptomatic ( $\leq 1\%$  per year).<sup>70-72</sup> Reported average symptom-free survival at 2 years ranges from 20 to more than 50%.<sup>21,22,70-72</sup> The lower numbers must be viewed with caution since some patients in these studies underwent surgery without symptoms. Finally, it has been speculated that myocardial fibrosis and severe LV hypertrophy, which may not be reversible after delayed surgery, could preclude an optimal postoperative long-term outcome. However, there are, so far, no data to confirm this hypothesis.

Predictors of the progression of AS and, therefore, of poor outcome in asymptomatic patients have recently been identified. They are:

- Clinical: older age, presence of atherosclerotic risk factors.<sup>65,66</sup>
- Echocardiography: valve calcification, peak aortic jet velocity, LVEF,<sup>71,72</sup> haemodynamic progression,<sup>71</sup> and increase in gradient with exercise.<sup>25</sup> The combination of a markedly calcified valve with a rapid increase in velocity of  $\geq 0.3 \text{ m/s}$  within 1 year has been shown to identify a high-risk group of patients ( $\sim 80\%$  death or requirement of surgery within 2 years<sup>71</sup>).
- Exercise testing: symptom development on exercise testing in physically active patients, particularly those younger than 70 years, predicts a very high likelihood of symptom development within 12 months. Recent data demonstrates a lower positive predictive value for abnormal blood pressure response, and even more so for ST-segment depression, than symptoms for poor outcome.<sup>22</sup>

As soon as symptoms occur, the prognosis is dismal and mortality has been reported to be quite significant even within months of symptom onset,<sup>73</sup> which is often not promptly reported by patients.

### Results of intervention

Aortic valve replacement is the definitive therapy for severe AS. In contemporary series, operative mortality of isolated aortic valve replacement is  $\sim 3-5\%$  in patients below 70 years and  $5-15\%$  in older adults (Table 5).<sup>3,51,52</sup> The following factors increase the risk of operative mortality: older age, associated comorbidities, female gender, higher functional class, emergency operation, LV dysfunction, pulmonary hypertension, coexisting coronary disease, and previous bypass or valve surgery. After successful valve replacement, long-term survival rates are close to those expected in the control population, symptoms are less marked, and quality of life is greatly improved.<sup>74</sup> Risk factors for late death include age, comorbidities, severe functional condition, LV dysfunction, ventricular arrhythmias, and untreated coexisting coronary artery disease. In addition, poor postoperative outcome may result from prosthesis-related complications and sub-optimal prosthetic valve haemodynamic performance.<sup>75</sup>

Balloon valvuloplasty plays an important role in the paediatric population but a very limited role in adults because its efficacy is low, complication rate is high ( $>10\%$ ), and restenosis and clinical deterioration occur within 6-12 months in most patients, resulting in a mid-term and long-term outcome similar to natural history.<sup>76</sup> Preliminary

reports show that percutaneous aortic valve replacement is feasible, but this procedure is at an early stage and further studies are needed to evaluate its potential role.<sup>77</sup>

### Indications for surgery

Surgical indications are as follows (Table 7, 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 mean gradient is still >40 mmHg, there is virtually no lower EF limit for surgery.

On the other hand, the management of patients with low-flow, low-gradient AS (severely reduced EF and mean gradient < 40 mmHg) is more controversial. The depressed EF in many patients in this group is predominantly caused by excessive afterload (afterload mismatch), and LV function usually improves after surgery.<sup>78,79</sup> Conversely, secondary improvement in LV function is uncertain if the primary cause is scarring due to extensive myocardial infarction. In patients with low gradient and with evidence of contractile reserve, surgery is advised since it carries an acceptable risk and improves long-term outcome in most patients. Conversely, the outcome of patients without contractile reserve is compromised by a high operative mortality despite a trend towards better survival after surgery.<sup>27</sup>

Surgery can, nonetheless, be performed in these patients but decision-making should take into account clinical condition (in particular, the presence of comorbidity), degree of valve calcification, extent of coronary disease, and feasibility of revascularization.

Management of asymptomatic patients with severe AS remains a matter of controversy.<sup>5,13,80</sup> The decision to operate on asymptomatic patients requires careful weighing of benefits against risks. Early elective surgery, at the asymptomatic stage, can only be recommended in selected patients, at low operative risk. This could be the case in:

- The rare asymptomatic patients with depressed LV function not due to another cause
- Those with echocardiographic predictors of poor outcome suggested by the combination of a markedly calcified valve with a rapid increase in peak aortic velocity of  $\geq 0.3$  m/s per year.
- If the exercise test is abnormal, particularly if it shows symptom development, which is a strong indication for surgery in physically active patients.
- However, on the other hand, breathlessness on exercise may be difficult to interpret in patients with only low physical activity, particularly the elderly, making decision-making more difficult. There is no strict age limit for performance of exercise testing and it is reasonable to propose it in patients >70 years old who are still highly active.

**Table 7** Indications for aortic valve replacement in aortic stenosis

	Class
Patients with severe AS and any symptoms	IB
Patients with severe AS undergoing coronary artery bypass surgery, surgery of the ascending aorta, or on another valve	IC
Asymptomatic patients with severe AS and systolic LV dysfunction (LVEF < 50%) unless due to other cause	IC
Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise	IC
Asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline	IlaC
Patients with moderate AS <sup>a</sup> undergoing coronary artery bypass surgery, surgery of the ascending aorta or another valve	IlaC
Asymptomatic patients with severe AS and moderate-to-severe valve calcification, and a rate of peak velocity progression $\geq 0.3$ m/s per year	IlaC
AS with low gradient (<40 mmHg) and LV dysfunction with contractile reserve	IlaC
Asymptomatic patients with severe AS and abnormal exercise test showing complex ventricular arrhythmias	IIBC
Asymptomatic patients with severe AS and excessive LV hypertrophy ( $\geq 15$ mm) unless this is due to hypertension	IIBC
AS with low gradient (<40 mmHg) and LV dysfunction without contractile reserve	IIBC

AS = aortic stenosis, EF = ejection fraction, LV = left ventricular.

<sup>a</sup>Moderate AS is defined as valve area 1.0–1.5 cm<sup>2</sup> (0.6 cm<sup>2</sup>/m<sup>2</sup> to 0.9 cm<sup>2</sup>/m<sup>2</sup> BSA) or mean aortic gradient 30–50 mmHg in the presence of normal flow conditions. However, clinical judgement is required.

### Indications for balloon valvuloplasty

This intervention can be considered as a bridge to surgery in haemodynamically unstable patients who are at high risk for surgery (Recommendation class IIb, Level of evidence C) or in patients with symptomatic severe AS who require urgent major non-cardiac surgery (Recommendation class IIb, Level of evidence C). Occasionally, balloon valvuloplasty could be considered as a palliative measure in individual cases when surgery is contraindicated because of severe comorbidities.

### Medical therapy

The progression of degenerative AS is an active process sharing a number of similarities with atherosclerosis.<sup>81</sup> Thus, modification of atherosclerotic risk factors must be strongly recommended following the guidelines of secondary prevention in atherosclerosis.

Although several retrospective reports have shown beneficial effects of statins<sup>82,83</sup> and ACE-inhibitors,<sup>84</sup> data are still conflicting and the only randomized trial assessing the effect of statin therapy is negative.<sup>85</sup> It is, therefore, too early for treatment recommendations.

Symptomatic patients require early surgery, as no medical therapy for AS is able to delay the inevitability of surgery. However, patients who are unsuitable candidates for surgery may be treated with digitalis, diuretics, ACE-inhibitors, or angiotensin receptor blockers if they are experiencing heart failure. Beta-blockers should be avoided in these circumstances. In selected patients with pulmonary oedema, nitroprusside can be used under haemodynamic monitoring.

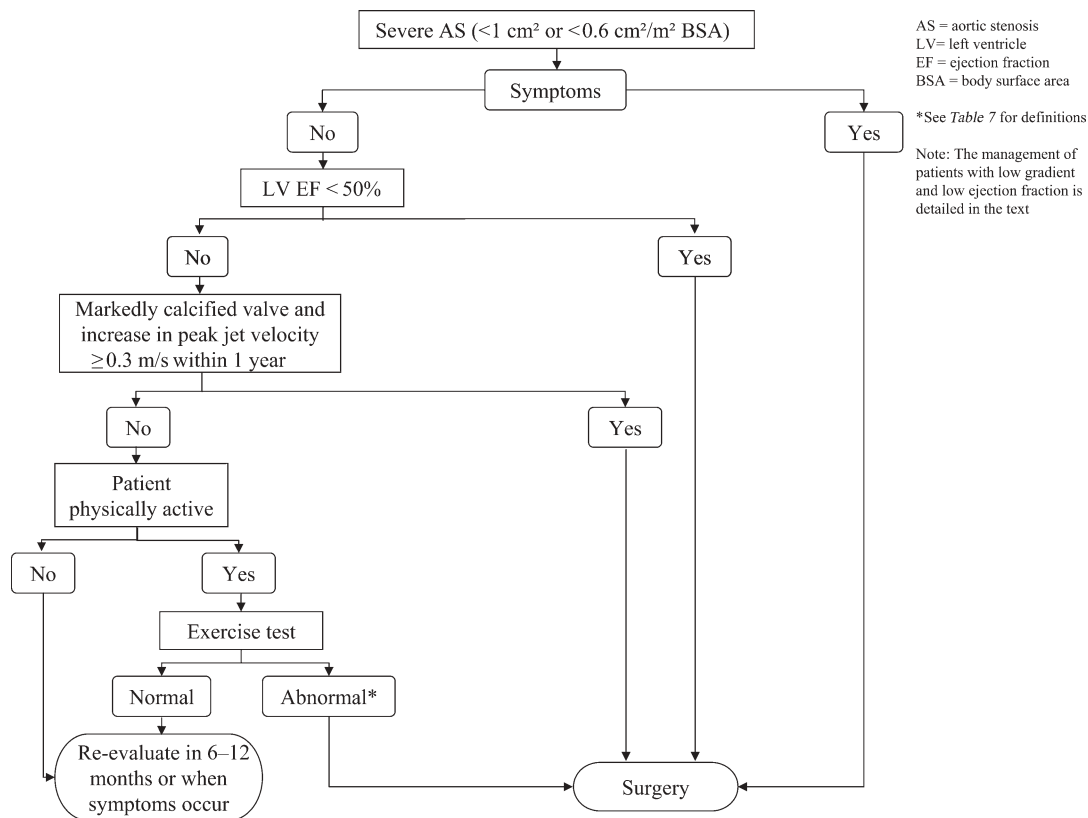


Figure 2 Management of severe aortic stenosis.

Co-existing hypertension should be treated; however, treatment should be carefully titrated to avoid hypotension and patients more frequently evaluated.

Maintenance of sinus rhythm is particularly important. Endocarditis prophylaxis is indicated in all patients with AS.<sup>10</sup>

### Serial testing

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. In the asymptomatic patient, stress tests should determine the recommended level of physical activity. Follow-up visits should include echocardiographic assessment since the rate of haemodynamic progression is important for management decisions. Type and interval of follow-up should be determined on the basis of the initial examination.

In cases of moderate-to-severe calcification of the valve and peak aortic jet velocity  $>4\text{ m/s}$  at initial evaluation, patients should be re-evaluated every 6 months for the occurrence of symptoms and change in exercise tolerance or in echo-parameters. If peak aortic jet velocity has increased since the last visit ( $>0.3\text{ m/s}$  per year) or if other evidence of haemodynamic progression is present, surgery should be considered. If no change has occurred and the patient remains asymptomatic, six-monthly clinical and six- to 12-monthly clinical and echocardiographic re-evaluations are recommended.

In patients who do not meet these criteria, a clinical yearly follow-up is necessary, follow-up being closer in

those with borderline values. The frequency of echocardiographic examinations should be adapted to clinical findings.

### Special patient populations

In patients with severe AS and severe coronary disease, the performance of concomitant CABG provides a lower mortality rate than that observed in patients who do not undergo combined bypass surgery. However, combined surgery carries a higher risk than isolated valve replacement in patients without coronary disease. Thus, CABG should be combined whenever possible with valve surgery. On the other hand, aortic valve replacement is not necessary during CABG in patients with only mild AS.

Finally, although there are no prospective randomized trials, data from retrospective analysis indicate that patients with moderate AS (mean gradient in the presence of normal flow 30–50 mmHg, valve area 1.0–1.5 cm<sup>2</sup>) will in general benefit from valve replacement at the time of coronary surgery.<sup>86</sup> However, individual judgement must be recommended considering BSA, individual haemodynamic data, life expectancy, expected progression rate of AS, expected outcome from associated disease (particularly comorbidity), and individual risk of valve replacement or eventual re-operation.

Patients with severe symptomatic AS and diffuse coronary artery disease, which cannot be revascularized, should not be denied aortic valve replacement, even though this is a high-risk group.

Recent studies have suggested the potential use of percutaneous coronary revascularization in place of bypass

surgery in patients with AS.<sup>87</sup> However, available data are not sufficient to currently recommend this approach, except for selected high-risk patients with acute coronary syndromes or in patients with non-severe AS.

AS is increasingly observed in octogenarians and even in nonagenarians who experience higher morbidity and operative mortality during aortic valve replacement. However, surgery can prolong and improve the quality of life.<sup>88</sup> Even though valve replacement is the procedure of choice in this population, a large percentage of suitable candidates currently are, unfortunately, not referred for surgery.<sup>3,33</sup> Age, *per se*, should not be considered a contraindication for surgery. Decisions should be made on an individual basis, taking into account patients' wishes and cardiac and non-cardiac factors (see also General comments section). In this population, the need for an emergency operation, or, at the other end of the clinical spectrum, very early intervention at an asymptomatic stage, should be avoided.

When MR is associated with AS, colour jet size and other Doppler findings may be increased by the high ventricular pressures. As long as there are no morphological 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 functional MR often resolves after the aortic valve is replaced.

Bicuspid valves are common in AS, and there is a clear relationship between the presence of bicuspid valves and abnormalities of the aortic root even in the absence of severe AS. Concomitant treatment of a dilated aorta is, therefore, recommended at the same thresholds as in AR.<sup>89</sup>

## Mitral regurgitation

MR is now the second most frequent valve disease after AS. The treatment has been re-orientated as a result of the good results of valve repair. This section deals with organic, ischaemic, and functional MR.

### Organic mitral regurgitation

Organic MR covers all aetiologies in which leaflet abnormality is the primary cause of the disease, in opposition to ischaemic and functional MR, in which MR is the consequence of LV disease.

Reduced prevalence of rheumatic fever and increased life span in industrialized countries have progressively changed the distribution of aetiologies. Degenerative MR is the most common aetiology in Europe, whereas ischaemic and functional MR are increasingly frequent.<sup>3</sup> Endocarditis is dealt with in separate specific ESC guidelines.<sup>10</sup>

### Evaluation

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 sound.<sup>15</sup> The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the General comments section.

The specific issues in MR are as follows:

Echocardiography is the principal examination and must include an assessment of severity, mechanisms and reparability, and, finally, consequences.

Several methods can be used to determine the severity of MR. Colour-flow mapping of the regurgitant jet is the easiest method but its accuracy is limited. The width of the vena contracta—the narrowest part of the jet—correlates with quantitative measurements of MR. The two quantitative methods of evaluating regurgitant volume and calculating ERO are useful in experienced hands.<sup>90,91</sup> The criteria for defining severe organic MR are described in *Table 2*.

It should be emphasized again here that the assessment of severity should not rely entirely on one single parameter, but requires an approach integrating blood flow data from Doppler with morphologic information and careful cross-checking of the validity of such data against the consequences on LV and pulmonary pressures<sup>19</sup> (*Table 2*).

In case of acute severe MR, physical examination and auscultation may be misleading, in particular, with a murmur of low intensity, and colour Doppler flow may underestimate the severity of the lesion. The presence of hyperdynamic function in acute heart failure suggests the presence of severe MR.

Transthoracic echocardiography provides 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 subsequently assess the feasibility of repair.<sup>92</sup>

TEE is frequently carried out before surgery for this purpose,<sup>93</sup> although transthoracic echocardiography, in experienced hands and when using recent imaging techniques, can be sufficient when images are of high quality.<sup>94</sup> The results of mitral valve repair should be assessed intraoperatively by TEE to enable immediate further surgical correction if necessary.

The consequences of MR are assessed by measuring left atrial diameter, LV diameter and EF, and systolic pulmonary arterial pressure.

Evaluation of contractile reserve may be accomplished by exercise echocardiography, but the usefulness of this method for decision-making requires validation.<sup>26</sup>

Preliminary series have also suggested the value of elevated BNP levels as predictors of long-term outcome but this also remains to be validated.<sup>31</sup>

### Natural history

Acute MR is poorly tolerated and carries a poor prognosis in the absence of intervention.

Our knowledge of the natural history of chronic MR has greatly improved due to recent observational studies.<sup>34,91,95,96</sup>

In asymptomatic MR, the estimated 5 year rates ( $\pm$  standard error) of death from any cause, death from cardiac causes, and cardiac events (death from cardiac causes, heart failure, or new AF) with medical management were  $22 \pm 3$ ,  $14 \pm 3$ , and  $33 \pm 3\%$ , respectively.<sup>91</sup>

In addition to symptoms, age, atrial fibrillation, degree of MR (particularly ERO), left atrial dilatation, LV dilatation, and low LVEF are all predictors of poor outcome.

In patients with chordal rupture, clinical condition may stabilize after an initial symptomatic period. However, it

carries a poor spontaneous prognosis owing to subsequent development of pulmonary hypertension.

### Results of surgery

Despite the absence of randomized comparison between the results of valve replacement and repair and the possible inherent biases resulting from this, it is widely accepted that valve repair, when feasible, is the optimal surgical treatment in patients with severe MR. When compared with valve replacement, repair has a lower perioperative mortality (Table 5), improved survival, better preservation of postoperative LV function, and lower long-term morbidity.<sup>97–101</sup>

Besides symptoms, the most important predictors of postoperative outcome after surgery for MR are age, AF, preoperative LV function, and the reparability of the valve.

The best results of surgery are observed in the patients with a preoperative LVEF >60%. A preoperative end-systolic diameter <45 mm (no indexed value has been validated in MR) is also closely correlated with a good postoperative prognosis.<sup>93,95–98</sup> However, a value about which postoperative LV dysfunction will not occur has not been demonstrated, rendering prediction of the postoperative dysfunction difficult in the individual patient. In addition to the initial measurements, the temporal changes of LV function should also be taken into account when making decisions about surgery. Progressive development of pulmonary hypertension is also a marker for poor prognosis.

The probability of a durable valve repair is of crucial importance.<sup>102,103</sup> Degenerative MR due to segmental valve prolapse can usually be repaired with a low risk of reoperation. The reparability of extensive prolapse, rheumatic lesions, and, even more so, MR with leaflet calcification or extensive annulus calcification is not as consistent even in experienced hands.

The results of valve repair are also highly dependent on the experience of the surgeon; this holds to be even more true as the lesions get more complex.

In current practice, surgical expertise in mitral valve repair is growing and becoming widespread since it is used in almost 50% of patients in registries in Europe<sup>3</sup> and the USA and in up to 90% in experienced centres.<sup>103</sup>

When repair is not feasible, mitral valve replacement with chordal preservation is preferred.

Recently, additional anti-arrhythmic procedures derived from the Cox maze intervention have been proposed in patients with preoperative AF to return them to and maintain sinus rhythm. The data available are still limited and the definitive role of these procedures remains to be determined.<sup>104</sup>

The first percutaneous mitral valve repairs in man have been performed using either implants introduced via the coronary sinus or stitches mimicking the Alfieri operation (edge-to-edge method) introduced transseptally.<sup>105,106</sup> Further evaluation is needed before defining the potential role of these approaches.

### Indications for intervention

Indications for surgery in severe chronic organic MR are as follows (Table 8, Figure 3):

Urgent surgery is indicated in symptomatic patients with acute MR.

**Table 8** Indications for surgery in severe chronic organic mitral regurgitation

	Class
Symptomatic patients with LVEF >30% and ESD <55 mm	IB
Asymptomatic patients with LV dysfunction (ESD >45 mm <sup>a</sup> and/or LVEF ≤60%)	IC
Asymptomatic patients with preserved LV function and atrial fibrillation or pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg at rest)	IlaC
Patients with severe LV dysfunction (LVEF <30% and/or ESD >55 mm) <sup>a</sup> refractory to medical therapy with high likelihood of durable repair, and low comorbidity	IlaC
Asymptomatic patients with preserved LV function, high likelihood of durable repair, and low risk for surgery	IIBB
Patients with severe LV dysfunction (LVEF <30% and/or ESD >55 mm) <sup>a</sup> refractory to medical therapy with low likelihood of repair and low comorbidity	IIBc

Severity is based on clinical and echocardiographic assessment. ESD = end-systolic dimension, EF = ejection fraction, LV = left ventricular, MR = mitral regurgitation.

<sup>a</sup>Lower values can be considered for patients of small stature.

Surgery is indicated in patients who have symptoms due to chronic MR, but no contraindications to surgery. Besides valve anatomy, the decision of whether to replace or repair depends very much on the surgical expertise available. When LVEF is <30%, a durable surgical repair can still improve symptoms, although the effect on survival is largely unknown. In the latter situation, the decision whether to operate will take into account the response to medical therapy, comorbidity, and the likelihood of valve repair.

The management of asymptomatic patients is an area of controversy since there are no randomized trials to support any particular course of action. On the one hand, the good results of valve repair and the potential risk of postoperative LV dysfunction are incentives for early surgery. On the other hand, even in low-risk cases, there is a small but definite risk of surgical mortality. The indications for surgery depend on risk stratification, the possibility of valve repair, and the preference of the informed patient.

Surgery can be recommended in selected asymptomatic patients with severe MR:

- Patients with signs of LV dysfunction (LVEF ≤ 60% and/or end-systolic dimension >45 mm). Surgery in this group should be considered, even in patients with a high likelihood of valve replacement. Lower end-systolic dimension values can be considered for patients of small stature.
- Patients with atrial fibrillation and preserved LV function.
- Patients with preserved LV systolic function and pulmonary hypertension.

Further proof of the validity of a strategy using the criteria cited previously, in carefully followed-up patients, has been provided by recent data showing that the use of

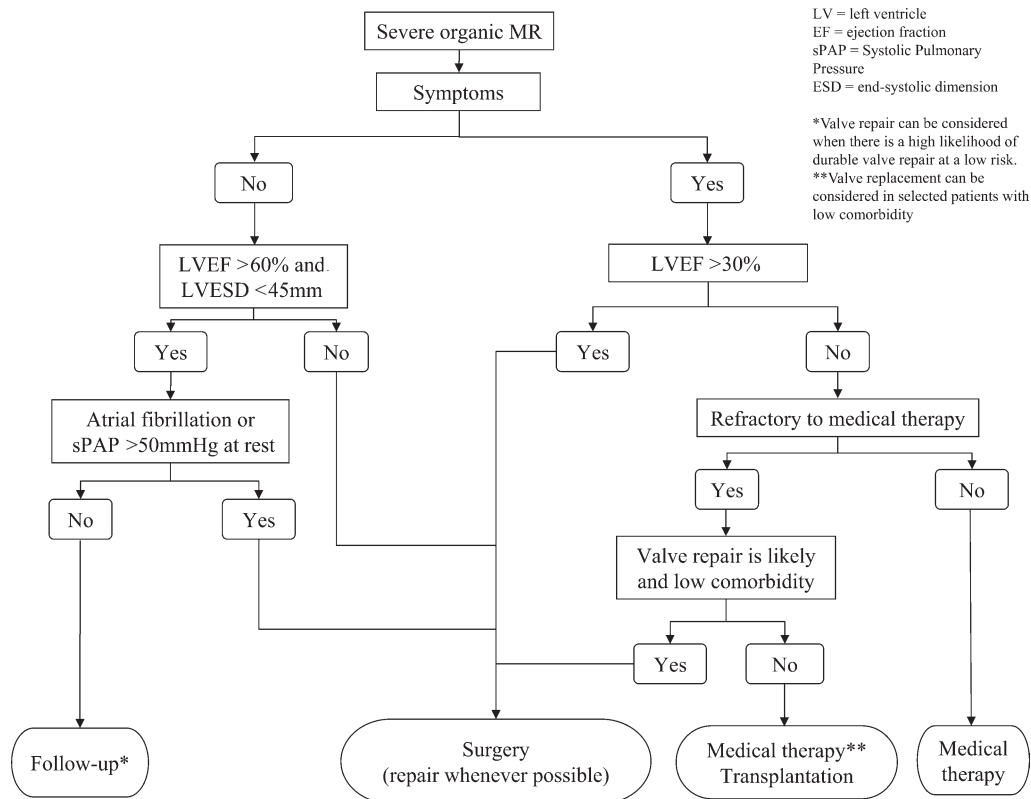


Figure 3 Management of severe chronic organic mitral regurgitation.

this strategy allows surgery at low risk and with good long-term outcome.<sup>107</sup>

Intervention is debatable in asymptomatic patients with severe MR with neither signs of LV dysfunction, nor AF, nor pulmonary hypertension. It can be considered if there is a high likelihood of valve repair on the basis of valve lesion and experience of the surgeon, and a low operative risk.

Conversely, attentive clinical follow-up is clearly recommended for patients at relatively high operative risk (e.g. elderly) or with doubt about the feasibility of valve repair. In this latter group of patients, operative risk and/or prosthetic valve complications probably outweigh the advantages of correcting MR. These patients should be reviewed carefully and surgery indicated when symptoms or objective signs of LV dysfunction occur.

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

### Medical therapy

In acute MR, reduction of filling pressures can be obtained with nitrates and diuretics. Nitroprusside reduces afterload and regurgitant fraction. Inotropic agents should be added in case of hypotension.

Anticoagulant therapy, with a target international normalized ratio (INR) range between 2 and 3, should be given in patients with MR and permanent or paroxysmal AF or whenever there is a history of systemic embolism or evidence of left atrial thrombus and during the first 3 months following mitral valve repair.<sup>108</sup>

In severe MR, maintenance of sinus rhythm after cardioversion is unlikely unless the MR is treated surgically. If AF occurs, heart rate should be controlled.

There is no evidence to support the use of vasodilators, including ACE-inhibitors, in chronic MR without heart failure and therefore they are not recommended in this group of patients.<sup>109</sup>

On the other hand, when heart failure has developed, ACE-inhibitors have a benefit and may be used in patients with advanced MR and severe symptoms who are not suitable for surgery or when there are still residual symptoms following the operation, usually as a result of impaired LV function. Beta-blockers and spironolactone should also be considered as appropriate. Endocarditis prophylaxis is also required.<sup>10</sup>

### Serial testing

Asymptomatic patients with moderate MR and preserved LV function can be clinically 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 every year, the follow-up being closer if no previous evaluation is available, and in patients with borderline values, or significant changes since the last visit. These patients should be instructed to promptly report any change in functional status.

Following valve repair, as is the case after valve replacement, it is sensible to establish a baseline for ECG, X-ray, and echocardiography so that this is available for later comparison, particularly if clinical changes occur.



## Ischaemic mitral regurgitation

Ischaemic MR is a frequent entity, which is, however, frequently overlooked in the setting of acute or chronic coronary disease.<sup>110,111</sup> Chronic ischaemic MR is the consequence of a restriction in leaflet motion, which is due to tethering by the subvalvular apparatus in patients who have LV enlargement and/or dysfunction, in particular of the posterolateral wall.

### Evaluation

Acute MR due to papillary muscle rupture should be envisaged in a patient presenting with shock during acute myocardial infarction. The murmur may even be inaudible, which stresses the importance of performing echocardiography urgently in this setting. In chronic ischaemic MR, the murmur is of low intensity, which should not lead to the conclusion that MR is trivial.

It should be remembered that ischaemic MR is a dynamic condition and its severity may vary from time to time in relation to arrhythmias, ischaemia, hypertension, or exercise. Acute pulmonary oedema may result from a large exercise-induced increase in ischaemic MR.<sup>112</sup>

Echocardiographic examination is useful for establishing the diagnosis and differentiating true ischaemic MR, where valves are normal, from organic MR in patients with coronary disease.

After myocardial infarction, ischaemic MR should be routinely looked for and Doppler assessment of MR should be done. Colour flow mapping of the regurgitant jet overestimates the severity of ischaemic MR. The use of quantitative methods adds important information. In ischaemic MR, lower thresholds of severity, using quantitative methods, have been proposed (20 mm<sup>2</sup> for ERO and 30 mL for regurgitant volume).<sup>24,110</sup>

Ischaemic MR is a dynamic disease, which makes it logical to think that stress testing is likely to play an important role in the evaluation. Preliminary studies have shown that quantitation of MR during exercise is feasible, provides a good appreciation of dynamic characteristics, and has prognostic importance.<sup>24,112-114</sup> The prognostic value of exercise tests to predict the results of surgery has, however, to be evaluated.

TEE in the operating room should not be used to decide upon treatment of MR because in some patients, the afterload reduction during surgery decreases the degree of MR.

Limited studies using low-dose dobutamine or positron emission tomography have explored preoperative myocardial viability as a predictor of outcome.<sup>115</sup>

The assessment of coronary status is of particular importance since it completes the diagnosis and allows evaluation of the revascularization options.

### Natural history

Acute MR, secondary to papillary muscle rupture, has a dismal short-term prognosis and requires urgent treatment.

Patients with chronic ischaemic MR have a poor prognosis.<sup>110</sup> Although coronary artery disease and LV dysfunction have prognostic importance, the presence and severity of MR are independently associated with increased mortality.

### Results of surgery

The data are far more limited and heterogeneous in ischaemic MR than in organic MR. Overall, surgery of ischaemic MR

remains a challenge. Operative mortality is higher than in organic MR, and long-term prognosis is less satisfactory with a higher recurrence rate of MR after valve repair.<sup>116</sup> These less favourable results are partly due to the more severe comorbidities in ischaemic MR patients.<sup>116-119</sup> If intervention is indicated, the preferred surgical procedure remains controversial. There is a trend favouring valve repair even if it carries a higher risk of mortality and of recurrence of MR than in the other aetiologies. Most patients with ischaemic MR seem to benefit from valve repair, using undersized rigid ring annuloplasty,<sup>120,121</sup> except in the most complex high-risk settings where survival after repair or replacement is similar.<sup>122</sup> Finally, the presence of significant myocardial viability is a predictor of good outcome after repair combined with bypass surgery.

Most studies show that severe ischaemic MR is not usually improved by revascularization alone.<sup>123,124</sup> There are studies that suggest that there is improved survival with valve surgery in patients with moderate ischaemic MR; however, this is still debated since these studies are not controlled and are of limited size.<sup>125</sup>

### Indications for surgery

Rupture of a papillary muscle necessitates urgent surgical treatment after stabilization of the haemodynamic status, using an intra-aortic balloon pump and vasodilators. In addition to CABG, surgery consists of valve replacement in most cases.<sup>126</sup>

The limited data in the field of ischaemic MR result in less evidence-based management (*Table 9*).

Severe MR should be corrected at the time of bypass surgery. However, there is a continuing debate on the management of moderate ischaemic MR. In such cases, valve repair is preferable and the decision must be made preoperatively, since intraoperative echocardiographic assessment underestimates the severity of ischaemic MR. In patients with low EF, surgery is more likely to be considered if myocardial viability is present and if comorbidity is low.

There are no data to support surgically correcting mild MR due to ischaemia when the patient is asymptomatic from the point of view of MR and particularly when coronary revascularization can be carried out by percutaneous coronary intervention. However, these patients should be carefully followed up to detect any later change in the degree and the consequences of ischaemic MR.

**Table 9** Indications for surgery in chronic ischaemic mitral regurgitation

	Class
Patients with severe MR, LVEF >30% undergoing CABG	IC
Patients with moderate MR undergoing CABG if repair is feasible	IIaC
Symptomatic patients with severe MR, LVEF <30% and option for revascularization	IIaC
Patients with severe MR, LVEF >30%, no option for revascularization, refractory to medical therapy, and low comorbidity	IIbC

CABG = coronary artery bypass grafting, MR = mitral regurgitation, LV = left ventricular, EF = ejection fraction.

## Functional mitral regurgitation

In this group, mitral valves are also structurally normal and MR is secondary to the changes in LV geometry resulting from impaired LV function. It includes MR observed in cardiomyopathy and in ischaemic disease with severe LV dysfunction. Evaluation is the same as in ischaemic MR.

The data on the natural history and results of surgery are even more limited than in ischaemic MR. A precise analysis is difficult because of the limited number of series including small numbers of patients and mixing patients with or without revascularization.

Several observational studies have shown the high prevalence of significant MR in chronic heart failure, as well as its independent association with a poor prognosis.<sup>127</sup> However, its true prevalence and its pathogenic contribution to prognosis remain uncertain.

The main surgical technique is restrictive annuloplasty.<sup>120,121,128,129</sup> Other techniques can be combined aiming at LV remodelling and are currently being evaluated.

Surgical treatment of MR in these patients was previously avoided owing to concerns about the high operative risk and the potential deleterious effect of increasing afterload. Opinions have changed as a result of case series from highly experienced centres reporting good results.<sup>120,121,128,129</sup> Depending on the degree of urgency, operative mortality has been reported between 5 and 18%. In patients with EF <30%, a 2 year survival rate of 70% and a 5 year survival rate of 61% have been reported with good functional results.<sup>120,121</sup> These data suggest that valve surgery using stringent restrictive annuloplasty combined with surgery of the LV may improve symptoms at an acceptable risk. However, it is not clear if surgery improves prognosis since more recent studies have shown that valve surgery does not improve survival.<sup>130,131</sup> This may be due to the fact that it may not influence LV remodelling, in particular, in patients with severe LV dilatation. In addition, little information is available on the durability of valve repair in this setting.

The limited data available suggest that isolated mitral valve surgery in combination with LV reconstruction techniques may be considered in selected patients with severe functional MR and severely depressed LV function, including those with coronary disease, where bypass surgery is not indicated, who remain symptomatic despite optimal medical therapy, and if comorbidity is low, the aim being to avoid or postpone transplantation.<sup>132,133</sup> Ongoing trials are expected to better define appropriate strategies. In the other patients, medical therapy followed by transplantation when this fails is probably the best option. However, surgery on the regurgitant mitral valve should not be considered in 'in extremis patients' with low output, severe right ventricular failure, and high comorbidity.

Medical therapy is the preferred treatment which should be used before considering surgical correction of the functionally regurgitant valve. ACE-inhibitors and beta-blockers, which may reduce MR by progressive inverse LV remodelling, are indicated. Nitrates and diuretics are useful for treating acute dyspnoea, secondary to any dynamic component.

LV dilatation, distortion, and dyssynchrony are linked to functional MR in patients with heart failure and LV dysfunction. Thus, in patients with increased QRS duration and intra-ventricular asynchrony, cardiac resynchronization

therapy may reduce MR severity and improve LV function.<sup>134</sup> Defibrillators should be used according to the appropriate recommendations.

## Mitral stenosis

### Introduction

Although the prevalence of rheumatic fever has greatly decreased in industrialized countries, MS still results in significant morbidity and mortality worldwide.<sup>2,3</sup> Since its development 20 years ago, percutaneous mitral commissurotomy (PMC) has impacted significantly upon the management of MS.<sup>135</sup>

### Evaluation

It may be difficult to evaluate precisely the functional disability in these patients who often present with a gradual decrease in activity and may feel asymptomatic for years. Physical examination, chest X-ray, and ECG establish the diagnosis in most cases and allow for initial evaluation of consequences such as atrial fibrillation and pulmonary hypertension.<sup>15</sup>

The general principles for the use of invasive and non-invasive investigations follow the recommendations made in the General comments section.

Specific issues in MS are as follows:

Echocardiography is the main method to assess the severity and consequences of MS, as well as the extent of anatomic lesions. Severity of MS should be quantified using two-dimensional planimetry and the pressure half-time method, which are complementary approaches for measuring valve area. Planimetry, when it is feasible, is the method of choice, in particular, immediately after PMC. Measurements of mean transvalvular gradient calculated using Doppler velocities are highly rate- and flow-dependent; however, they are useful to check consistency of the assessment of severity, in particular, in patients in sinus rhythm.<sup>136</sup> MS usually does not have clinical consequences at rest when valve area is >1.5 cm<sup>2</sup>, except in patients with particularly large body size.

The assessment of valve morphology is important for the selection of candidates for PMC. Scoring systems have been developed to assess suitability, taking into account valve thickening, mobility, calcification, subvalvular deformity, and commissural areas<sup>135,137,138</sup> (Tables 10, 11).

Echocardiography also evaluates pulmonary artery pressures, the presence of associated MR, concomitant valve disease, and the size of the left atrium.

The transthoracic approach usually provides sufficient information for routine management. However, transoesophageal examination should also be performed to exclude left atrial thrombosis before PMC or after an embolic episode or if transthoracic echocardiography provides suboptimal information on anatomy or associated MR.

In patients with no or doubtful symptoms, stress testing aids decision-making by unmasking symptoms. Exercise echocardiography provides other information by assessing the evolution of mitral gradient and pulmonary pressures.<sup>139</sup> Its additional value for decision-making has to be further defined.

**Table 10** Anatomic scores predicting outcome after percutaneous mitral commissurotomy: Wilkins' mitral valve morphology score<sup>137</sup>

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

**Table 11** Anatomic scores predicting outcome after percutaneous mitral commissurotomy: Cormier's grading of mitral valve anatomy<sup>142</sup>

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

Echocardiography also plays an important role in monitoring the results of PMC during the procedure and in evaluating the final results at least 24 h after its completion.

### Natural history

Studies on natural history are old and non-controlled. In asymptomatic patients, survival was good up to 10 years, progression being highly variable with sudden deterioration, precipitated by complications, such as atrial fibrillation or embolism, in half of the patients.<sup>140,141</sup> Symptomatic patients have a poor prognosis.

### Results of intervention

#### Percutaneous balloon commissurotomy

PMC usually provides at least a 100% increase in valve area. Good initial results are usually defined by a valve area  $>1.5$  cm<sup>2</sup> without more than mild MR. Technical success and complications are related to the condition of the patient and the team's experience.<sup>142–145</sup> Failure rates range from 1 to 15%. Major complications rates are as follows: procedural mortality, 0.5–4%; haemopericardium, 0.5–10%; embolism, 0.5–5%; severe regurgitation, 2–10%. Emergency surgery is seldom needed (<1%).

Clinical follow-up data confirm the late efficacy of PMC since event-free survival ranges from 35 to 70% after 10–15 years, depending on patient characteristics.<sup>135,144,145</sup> When the immediate results are unsatisfactory, surgery is usually required in the following months. Conversely, after successful PMC, long-term results are good in the majority of cases. When functional deterioration occurs, it is late and mainly related to re-stenosis. Successful PMC has also been shown to reduce embolic risk. The prediction of long-term results is related to preoperative anatomic and clinical characteristics and to the quality of the immediate results.<sup>135,145</sup> Identification of the variables linked to outcome has enabled predictive models to be developed with a high sensitivity; however, their specificity is low, indicating insufficient prediction of poor immediate results.

### Surgery

#### Conservative surgery

In industrialized countries, closed mitral valve commissurotomy has been replaced by open-heart mitral commissurotomy using cardiopulmonary bypass, which not only corrects commissural fusion but also acts on subvalvular deformity. In selected series from experienced centres, mostly including young patients, long-term results are good: at 15 years, survival was 96%, and freedom from valve-related complications 92%.<sup>146</sup> The recent Euro Heart Survey shows that in current practice, open-heart commissurotomy is seldom performed.<sup>3</sup>

#### Valve replacement

Operative mortality ranges between 3 and 10% and correlates with age, functional class, pulmonary hypertension, and presence of coronary artery disease. Long-term survival is related to age, functional class, atrial fibrillation, pulmonary hypertension, preoperative LV function, and complications of the prosthetic valve, especially thromboembolism and haemorrhage or structural deterioration.<sup>147</sup>

### Indications for intervention

Type of treatment, as well as its timing, should be decided on the basis of clinical characteristics (including functional status and predictors of operative risk and of the results of PMC),

**Table 12** Indications for percutaneous mitral commissurotomy in mitral stenosis with valve area < 1.5 cm<sup>2</sup>

	Class
Symptomatic patients with favourable characteristics <sup>a</sup> for PMC	IB
Symptomatic patients with contraindication or high risk for surgery	IC
As initial treatment in symptomatic patients with unfavourable anatomy but otherwise favourable clinical characteristics <sup>a</sup>	IlaC
Asymptomatic patients with favourable characteristics <sup>a</sup> and high thrombo-embolic risk or high risk of haemodynamic decompensation:	
Previous history of embolism	IlaC
Dense spontaneous contrast in the left atrium	IlaC
Recent or paroxysmal atrial fibrillation	IlaC
Systolic pulmonary pressure > 50 mmHg at rest	IlaC
Need for major non-cardiac surgery	IlaC
Desire of pregnancy	IlaC

PMC = percutaneous mitral commissurotomy.

<sup>a</sup>Favourable characteristics for PMC can be defined by the absence of several of the following:

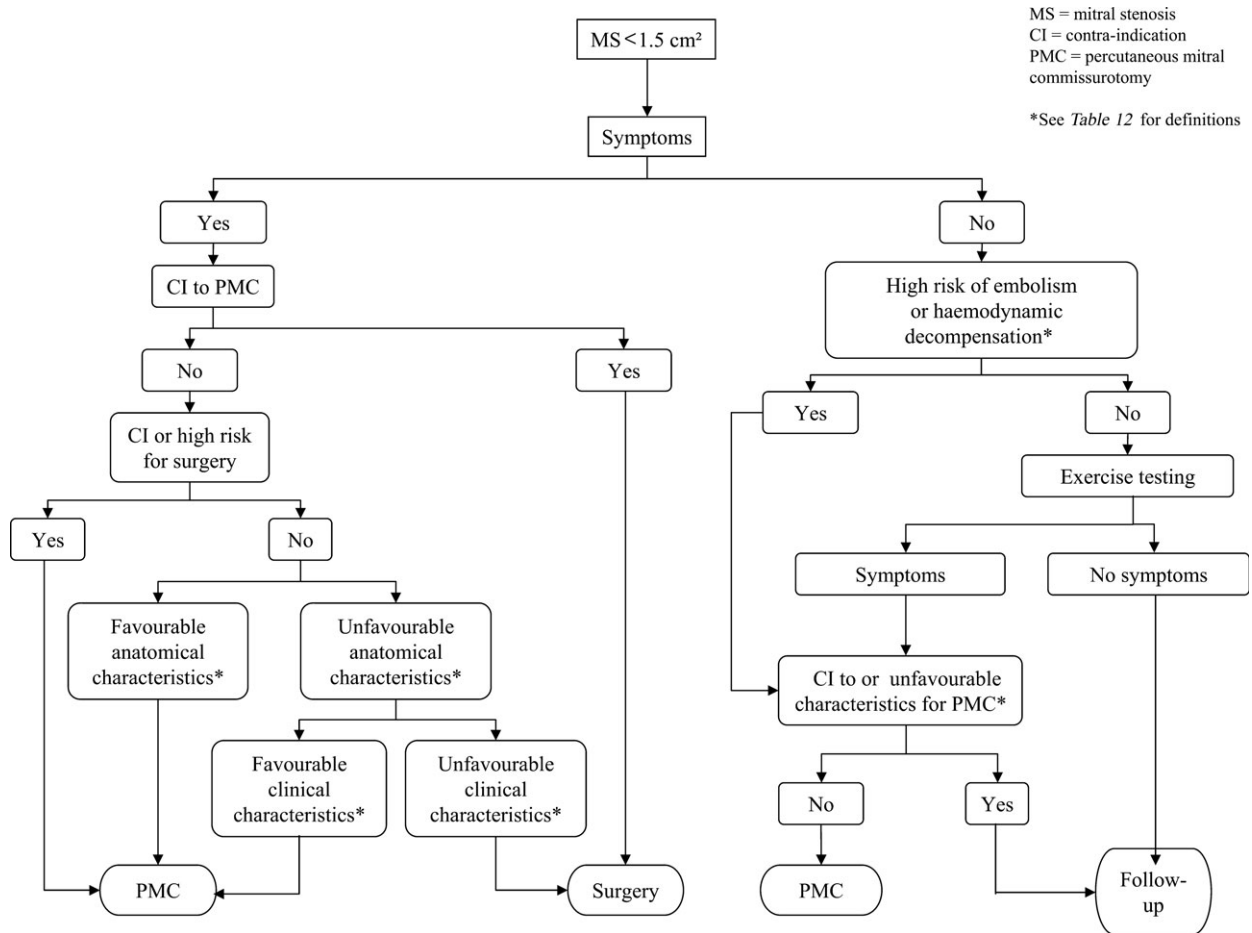
- *Clinical characteristics:* old age, history of commissurotomy, NYHA class IV, atrial fibrillation, severe pulmonary hypertension,
- *Anatomic characteristics:* echo score >8, Cormier score 3 (Calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, severe tricuspid regurgitation.

valve anatomy, and local expertise and availability in the fields of PMC and surgery.

Indications for intervention are as follows (Table 12, Figure 4):

Intervention should only be performed in patients with clinically significant MS (valve area <1.5 cm<sup>2</sup> or <1.7-1.8 cm<sup>2</sup> in particular in cases of unusually large patients).<sup>5,13</sup>

Intervention should be performed in symptomatic patients. In the PMC era, most symptomatic patients with favourable valve anatomy undergo PMC. However, open commissurotomy may be performed by experienced operators in young patients with no or mild calcification and mild-to-moderate MR. PMC is the procedure of choice when surgery is contraindicated or high risk, or for patients with favourable characteristics. Indications are a matter of debate for patients with unfavourable anatomy. Decision-making in this heterogeneous group of patients must take into account the multifactorial nature of result prediction of PMC and the relative experience in PMC and surgery of the treating centre.<sup>135,144,145</sup> In current practice in Europe, surgery for MS is mostly valve replacement.<sup>3</sup> PMC can be offered as initial treatment for selected patients with mild-to-moderate calcification or impairment of the subvalvular apparatus, who have otherwise favourable clinical characteristics, in particular, in young patients in whom



MS = mitral stenosis  
 CI = contra-indication  
 PMC = percutaneous mitral commissurotomy  
 \*See Table 12 for definitions

**Figure 4** Management of severe mitral stenosis. Patients at high risk of embolism or haemodynamic decompensation are defined by previous history of embolism, dense spontaneous contrast in the left atrium, recent or paroxysmal atrial fibrillation, systolic pulmonary pressure >50 mmHg at rest, need for major non-cardiac surgery, desire of pregnancy.

postponing valve replacement is particularly attractive. In the other patients, surgery is preferable.

Because of the small but definite risk inherent in PMC, truly asymptomatic patients are not usually candidates for the procedure, except in the cases where there is increased risk of thrombo-embolism or of haemodynamic decompensation such as severe pulmonary hypertension or a desire for pregnancy. In such patients, PMC should only be performed if they have favourable characteristics and by experienced operators.

In asymptomatic patients with MS, because of the inherent risks, surgery is seldom considered and is limited to the rare patients at high risk of complications and with contraindications for PMC.

Surgery is the only alternative when PMC is contraindicated (Table 13). The most important contraindication is left atrial thrombosis. A contraindication is self-evident if the thrombus is localized in the cavity. When the thrombus is localized in the left atrial appendage, the indications for PMC are limited to patients with contraindications to surgery or those without urgent need for intervention when oral anticoagulation can be given for a minimum of 2 months and a maximum of 6 months and provided a new TEE examination shows the disappearance of the thrombus.<sup>148</sup> If the thrombus persists, surgery is preferred.

Intraoperative correction of AF can be combined with valve surgery in selected cases; the benefit of this approach, however, requires further validation.

## Medical therapy

Diuretics or long-acting nitrates transiently ameliorate dyspnoea. Beta-blockers or heart-rate regulating calcium channel blockers are useful to slow the heart rate and can greatly improve exercise tolerance by prolonging diastole and hence the time available for LV filling via the stenosed valve. Anticoagulant therapy with a target INR in the upper half of the range 2–3 is indicated in patients with either permanent or paroxysmal AF.<sup>108</sup> In patients with sinus rhythm, anticoagulation is mandatory when there has been prior embolism or a thrombus is present in the left atrium (Recommendation class I, Level of evidence C), and recommended when TEE shows dense spontaneous echo contrast or in patients who have an enlarged left atrium (diameter >50 mm) (Recommendation class IIa, Level of evidence C).<sup>12,13</sup>

Cardioversion is not indicated before intervention in patients with severe MS, as it does not usually restore

**Table 13** Contraindications to percutaneous mitral commissurotomy

Mitral valve area >1.5 cm <sup>2</sup>
Left atrial thrombus
More than mild MR
Severe- or bicommissural calcification
Absence of commissural fusion
Severe concomitant aortic valve disease or severe combined TS and TR
Concomitant coronary artery disease requiring bypass surgery

MR = mitral regurgitation, TR = tricuspid regurgitation, TS = tricuspid stenosis.

sinus rhythm in the medium or long term. If atrial fibrillation is of recent onset and the left atrium only moderately enlarged, cardioversion should be performed soon after successful intervention. Sinus rhythm can be maintained with the use of class IC or III anti-arrhythmic drugs.

Infective endocarditis prophylaxis is indicated.<sup>10</sup> In countries with a high prevalence of rheumatic disease, rheumatic fever prophylaxis should be given to young patients and be continued after conservative intervention until adult age.

## 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 in cases with stenosis of a lesser degree.

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

## Special patient populations

When re-stenosis with symptoms occurs after surgical commissurotomy, reoperation in most cases requires valve replacement. PMC can be considered in such patients if they have favourable characteristics and no contraindications and if the predominant mechanism of re-stenosis is commissural re-fusion.<sup>149</sup>

Similarly, repeat PMC can be proposed in selected patients with the same characteristics as mentioned earlier if re-stenosis occurs several years after an initially successful PMC. In patients who present with valve anatomy that is not ideal for PMC but who are not surgical candidates, repeat PMC may have a palliative role.

For information on MS during pregnancy, see Management of pregnancy section.

In the elderly, when surgery is high risk or contraindicated, 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 if not contraindicated.<sup>150,151</sup>

In patients with MS combined with severe aortic valve disease, surgery is usually preferable. In cases of coexisting MS and moderate aortic valve disease, PMC can be performed as a means of postponing the surgical treatment of both valves. PMC can be attempted in patients with severe MS and severe functional tricuspid regurgitation (TR). In the others, with severe organic disease of the tricuspid valve, surgery on both valves may be preferred.

## Tricuspid disease

### Tricuspid stenosis

Tricuspid stenosis (TS), which is almost exclusively of rheumatic origin, is rarely observed in developed countries, although it is still seen in developing countries.<sup>2,4</sup> Detection requires careful evaluation, as it is almost always associated with left-sided valve lesions that dominate the presentation.

## Evaluation

Clinical signs are often masked by those of the associated valvular lesions, especially MS.<sup>15</sup> Echocardiography provides the most useful information. TS is often overlooked and requires careful evaluation. The pressure half-time method has never been validated for the tricuspid valve and the continuity equation is rarely applicable because of the frequency with which associated regurgitation is present. Planimetry of the valve area is usually impossible unless three-dimensional echocardiography is used. No generally accepted grading of TS severity exists. A mean gradient >5 mmHg is considered indicative of clinically significant TS.<sup>17</sup> 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 reparability, and the degree of concomitant regurgitation.

## Surgery

The lack of pliable leaflet tissue is the main limitation for conservative techniques.

For valve replacement, even though this is still a matter of debate, biological prostheses are usually preferred to 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.<sup>152–154</sup>

## Percutaneous intervention

Percutaneous balloon tricuspid dilatation has been performed in a limited number of cases, either alone or alongside PMC, but frequently induces significant regurgitation. Data on evaluation of long-term results are lacking.<sup>155,156</sup>

## 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<sup>76</sup> (Table 14).

## Medical therapy

In the presence of heart failure, diuretics are useful but of limited efficacy. Endocarditis prophylaxis should be given as appropriate.<sup>10</sup>

## Tricuspid regurgitation

Trivial TR is frequently detected by echocardiography in normal subjects. Pathological TR is more often functional rather than due to a primary valve lesion. Functional TR is due to annular dilatation and secondary to right ventricular 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, idiopathic pulmonary artery hypertension, and right ventricular volume overload possibly relating to atrial septal defects or intrinsic disease of the right ventricle.<sup>157,158</sup>

**Table 14** Indications for intervention in tricuspid valve disease

	Class
Severe TR in a patient undergoing left-sided valve surgery	IC
Severe primary TR and symptoms despite medical therapy without severe right ventricular dysfunction	IC
Severe TS ( $\pm$ TR), with symptoms despite medical therapy <sup>a</sup>	IC
Severe TS ( $\pm$ TR) in a patient undergoing left-sided valve intervention <sup>a</sup>	IC
Moderate organic TR in a patient undergoing left-sided valve surgery	IIaC
Moderate secondary TR with dilated annulus (>40 mm) in a patient undergoing left-sided valve surgery	IIaC
Severe TR and symptoms, after left-sided valve surgery, in the absence of left-sided myocardial, valve, or right ventricular dysfunction and without severe pulmonary hypertension (systolic pulmonary artery pressure > 60 mmHg)	IIaC
Severe isolated TR with mild or no symptoms and progressive dilation or deterioration of right ventricular function	IIbC

TR = tricuspid regurgitation, TS = tricuspid stenosis.

<sup>a</sup>Percutaneous technique can be attempted as a first approach if TS is isolated.

## Evaluation

Predominant symptoms are those of associated diseases and even severe TR may be well tolerated for a long period of time. Although they are load dependent, clinical signs of right heart failure are of value in evaluating the severity of TR.<sup>15</sup>

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

- Structural abnormalities of the valve distinguishing between its functional and primary forms. In the latter form, the aetiology can usually be identified from specific abnormalities such as vegetations in endocarditis,<sup>159</sup> leaflet retraction in rheumatic and carcinoid, and flail leaflet in myxomatous or post-traumatic disease. The degree of dilatation of the annulus should also be measured.
- Semi-quantitative evaluation of TR severity should be based on the proximal convergence zone, proximal jet width, dilatation of the inferior vena cava, and reduction or reversal of systolic blood flow in the hepatic veins<sup>19,160</sup> (Table 2). It is important that this assessment should integrate the quantitative data and the parameters evaluating the consequences of TR, taking into account the sensitivity of the different indices to loading conditions.<sup>19</sup> The criteria for defining severe TR are described in Table 2.
- Evaluation of the right ventricle, despite existing limitations of any assessment of right ventricular function.
- Measurement of peak right ventricular systolic pressure as an estimate of pulmonary pressure by measuring peak tricuspid regurgitant velocity.
- Assessment of the degree of the combined lesions, looking carefully at the LV and the associated valve lesions, particularly on the left side, and LV function.

When available, MRI may provide additional useful information on the size and function of the right ventricle, which is difficult to evaluate using other imaging techniques.

### 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.

Functional TR may diminish or disappear as right ventricular 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.<sup>157</sup> Pulmonary hypertension, increased right ventricular pressure and dimension, reduced right ventricular function, and the diameter of the tricuspid annulus are important risk factors for persistence or late worsening of TR.<sup>161,162</sup> However, TR may persist even after successful correction of left-sided lesions.

### Results of surgery

Annuloplasty is key to conservative surgery. Better long-term results are observed with prosthetic rings than with the stitch technique, the incidence of residual TR being, respectively, 10 and 20–35% at 5 years.<sup>158,161,163</sup> Valve replacement carries a risk of operative mortality ranging from 7 to 40%. Ten year survival ranges from 30 to 50%, the predictors being preoperative functional class, LV function and right ventricular function, and prosthetic complications.<sup>152–154</sup> The current experience favours the use of large bioprostheses over mechanical valves.

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 patients (including age and the number of previous cardiac interventions) and may well have poor long-term results related to the presence of irreversible right ventricular dysfunction prior to reoperation.

### Indications for surgery

The timing of surgical intervention and the appropriate technique remain controversial mostly due to the limited data available and their heterogeneous nature (Table 14).

As general principles, we can say, if technically possible, conservative surgery is preferable to valve replacement, and surgery should be carried out early enough to avoid irreversible right ventricular dysfunction.

The possible need for correction of TR is usually considered at the time of surgical correction of left-sided valvular lesions. In these circumstances, the relative simplicity of tricuspid valve repair and the high risk of secondary surgical correction are incentives to earlier indications for tricuspid repair. In these circumstances, severe TR should be corrected. In the other cases with lesser degree of TR, surgical correction can be recommended when there is pulmonary hypertension or severe dilatation of the annulus<sup>161,162</sup> (diameter >40 mm or >21 mm/m<sup>2</sup> BSA) and, even more so, if TR is of organic origin. Finally, mild TR does not warrant intervention.

Surgery limited to the tricuspid valve can be required in patients with severe primary TR resulting from endocarditis or trauma who remain symptomatic or in those with no or

mild symptoms who have objective signs of significant impairment of right ventricular function.

In the particular circumstances of persistent or recurrent severe TR despite medical therapy after mitral valve surgery, isolated operation on the tricuspid valve should be considered in the absence of left-sided valve, myocardial, or severe right ventricular dysfunction.

### Medical therapy

Diuretics improve signs of congestion. Specific therapy of the underlying disease is warranted.

## Combined and multiple valve diseases

The data on mixed and multiple valve diseases are lacking and do not allow for evidence-based recommendations. In addition, the large number of combinations possible leads to the necessity of individualized decisions in this domain.

Significant stenosis and regurgitation can be found on the same valve. Such combined VHDs are encountered in rheumatic valve disease and, less frequently, in degenerative valve disease. When stenosis or regurgitation is largely predominant, the management follows the recommendations concerning the predominant VHD. When the severity of both stenosis and regurgitation is balanced, indications for interventions should be based on how well the patient tolerates the combined VHD rather than indices of severity of stenosis or regurgitation. Intervention can be considered when a non-severe stenosis is combined with a non-severe regurgitation in patients who have symptoms or in whom it is clear the combined lesion is leading to LV impairment. Intervention is nearly always prosthetic valve replacement in this setting.

Disease of multiple valves may be encountered in several conditions but particularly rheumatic heart disease. Besides the separate assessment of each separate valve lesion, it is necessary to take into account the interaction between the different valve lesions. As an illustration, associated MS may lead to underestimation of the severity of AS, since decreased stroke volume due to MS 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. Associated MR and AR can be encountered, in particular, in Marfan's syndrome. In these patients, besides severity, the assessment of valve anatomy is of importance to evaluate the possibility of conservative surgery on each valve.

Indications for intervention are based on global assessment of the consequences of the different valve lesions, i.e. symptoms or consequences on LV dimensions and function. In addition, 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. For example, the desire to repair one valve may be decreased if prosthetic valve replacement is needed on another valve. The management of other specific associations of VHD is detailed in the individual sections.

## Prosthetic valves

Patients who have undergone previous valve surgery represent an important proportion of patients with VHD, accounting for 28% of all patients with VHD in the Euro Heart Survey.<sup>3</sup> The extent of prosthesis-related complications in patient outcome after surgery emphasizes the importance of optimizing the choice of the valve substitute as well as the subsequent management of patients with prosthetic valves.

### Choice of prosthetic valve

There is no perfect valve substitute. All involve some compromise and all introduce new disease processes, whether they are mechanical or biological. The latter include xenografts, homografts, and autografts. Autografts and homografts in the aortic position provide the best effective orifice area (EOA). Stentless bioprostheses provide better EOA than stented bioprostheses, which are relatively stenotic in the small sizes (annulus size  $\leq 21$  mm). Modern mechanical valves provide better haemodynamic performance than stented bioprostheses.

All mechanical valves require long-term anticoagulation. Biological valves are less thrombogenic and do not require long-term anticoagulation unless there are other indications, e.g. persistent atrial fibrillation. However, all are subject to structural valve deterioration (SVD) over time.

Two randomized trials, which began in the 1970s, comparing now obsolete models of mechanical and bioprosthetic valves found no significant difference in rates of valve thrombosis and thrombo-embolism, in accordance with numerous individual valve series in the literature. Long-term survival was also very similar.<sup>147,164</sup> A recent meta-analysis of mechanical and bioprosthetic valve series found no difference in survival when age and risk factors were taken into account.<sup>165</sup>

Apart from haemodynamic considerations, choice between a mechanical valve and a bioprosthesis in adults is thus determined primarily by assessing the risk of anticoagulant-related bleeding with a mechanical valve vs. the risk of SVD with a bioprosthesis.<sup>166,167</sup> The former is determined mainly by the target INR chosen, the quality of anticoagulation control, the concomitant use of aspirin, and the patient's own risk factors for bleeding.<sup>168</sup> The risk of SVD must take into account the gradual deterioration in performance status with increasing SVD, the risk of re-operation and length of the recovery period after subsequent surgery.

Homografts and pulmonary autografts are mainly used in the aortic position, though even here they together account for less than 0.5% of aortic valve replacements in most large databases. Like bioprostheses, homografts are subject to SVD.<sup>169</sup> Besides technical concerns, limited availability and increased complexity of reoperation contribute to restrict the use of homografts to complicated aortic valve endocarditis.

Although the pulmonary autograft in the aortic position (Ross operation) provides excellent haemodynamics, it requires specific expertise and has several disadvantages: the risk of SVD in the homograft in the pulmonary position, the risk of moderate AR due to dilatation of the aortic root, and the risk of rheumatic involvement. Apart from short-term advantages in selected young adults, such as

professional athletes, the main advantage of the autograft is in growing children, as the valve and new aortic annulus appear to grow with the child.<sup>170</sup> However, the homograft pulmonary valve replacement does not and, therefore, usually needs replacement as the child gets bigger.

In practice, the choice is between mechanical prosthesis and bioprosthesis in most patients. Rather than setting arbitrary age limits, prosthesis choice should be individualized<sup>167</sup> and discussed in detail with the patient, taking into account the following factors (*Tables 15, 16*):

- (1) Life expectancy should be estimated according to country and patient's age, and take into account comorbidities.
- (2) A mechanical valve should be recommended if a mechanical valve is implanted on another valve and should

**Table 15** Choice of the prosthesis: in favour of mechanical prosthesis<sup>a</sup>

	Class
Desire of the informed patient and absence of contraindication for long-term anticoagulation	IC
Patients at risk of accelerated SVD <sup>b</sup>	IC
Patient already on anticoagulation because of other mechanical prosthesis	IC
Patients already on anticoagulation because at high risk for thrombo-embolism <sup>c</sup>	IIaC
Age <65–70 and long life expectancy <sup>d</sup>	IIaC
Patients for whom future redo valve surgery would be at high risk (due to LV dysfunction, previous CABG, multiple valve prosthesis)	IIaC

CABG = coronary artery bypass grafting, LV = left ventricular, SVD = structural valve deterioration.

<sup>a</sup>The decision is based on the integration of several of the factors given in the table.

<sup>b</sup>Young age, hyperparathyroidism.

<sup>c</sup>Risk factors for thrombo-embolism: severe LV dysfunction, atrial fibrillation, previous thrombo-embolism, hypercoagulable state.

<sup>d</sup>According to age, gender, the presence of comorbidity, and country-specific life expectancy.

**Table 16** Choice of the prosthesis: in favour of bioprosthesis<sup>a</sup>

	Class
Desire of the informed patient	IC
Unavailability of good-quality anticoagulation (contraindication or high risk, unwillingness, compliance problems, lifestyle, occupation)	IC
Re-operation for mechanical valve thrombosis in a patient with proven poor anticoagulant control	IC
Patient for whom future redo valve surgery would be at low risk	IIaC
Limited life expectancy <sup>b</sup> , severe comorbidity, or age >65–70	IIaC
Young woman contemplating pregnancy	IIbC

<sup>a</sup>The decision is based on the integration of several of the factors given in the table.

<sup>b</sup>According to age, gender, the presence of comorbidity, and country-specific life expectancy.



be also considered if the patient is already on anticoagulants for another reason.

- (3) If there are definite contraindications to anticoagulation or the patients' lifestyle exposes them to frequent injury, a biological substitute should be recommended.<sup>171,172</sup>
- (4) SVD occurs more rapidly in young patients and in case of hyperparathyroidism, including renal failure.<sup>173</sup> Bioprostheses should be avoided if possible before the age of 40. SVD progresses more slowly in elderly patients but this conclusion is based upon reports of lower rates of re-operation, often without taking into account those patients with SVD who are too frail to undergo re-operation. Bioprostheses should be recommended in patients whose life expectancy is lower than the presumed durability of the bioprosthesis, particularly if comorbidities will necessitate other surgical procedures in the future, 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.<sup>174</sup>
- (5) In women of childbearing age who wish to become pregnant, choice between mechanical and bioprosthetic valves depends on a balance of risks, both for the mother and the foetus. Using warfarin in a dose of 5 mg/day or less throughout pregnancy until the 36th week minimizes the risk of both foetal malformation and maternal valve thrombosis.<sup>175</sup> On the other hand, although SVD occurs rapidly in this age group, the risk of reoperation is relatively low (if surgery is not required in an emergency during pregnancy) and compares favourably with the risk of a pregnancy under anticoagulant therapy.
- (6) Quality of life issues must also be taken into account. Inconvenience of oral anticoagulation can be minimized by home monitoring and self-management of anticoagulation.<sup>176</sup> Although bioprosthetic recipients can avoid long-term anticoagulation, they face the possibility of deterioration in functional status owing to SVD and the prospect of reoperation if they live long enough.

### Management after valve replacement

Thrombo-embolism and anticoagulant-related bleeding together account for ~75% of complications experienced by prosthetic valve recipients and most space is therefore devoted to this topic. Endocarditis prophylaxis and management of prosthetic valve endocarditis are detailed in separate ESC Guidelines devoted to endocarditis.<sup>10</sup> A more comprehensive review of management after valve surgery is available in a previous Special ESC article.<sup>14</sup>

### Baseline assessment and modalities of follow-up

A complete baseline assessment should be ideally performed 6–12 weeks after surgery. If for practical reasons this outpatient evaluation cannot be organized, it could be done at the end of the postoperative stay. This will include clinical assessment, chest X-ray, ECG, transthoracic echocardiography, and blood testing. This reference assessment is of utmost importance to interpret subsequent changes in murmur, prosthetic sounds, as well as ventricular function

and transprosthetic gradients as assessed by Doppler echocardiography. This postoperative visit is also useful to improve patient education on endocarditis prophylaxis and, if needed, on anticoagulant therapy, as well as emphasizing 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 progression of disease in a further heart valve. Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. Transthoracic echocardiography 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 bioprosthesis. Transprosthetic gradients during follow-up are best interpreted in comparison with the baseline values in the same patient, rather than in comparison with theoretical values for a given prosthesis, which lack reliability. TEE should be considered if transthoracic echocardiography is of poor quality and in all cases of suspected prosthetic dysfunction or endocarditis. Cinefluoroscopy can provide useful additional information if valve thrombus or pannus is suspected.<sup>14</sup>

### Antithrombotic management

#### General management

Antithrombotic management should encompass the effective management of risk factors for thrombo-embolism in addition to the prescription of antithrombotic drugs.<sup>177,178</sup>

Oral anticoagulation is recommended for the following situations:

- Lifelong for all patients with mechanical valves.<sup>5,14,178</sup>
- Lifelong for patients with bioprostheses who have other indications for anticoagulation, e.g. atrial fibrillation, or with a lesser degree of evidence, e.g. heart failure, impaired LV function (EF <30%).
- For the first 3 months after insertion in all patients with bioprostheses with a target INR of 2.5. However, there is widespread use of aspirin (low dose: 75–100 mg) as an alternative to anticoagulation for the first 3 months, but there are no randomized studies to support the safety of this strategy.<sup>179</sup>

Although there is no consensus regarding the initiation of anticoagulant therapy immediately after valve replacement, oral anticoagulation should be started during the first postoperative days. Intravenous heparin enables effective anticoagulation to be obtained before the INR rises.

The first postoperative month is a particularly high-risk period for thrombo-embolism, and anticoagulation should avoid being lower than the target value during this period.<sup>180</sup> In addition, anticoagulation should be monitored more frequently during this period.

#### Target INR

The choice of optimum INR should take into account 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 17*). Reported thrombo-embolic rates do not provide sufficient

**Table 17** Target international normalized ratio for mechanical prostheses

Prosthesis thrombogenicity <sup>a</sup>	Patient-related risk factors <sup>b</sup>	
	No risk factor	≥ 1 Risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

LVEF = left ventricular ejection fraction, MS = mitral stenosis.

<sup>a</sup>Prosthesis thrombogenicity: Low = Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without Silzone); Medium = Bjork-Shiley, other bileaflet valves; High = Lillehei-Kaster, Omniscience, Starr-Edwards.

<sup>b</sup>Patient-related risk factors: mitral, tricuspid, or pulmonary valve replacement; previous thrombo-embolism; atrial fibrillation; left atrial diameter > 50 mm; left atrial dense spontaneous contrast; MS of any degree; LVEF < 35%; hypercoagulable state.

guidance about individual prosthesis thrombogenicity, as they are heavily influenced by so many other patient-related factors and the methods of data collection. Unfortunately, currently available randomized trials comparing different INRs offer little general guidance owing to limitations imposed by their selection criteria, small numbers of patients with short follow-up, and varied methodologies, making them unsuitable for meta-analysis.<sup>181,182</sup>

In selecting the optimum INR, certain caveats apply:

- Prostheses cannot be conveniently categorized by basic design (e.g. bileaflet, tilting disc, etc.) or date of introduction for the purpose of determining thrombogenicity.
- For many currently available prostheses, particularly newly introduced prostheses, sufficient data on valve thrombosis rates at different levels of INR do not exist to allow categorization. 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 from a source not amenable to treatment, or revised upwards in case of embolism.

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

The risk of major bleeding rises considerably when the INR exceeds 4.5, and exponentially above an INR of 6.0. An INR of ≥ 6.0 therefore requires reversal of anticoagulation. However, in patients with prosthetic valves who are not bleeding, intravenous vitamin K should not be used because of the risk of valve thrombosis if the INR falls rapidly. The patient should be admitted to hospital, the oral anticoagulant stopped, and the INR allowed to fall gradually. Spontaneous fall in the INR after anticoagulant cessation occurs more slowly in the elderly and in the presence of heart failure.<sup>183</sup> It is permissible to use oral vitamin K, given in increments of 1 mg, in patients who are treated using long half-life vitamin K blockers such as phenprocoumon. If the INR is > 10.0, consideration should be given to the use of fresh frozen plasma. Reversal of anticoagulation should be more aggressive, using fresh frozen plasma and adapted doses of intravenous vitamin K,<sup>184</sup> if there is active bleeding

not amenable to local control. Bleeding with a therapeutic INR is often related to an underlying pathological cause and it is important to identify and treat it.

High variability of the INR is the strongest independent predictor of reduced survival after valve replacement.<sup>168</sup> Self-management of anticoagulation has been shown to reduce INR variability and should therefore be recommended in all patients who, after education and training, have the ability to control their own anticoagulation.<sup>176</sup>

#### 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 vascular disease and those specific to prosthetic valves. Trials showing a benefit from antiplatelet drugs in vascular disease<sup>185</sup> and in patients with prosthetic valves and vascular disease<sup>186</sup> should not be taken as evidence that patients with prosthetic valves and no vascular disease will also benefit. When added to anticoagulation, antiplatelet agents increase the risk of major bleeding.<sup>185-191</sup> They should therefore not be prescribed for all patients with prosthetic valves, but reserved for specific indications, according to the analysis of the benefit and the increased risk of major bleeding.

Indications for the addition of an antiplatelet agent to anticoagulation include concomitant arterial disease, in particular, coronary disease and other significant atherosclerotic disease. Antiplatelet agents can also be added after recurrent or one definite embolic episode with adequate INR. Addition of antiplatelet agents should be associated with a full investigation and treatment of identified risk factors and optimization of anticoagulation management (Recommendation class IIa, Level of evidence C).

Addition of aspirin and clopidogrel is necessary following intracoronary stenting but increases bleeding risk.<sup>192,193</sup> The use of drug-eluting stents should be restricted in patients with mechanical prostheses to shorten as much as possible the use of triple antithrombotic therapy. During this period, weekly monitoring of INR is advised and any over-anticoagulation should be avoided.

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

#### Interruption of anticoagulant therapy

Although most instances of short-term anticoagulation interruption do not lead to thrombo-embolism or valve thrombosis, the corollary is that most cases of valve thrombosis occur following a period of anticoagulation interruption for bleeding or another operative procedure.<sup>194</sup> Anticoagulation management during subsequent non-cardiac surgery therefore requires very careful management on the basis of risk assessment.<sup>177,195,196</sup> Besides prosthesis- and patient-related prothrombotic factors (Table 17), surgery for malignant disease or an infective process carries a particular risk, due to the hypercoagulability associated with these conditions. For very high-risk patients, anticoagulation interruption should be avoided if at all possible. Many minor surgical procedures (including dental extraction) and those where bleeding is easily controlled do not require anticoagulation interruption. The INR should be

lowered to a target of 2.0.<sup>197,198</sup> (Recommendation class I, Level of evidence B).

For major surgical procedures, in which anticoagulant interruption is considered essential (INR <1.5), patients should be admitted to hospital in advance and transferred to intravenous unfractionated heparin (Recommendation class IIa, Level of evidence C). Heparin is stopped 6 h before surgery and resumed 6–12 h after. Low molecular weight heparin (LMWH) can be given subcutaneously as an alternative preoperative preparation for surgery (Recommendation class IIb, Level of evidence C). However, despite their wide use and the positive results of observational studies,<sup>199–201</sup> the safety of LMWHs in this situation has not been widely established and their efficacy has not been proved by controlled studies, particularly in patients at high risk of valve thrombosis. When LMWHs are used, they should be administered twice a day, using therapeutic rather than prophylactic doses, adapted to body weight and if possible according to monitoring of anti-Xa activity. LMWHs are contraindicated in case of renal failure.

Despite the low level of evidence for both strategies, the committee favours the use of unfractionated intravenous heparin.

Effective anticoagulation should be resumed as soon as possible after the surgical procedure and maintained until the INR is once again in the therapeutic range.

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

Oral anticoagulation can be continued at modified doses in the majority of patients who undergo cardiac

catheterization. Percutaneous arterial puncture is safe with an INR <2.0. If a higher target INR is needed, radial approach may be recommended if the appropriate expertise is available. In the rare patients who require transeptal catheterization, direct LV puncture, or pericardiocentesis, the INR should be <1.2 and bridging anticoagulation is needed as described previously.<sup>14</sup>

### Management of valve thrombosis

Obstructive valve thrombosis should be suspected promptly in any patient with any type of prosthetic valve who presents with a recent increase in shortness of breath or embolic event. Suspicion should be higher if there has been recent inadequate anticoagulation or a cause for increased coagulability (e.g. dehydration, infection, etc.). The diagnosis should be confirmed by transthoracic echocardiography and/or TEE or cinefluoroscopy.<sup>202,203</sup>

The management of prosthetic thrombosis is high risk whatever the option taken. Surgery is high risk because it is most often performed in emergency conditions and is reintervention. On the other hand, fibrinolysis carries risks of bleeding, systemic embolism, and recurrent thrombosis.

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

Indications for surgery or antithrombotic therapy are as follows (Figure 5):

Urgent or emergency valve replacement is the treatment of choice for obstructive thrombosis in critically ill patients without serious comorbidity (Recommendation class I, Level of evidence C). If the thrombogenicity of the prosthesis is an

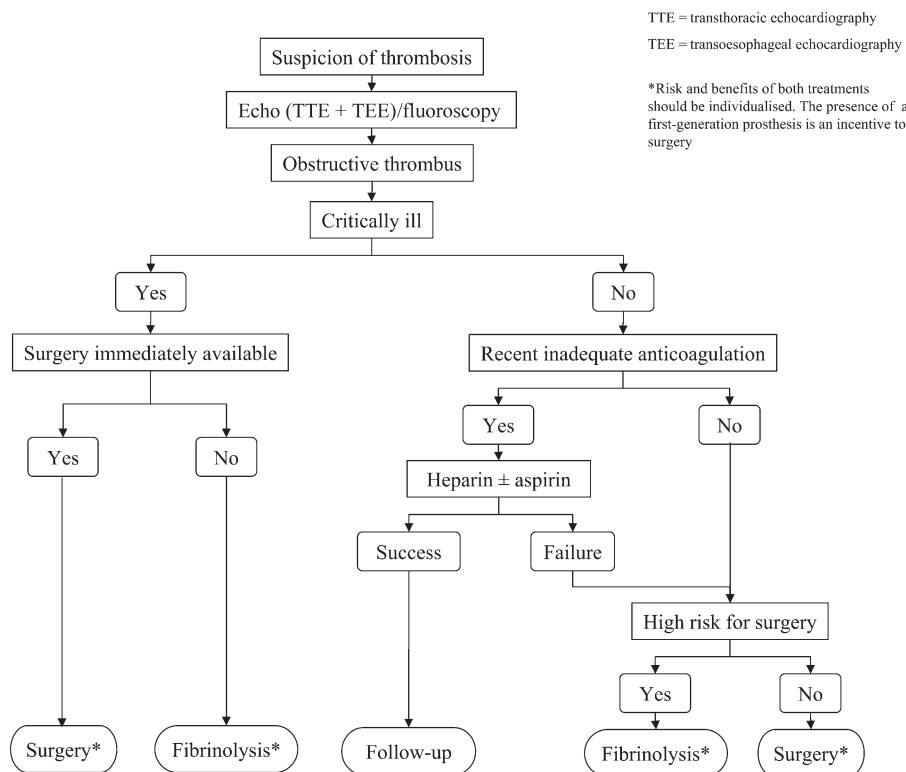


Figure 5 Management of left-sided obstructive prosthetic thrombosis.

important factor, it should be replaced with a less thrombo-genic prosthesis.

Fibrinolysis should be considered in:

- Critically ill patients unlikely to survive surgery because of comorbidities or severely impaired cardiac function prior to 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 incidence of embolism.

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.<sup>204-206</sup>

Management of left-sided non-obstructive prosthetic thrombosis is as follows (Figure 6):

Non-obstructive prosthetic thrombosis is diagnosed using TEE performed after an embolic event, or systematically following mitral valve replacement with a mechanical prosthesis. The management depends mainly on the occurrence of a thrombo-embolic event and the size of the thrombus. Close monitoring by echocardiography and/or cinefluoroscopy 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 either surgery or fibrinolysis. Conversely, surgery is recommended for large (≥10 mm) non-obstructive prosthetic thrombus complicated by embolism (Recommendation class IIa, Level of evidence C) or which persists despite optimal anticoagulation.<sup>207,208</sup> Fibrinolysis may be considered as an alternative if surgery is at high risk. However, the use of fibrinolysis for non-obstructive prosthetic thrombosis raises serious concerns regarding the risk of bleeding and thrombo-embolism and should therefore be very limited.

TTE = transthoracic echocardiography  
 TEE = transoesophageal echocardiography  
 TE = thromboembolism

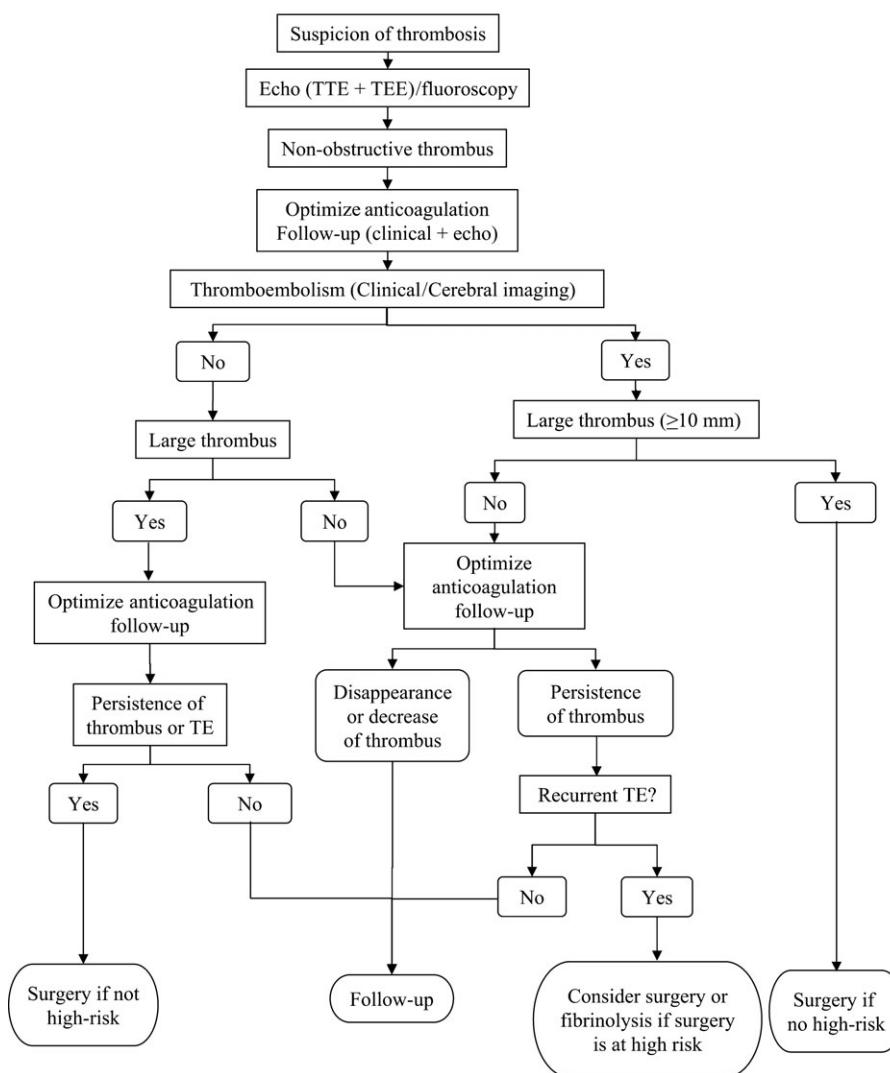


Figure 6 Management of left-sided non-obstructive prosthetic thrombosis.

### Management of thrombo-embolism

Thrombo-embolism after valve surgery is multifactorial both in its aetiology and its origin.<sup>209</sup> Although many thrombo-embolic events will have originated from thrombus or a vegetation on a prosthesis or as the result of the abnormal flow conditions created by a prosthesis, many others will have arisen from other sources as the result of other pathogenic mechanisms and be part of the background incidence of stroke and transient ischaemic attack in the general population.

Thorough investigation of each episode of thrombo-embolism is therefore essential (including cardiac and non-cardiac imaging when appropriate) to allow for appropriate management (Figure 6), rather than simply increasing the target INR or adding an antiplatelet agent.

Prevention of further thrombo-embolic events involves:

- Treatment or reversal of remediable risk factors such as AF, hypertension, hypercholesterolaemia, diabetes, smoking, chronic 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.
- Aspirin should be added, if it was not prescribed before, after a careful analysis of the risk-benefit ratio. Aspirin should be prescribed in a low-dose formulation ( $\leq 100$  mg daily) and any over-anticoagulation should be avoided.

### Management of haemolysis and paravalvular leak

Blood tests for haemolysis should be part of routine follow-up. 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 TEE to detect a paravalvular leak (PVL). Only limited data are available regarding therapeutic options. There is a consensus to recommend reoperation if PVL is related to endocarditis or if PVL causes haemolysis needing repeated blood transfusions or leading to severe symptoms (Recommendation class I, Level of evidence C). In patients with haemolytic anaemia and PVL, where surgery is contraindicated, or those unwilling to undergo re-operation, medical therapy includes iron supplementation, beta-blockers, and erythropoietin if haemolysis is severe.<sup>210,211</sup> Percutaneous closure of PVL has only been the subject of isolated case reports and could not be considered so far as a validated alternative to surgery.

### Management of bioprosthetic failure

SVD occurs in all bioprostheses and homografts if they remain *in situ* long enough. After the first 5 years from implantation, yearly echocardiography is required to detect early signs of SVD: leaflet stiffening, calcification, reduced EOA and/or regurgitation. Auscultatory and echocardiographic findings should be carefully compared with previous examinations in the same patient. Reoperation is advised in symptomatic patients with significant prosthetic dysfunction (significant increase in trans-prosthetic gradient or severe regurgitation) (Recommendation class I, Level of evidence C) and in asymptomatic patients with any significant prosthetic dysfunction, if 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, could be considered during an intervention on another valve or coronary artery.

The decision to reoperate should take into account the risk of reoperation, which increases with older age, high functional class, LV dysfunction, comorbidities, and, above all, the emergency situation. This underlines the need for careful follow-up to allow for reoperation at an early stage, in particular, in patients who are at low risk for reoperation.<sup>212,213</sup>

Percutaneous balloon interventions should be avoided in the treatment of stenotic left-sided bioprostheses and have a limited short-term efficacy in right-sided prosthetic valves.

### Heart failure

Heart failure after valve surgery should lead to a search for prosthetic-related complications, deterioration of repair, LV dysfunction (in particular after correction of regurgitation), or progression of another valve disease. Non-valvular-related causes such as coronary disease, hypertension, or sustained arrhythmias should also be considered.

The management of patients with persistent LV systolic dysfunction should follow the guidelines on the management of chronic heart failure.<sup>16</sup>

### Management during non-cardiac surgery

There is a significant risk of cardiovascular morbidity and mortality in patients with VHD undergoing non-cardiac surgery, especially in patients with severe AS, which is the most common type of valve disease seen in Europe<sup>3</sup> and it is particularly common in the elderly.

The problem of valvular patients undergoing non-cardiac surgery is only partially addressed in the literature. The existing guidelines for perioperative cardiovascular evaluation for non-cardiac surgery<sup>214</sup> are mainly devoted to the field of ischaemic heart disease.

The present recommendations arise from extrapolation from studies concerning cardiovascular risk in other instances, personal experience, and clinical judgement.

### Clinical predictors of increased perioperative cardiovascular risk

The major predictors of cardiovascular risk during non-cardiac surgery are unstable coronary syndromes, decompensated heart failure, significant arrhythmias (including high-grade atrio-ventricular block, ventricular arrhythmias, or supraventricular arrhythmias with uncontrolled ventricular rate), and severe valvular disease.<sup>214</sup>

Among patients with valvular disease, risk assessment should incorporate symptomatic status, presence or not of arrhythmias, severity of the valvular lesion, LV function, and level of pulmonary pressure and comorbidities, including ischaemic heart disease.

Cardiovascular risk can also be stratified according to the different non-cardiac surgical procedures.<sup>214</sup>

## Preoperative clinical evaluation

Before non-cardiac surgery, severe VHD should be identified and the clinical status of the patient carefully evaluated.

The presence of symptoms, that is, dyspnoea, angina, syncope, or heart failure, as well as the presence of arrhythmias, like atrial fibrillation, should be recorded. Physical examination and the ECG should focus on identification of VHD. In patients with a murmur, an echocardiographic study should be done to rule out the diagnosis of significant valve disease. This is particularly important in aged patients, because a mild systolic murmur can be the only physical sign of significant AS.

The severity of the valve lesion, ventricular function, and pulmonary pressure should be carefully evaluated by echocardiography before surgery.

Each case should be individualized and agreement reached after a full discussion with cardiologists, anaesthesiologists, ideally with a particular skill in cardiology, and surgeons.

## Specific valve lesions

### Aortic stenosis

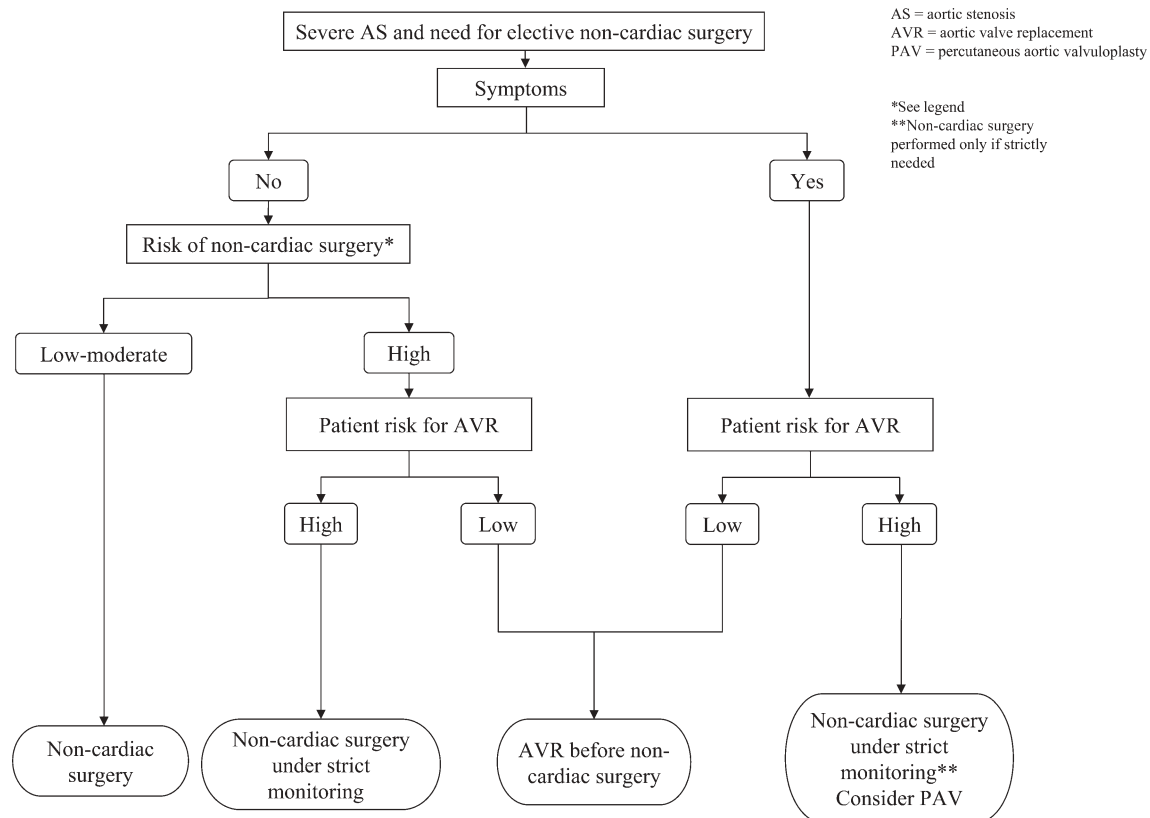
Several studies<sup>215–219</sup> have clearly shown that severe AS (aortic valve area  $<1\text{ cm}^2$  or  $0.6\text{ cm}^2/\text{m}^2$  BSA) increases the risk of non-cardiac surgery, and among patients with valve disease undergoing non-cardiac surgery, those with significant AS have the highest risk.

Recommendations for management are as follows:

In patients with significant AS who need urgent non-cardiac surgery, surgical procedures should be performed under careful haemodynamic monitoring.

When elective non-cardiac surgery is needed in a patient with AS, the risk of cardiac complications during surgery should be balanced with the risk and benefits of having the valve replaced before non-cardiac surgery. The severity of the valvular lesion and the presence of clinical symptoms as well as the risk and the urgency of non-cardiac surgery itself should be considered. It is also important to re-evaluate whether non-cardiac surgery is essential. A decision algorithm is proposed for patients with significant AS facing elective non-cardiac surgery (Figure 7).

In asymptomatic patients with severe AS, a non-cardiac procedure of low or moderate risk can be performed safely. If high-risk non-cardiac surgery is needed, the patient should be carefully evaluated for aortic valve replacement before non-cardiac surgery including coronary angiography to rule out coexistent coronary artery disease. Factors influencing the preference for valve replacement performed before non-cardiac surgery would be the degree of severity of AS, the likelihood of early symptom development (high degree of valve calcification or abnormal exercise test), as well as the overall status of the patient (low comorbidity and long-life expectancy). In these patients, a bioprosthesis is the preferred valve substitute,



**Figure 7** Management of severe aortic stenosis and elective non-cardiac surgery. \*Assessment of the risk of cardiac complications for non-cardiac surgery (from Eagle *et al.*<sup>214</sup>). High risk (>5%): emergent major operations, particularly in the elderly, aortic and other major vascular surgery, peripheral vascular surgery, anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss. Intermediate risk (1 to 5%): carotid endarterectomy, head and neck surgery, intraperitoneal and intrathoracic surgery, orthopedic surgery, prostate surgery. Low risk (<1%): endoscopic procedures; superficial procedure; cataract surgery; breast surgery.

in order to avoid anticoagulation problems during the subsequent non-cardiac surgery.

In asymptomatic patients who are poor candidates for valve replacement because of severe comorbidities as assessed by a high Euroscore<sup>39</sup> or poor life expectancy, non-cardiac surgery should be carefully discussed and, if really needed, performed under strict haemodynamic monitoring.

In symptomatic patients with severe AS facing non-cardiac surgery, valve replacement should always be considered even before non-cardiac surgery at low-to-moderate risk. If valve replacement is contraindicated, non-cardiac surgery should be performed only if absolutely necessary. Although its practice has not been rigorously evaluated, percutaneous aortic valvuloplasty to create a time window of reduced cardiac risk during which the non-cardiac surgery can be performed has been considered<sup>76</sup> and could have a role depending on local expertise.

### Mitral stenosis

In non-significant MS (valve area  $>1.5$  cm<sup>2</sup>), non-cardiac surgical procedures can be performed at low risk.

In asymptomatic patients with significant MS and a systolic pulmonary artery pressure  $<50$  mmHg, non-cardiac surgery can also be performed at low risk, although it should be remembered that the onset of atrial fibrillation may produce a sharp deterioration.

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.

This recommendation is stronger before high-risk non-cardiac procedures. If surgery, in particular, valve replacement, is needed, the decision to proceed before non-cardiac surgery should be taken with caution and based on strict individual considerations.

### Aortic regurgitation and mitral regurgitation

In non-significant AR or MR, non-cardiac procedures can be performed at low risk.

In asymptomatic patients with preserved LV function and severe MR or AR, non-cardiac surgery can be performed at low risk.

In symptomatic patients or in patients with depressed LV function (EF  $<30\%$ ), non-cardiac surgery should be performed only if strictly needed. The medical therapy of heart failure should be optimized before surgery and vasodilators are particularly useful in this context.<sup>220</sup>

### Prosthetic valves

In patients with prosthetic valves, valvular disease has already been corrected and non-cardiac surgery can be safely performed from the haemodynamic point of view, providing that there are no symptoms or signs of prosthetic dysfunction and recent echocardiographic assessment has been satisfactory. However, there is a high risk, mostly related to the changes in anticoagulation regimen, in patients with mechanical valves. Thus, the management of anticoagulation is of utmost importance in these circumstances (see Interruption of anticoagulant therapy section).

### Endocarditis prophylaxis

In valve disease patients, all surgical procedures, even minor, require scrupulous asepsis and avoidance of wound haematoma formation.

Antibiotic prophylaxis should be prescribed for those patients undergoing non-cardiac procedures at high bacteremic risk.<sup>10</sup>

### Perioperative monitoring

Valvular patients submitted to moderate or high-risk non-surgical procedures need particular perioperative care, especially ensuring that systemic hypotension or volume depletion or overload is avoided. Particular attention should be paid to avoid hypotension in patients with AS.

In patients with moderate-to-severe AS or MS, beta-blockers or amiodarone can be used prophylactically in order to maintain sinus rhythm in the postoperative period.<sup>221</sup> Whether the beneficial role of beta-blockers on cardiovascular mortality before major vascular surgery<sup>222</sup> applies to valvular patients is not known.

It is prudent to electively admit such patients to intensive care postoperatively even if they appear to be doing well.

### Management during pregnancy

Haemodynamic changes that normally occur during pregnancy may worsen tolerance of underlying heart disease. Native VHD is the most frequently acquired heart disease encountered during pregnancy even in developed countries. Certain native VHDs carry a poor prognosis for the mother and foetus. In patients with a valve prosthesis, the modalities of anticoagulant therapy are problematic.

### Cardiac risk of pregnancy

The main cardiovascular changes are increase in blood volume, decrease in systemic vascular resistance, and increase in heart rate. Cardiac output increases from 30 to 50% after the fifth month, increases further during labour and delivery, and normalizes within 3 days of delivery.<sup>223</sup> Pregnancy also induces changes in haemostasis, all of which contribute to increased coagulability and thromboembolic risk.<sup>224</sup>

The risk of maternal cardiac complications is high in cases of severe stenotic valvular disease, in particular, MS with pulmonary hypertension, severe regurgitation complicated by LV dysfunction, and Marfan's syndrome with aneurysm of the ascending aorta.<sup>223-227</sup> The risk is increased in women with a history of cardiac events, arrhythmias, or who are in NYHA class III or IV.<sup>225</sup> Thus, such patients must undergo intervention to correct their valve lesions and, if present, their aortic problems before considering pregnancy. However, pregnancy is often already present when the patient presents.

### Evaluation of the pregnant patient with heart valve disease

Ideally, valve disease should be evaluated before pregnancy and treated if necessary. Although dyspnoea may be difficult to interpret in pregnant women, its occurrence after the first trimester should lead to suspicion of underlying heart disease. In women with mechanical valve prostheses, it is

necessary to assess the effective adherence to anticoagulant therapy and to check for previous complications. Cardiac auscultation during pregnancy is mandatory to detect native valve disease or prosthesis dysfunction.

Echocardiographic examination should be performed in any pregnant patient presenting with a more than trivial heart murmur, dyspnoea, or who has a prosthetic valve. Valve stenosis should be quantified using the measurement of valve area. Gradients are modified because of the increase in cardiac output and are not reliable markers of the severity of stenosis; however, they have a prognostic value. Quantitation of regurgitation should combine different measurements and take into account loading conditions. According to the type of valve disease, echocardiographic examination should also assess mitral valve anatomy or size of the ascending aorta. The assessment of LV dimensions and EF, as well as systolic pulmonary artery pressure, indicates the tolerance of the valvular disease.

The use of chest X-rays should be limited and, when absolutely required, accompanied by appropriate shielding of the abdomen. CT is contraindicated because of the radiation dose, but MRI can be performed during pregnancy. The use of cardiac catheterization is restricted to the performance of interventional procedures and again abdominal shielding should be used.

## Specific risks related to pregnancy

### Native valve disease

MS, which is the most frequent VHD encountered during pregnancy, is often poorly tolerated when valve area is  $<1.5 \text{ cm}^2$ , even in previously asymptomatic patients.<sup>226</sup> Dyspnoea worsens between the third and fifth months, which corresponds to the increase in cardiac output. The persistence of dyspnoea or pulmonary hypertension is associated with a high risk of complications at delivery, thereby threatening the life of both the mother and foetus.<sup>223</sup>

Severe AS is less frequently encountered during pregnancy. Complications occur mainly in patients who were symptomatic before pregnancy.<sup>225</sup> The risk of heart failure during pregnancy or at delivery is low when mean aortic gradient is  $<50 \text{ mmHg}$ .<sup>224</sup>

Foetal prognosis is also impaired in the case of stenotic heart valve disease, due to growth retardation, preterm delivery, and low birth weight.<sup>226,227</sup>

For these reasons, patients with severe MS or AS should be treated before pregnancy if possible, even in asymptomatic patients.

Chronic AR and MR are well tolerated during pregnancy, even when severe, provided LV systolic function is preserved.<sup>224</sup> However, the risk of complications is high when LVEF is  $<40\%$ , the prognosis being close to that of cardiomyopathy. Conversely, acute regurgitation is poorly tolerated.

In patients with Marfan's syndrome, the risk of aortic-related complications including dissection during pregnancy increases markedly when AR is more than mild or when maximum aortic diameter is  $>40 \text{ mm}$ .<sup>228</sup> In these cases, pregnancy should be preceded by replacement of the ascending aorta, in particular, when the native aortic valve can be preserved. Aortic complications should be considered in any patient presenting with chest pain or pain in the posterior thorax.

### Patients with prosthetic valves

Maternal mortality is estimated between 1 and 4% and is mostly related to thrombo-embolism.<sup>229,230</sup>

The risks are particularly high in patients with mitral valve prostheses. Therefore, these patients should be informed of the risks and they require careful risk assessment and very close monitoring of anticoagulant therapy if pregnancy occurs.

Vitamin K antagonists increase the risk of miscarriage, prematurity, and embryopathy, the latter in  $\sim 5\%$  of cases, in particular, when used between the sixth and 12th weeks. The risk is lower when Warfarin dose is  $\leq 5 \text{ mg/day}$ .<sup>224</sup> Vitamin K antagonists are contraindicated during labour and delivery because of the risk of cerebral bleeding in the foetus. Unfractionated heparin therapy is safe for the foetus, but it is associated with a considerable increase in the thrombo-embolic risk for the mother, including occlusive prosthetic thrombosis. Experience with LMWHs remains limited and controversial, with uncertainties in dose remaining.<sup>229</sup>

## Treatment

All strategies (*Table 18*) should be discussed and approved between obstetricians, cardiologists, and the patient and her family.

**Table 18** Recommendations on the management of pregnant women with valvular heart disease

	Class
Patients with severe stenotic heart valve disease should be treated before pregnancy, if possible using percutaneous techniques in MS	IC
Echocardiographic examination should be performed in any pregnant patient with a murmur or unexplained dyspnoea	IC
Patients with Marfan's syndrome and aortic diameter $>40 \text{ mm}$ should be treated before pregnancy	IC
Medical therapy is favoured in most patients with regurgitant heart valve disease, even in symptomatic patients	IC
Surgery under extracorporeal circulation should be performed during pregnancy only in situations that threaten the mother's life and are not amenable to percutaneous treatment.	IC
Vaginal delivery can be performed safely in patients with heart valve disease who are in stable haemodynamic condition.	IC
Warfarin is the favoured anticoagulant therapy during the second and third trimesters until the 36th week <sup>a</sup>	IC
Close monitoring of anticoagulation is advised when unfractionated heparin used.	IC
PMC should be considered in pregnant patients who have severe symptoms or pulmonary artery pressure $>50 \text{ mmHg}$ owing to MS despite medical therapy	IIaC
Warfarin is favoured during the first trimester if dose is $\leq 5 \text{ mg/24 h}$ , after patient information	IIaC

MS = mitral stenosis, PMC = percutaneous mitral commissurotomy.

<sup>a</sup>Data are lacking on other vitamin K antagonists.



### Aims

The treatment should relieve symptoms and avoid maternal complications until the end of pregnancy and during delivery, without compromising foetal prognosis and subsequent growth. Strategies whose unique purpose is to improve long-term prognosis of the mother can be postponed until after delivery.

### Methods

The use of medical therapy should always take into account foetal hazards. Beta-blockers are safe but may induce neonatal bradycardia and possible growth retardation. Diuretics can be used at the lowest dose possible to avoid impairing foetal perfusion. The use of vasodilators should take into account the contraindication of ACE-inhibitors and angiotensin receptor blockers.

Valvular surgery under cardiopulmonary bypass is associated with a foetal mortality between 20 and 30%.<sup>231</sup>

Percutaneous valvular dilatation can be performed during pregnancy after the 20th week. It should be performed in experienced centres and associated with specific precautions to shorten the procedure and reduce the hazards of radiation, in particular, using abdominal shield protection.<sup>232</sup> TEE guidance is useful in addition to, but not instead of fluoroscopy.

### Management strategy

When the first visit occurs during pregnancy, early termination may be considered in the following situations:

- Severe LV dysfunction (EF <40%).
- Marfan's syndrome with aneurysm of ascending aorta >40 mm.
- Severe symptomatic stenotic valve disease, which cannot be treated using percutaneous procedures.

The Task Force did not reach a full agreement on the choice of prosthesis. However, the majority favours the use of a bioprosthesis if valve replacement is necessary during pregnancy.

During pregnancy, clinical and echocardiographic follow-up should be performed at 3 and 5 months, and every month thereafter in pregnant patients with severe valve stenosis. Symptomatic MS should be treated using bed rest, beta-blockers, favouring atenolol or metoprolol, possibly associated with diuretics. Doses are adapted according to symptoms and pulmonary artery pressure. Beta-agonist agents are contraindicated. In the case of persistent dyspnoea or pulmonary artery hypertension despite medical therapy, PMC should be considered, in particular, when anatomical conditions are favourable or in case of uncertainty regarding follow-up.

In patients with severe AS who remain symptomatic despite diuretics, balloon aortic valvuloplasty can be considered during pregnancy. The experience with this procedure during pregnancy is, however, much more limited

than that of PMC.

Patients with AR or MR who become symptomatic during pregnancy should be treated medically using diuretics and vasodilators. In most cases, surgery can be postponed until the postoperative period.

Beta-blockers should be used throughout pregnancy in patients with Marfan's syndrome to avoid aortic dissection.

In patients with a mechanical prosthesis, vitamin K antagonists are favoured during the second and third trimesters until the 36th week when they are replaced by unfractionated heparin. During the first trimester, the choice should take into account patient wishes after information, adherence to treatment, and the possibility to use low-dose warfarin; the use of warfarin is the safest regimen for the mother.<sup>224,229</sup> The use of warfarin throughout pregnancy until the 36th week is recommended when warfarin dose is  $\leq 5$  mg/day during the first trimester.<sup>14</sup> The target INR is the same as before pregnancy. There are no data regarding the use of other anticoagulant therapies. If unfractionated heparin is used, we strongly recommend frequent control of the target-activated partial thromboplastin time, which should be between 2 and 3<sup>14</sup>. The use of LMWH cannot be recommended on the basis of the information currently available.

### Delivery

Vaginal delivery is recommended whenever possible if the haemodynamic condition is stable at the end of pregnancy. Haemodynamic monitoring is recommended in women with severe MS or LV dysfunction. The use of epidural analgesia and obstetric procedures to shorten extraction time are recommended to reduce the total duration of labour, diminishing haemodynamic consequences. Caesarean section has the advantage of avoiding the haemodynamic consequences of labour, but it is associated with other consequences related to anaesthesia, blood volume shift, and assisted ventilation, which can be harmful from a haemodynamic point of view. It requires close haemodynamic monitoring and should be ideally performed in specialized centres. It is mainly considered in patients who have Marfan's syndrome, with an aortic diameter >40 mm, those in whom haemodynamic conditions are unstable, in particular, in the presence of AS, or in case of premature delivery under oral anticoagulation. Prophylactic antibiotic therapy can be given at the beginning of labour and during delivery in patients at high risk, i.e. with previous endocarditis or heart valve prosthesis.

When valvular surgery is required during pregnancy, caesarean section should be performed first if the foetus is viable. In the other cases, the mode of delivery should be discussed and planned by cardiologists, obstetricians, anaesthetists, and the patient before delivery, even more so for the patients who need to interrupt oral anticoagulation.

## References

- Committee for Practice Guidelines (CPG). European Society of Cardiology: recommendations for Task Force creation and report production. A document for Task Force members and expert panels responsible for the creation and production of Guidelines and Expert Consensus Documents. <http://www.escardio.org/knowledge/guidelines/Rules/>
- Soler-Soler J, Galve E. Worldwide perspective of valve disease. *Heart* 2000;**83**:721–725.
- lung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravnaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. *Eur Heart J* 2003;**24**:1231–1243.
- Rizvi SFH, Khan MA, Kundi A, Marsh DR, Samad A, Pasha O. Current status of rheumatic heart diseases in rural Pakistan. *Heart* 2004;**90**:394–399.
- Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Whitney Lytle B, Nishimura RA, O’Gara PT, O’Rourke RA, Otto CM, Shah PM, Shanewise JS. ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists. *J Am Coll Cardiol* 2006;**48**:e1–e148.
- Prendergast BD, Banning AP, Hall RJ. Valvular heart disease: recommendations for investigation and management. Summary of guidelines produced by a working group of the British Cardiac Society and the Research Unit of the Royal College of Physicians. *J R Coll Physicians Lond* 1996;**30**:309–315.
- Classen M, Dierkesmann R, Heimpel H, Kalden JR, Koch KM, Meyer J, Theiss W, Ziegler R. Rationale Diagnostik und Therapie in der inneren Medizin. Ein Beitrag zur Qualitätssicherung in Klinik und Praxis. München: Urban und Fischer; 1999.
- Azpitate J, Alonso AM, García Gallego F, Gonzalez Santos JM, Pare C, Tello A. Guías de practica clinica de la Sociedad Espanola de Cardiologia en valvulopatias. *Rev Esp Cardiol* 2000;**53**:1209–1278.
- Tribouilloy C, De Gevigney G, Acar J, Chassignolle JF, Cormier B, Habib G, Hanania G, lung B, Leguerrier A, Marchand M, Michel PL, Obadia JF, Roudaut R, Vahanian A, Villemot JP, Warembourg H. Recommendations de la Société Française de Cardiologie concernant la prise en charge des valvulopathies acquises et des dysfonctions de prothèse valvulaire. Indications opératoires et interventionnelles. *Arch Mal Coeur* 2005;**98**(Suppl.):5–61.
- Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernandez Burgos E, Lindahl B, Mazzotta G, Morais J, Smiseth OA, Lekakis J, Vahanian A, Delahaye F, Parkhomenko A, Filipatos G, Aldershvile J, Vardas P, Task Force Members on Infective Endocarditis of the European Society of Cardiology, ESC Committee for Practice Guidelines (CPG), Document Reviewers. Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis Executive Summary: The Task Force on Infective Endocarditis of the European Society of Cardiology. *Eur Heart J* 2004;**25**:267–276.
- Deanfield J, Thaulow E, Warnes C, Webb G, Kolbel F, Hoffman A, Sorenson K, Kaemmerer H, Thilen U, Bink-Boelkens M, Iserin L, Daliento L, Silove E, Redington A, Vouhe P, Priori SG, Alonso MA, Blanc JJ, Budaj A, Cowie M, Deckers JW, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth O, Trappe HJ. Management of grown up congenital disease. The Task Force on the management of grown up congenital disease of the European Society of Cardiology. *Eur Heart J* 2003;**24**:1035–1084.
- Gohlke-Barwolf C, Acar J, Oakley C, Butchart E, Burckhart D, Bodnar E, Hall R, Delahaye JP, Horstkotte D, Krayenbuhl HP, Krzeminska-Pakula M, Kremer R, Samama MM. Guidelines for prevention of thromboembolic events in valvular heart disease. Study Group of the Working Group on Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 1995;**16**:1320–1330
- lung B, Gohlke-Barwolf C, Tornos P, Tribouilloy C, Hall R, Butchart E, Vahanian A, Working Group on Valvular Heart Disease. Recommendations on the management of the asymptomatic patient with valvular heart disease. Working Group Report on behalf of the Working Group on Valvular Heart Disease. *Eur Heart J* 2002;**23**:1253–1266
- Butchart EG, Gohlke-Barwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, Prendergast B, lung B, Bjornstad H, Lepout C, Hall RJ, Vahanian A, Working Groups on Valvular Heart Disease, Thrombosis, Cardiac Rehabilitation, Exercise Physiology, European Society of Cardiology. Recommendations for the management of patients after heart valve surgery. *Eur Heart J* 2005;**26**:2463–2471.
- Vahanian A, lung B, Pierard L, Dion R, Pepper J. Valvular heart disease. In: Camm AJ, Lüscher TF, Serruys PW, eds. *The ESC Textbook of Cardiovascular Medicine*. Malden/Oxford/Victoria: Blackwell Publishing Ltd; 2006. p625–670.
- Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Niemenen MS, Pierard L, Remme WJ, Task Force for the Diagnosis Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;**26**:1115–1140.
- Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, for the Doppler Quantification Task Force of the Nomenclature Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;**15**:167–184.
- Bermejo J, Odreman R, Feijoo J, Moreno MM, Gomez-Moreno P, Garcia-Fernandez MA. Clinical efficacy of Doppler-echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. *J Am Coll Cardiol* 2003;**41**:142–151.
- Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802.
- Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O’Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO, American College of Cardiology, American Heart Association, American Society for Nuclear Cardiology. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging—Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2003;**42**:1318–1333.
- Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart* 2001;**86**:381–386.
- Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J* 2005;**26**:1309–1313.
- Pelliccia A, Fagard R, Bjørnstad HH, Anastassakis A, Arbustini E, Assanelli D, Biffi A, Borjesson B, Carre F, Corrado D, Delise P, Dorwarth U, Hirth A, Heidbuchel H, Hoffmann E, Mellwig KP, Panhuyzen-Goedkoop N, Pisani A, Solberg EE, van-Buuren F, Vanhees L, Blomstrom-Lundqvist C, Deligiannis A, Dugmore D, Glikson M, Hoff PI, Hoffmann A, Hoffmann E, Horstkotte D, Nordrehaug JE, Oudhof J, McKenna WJ, Penco M, Priori S, Reybrouck T, Senden J, Spataro A, Thiene G. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:1422–1445.
- Lancellotti P, Troisfontaines P, Toussaint AC, Pierard LA. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischaemic left ventricular dysfunction. *Circulation* 2003;**108**:1713–1717.
- Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation* 2005;**112**(Suppl. 1):I-377–I-382.
- Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH. Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. *Heart* 2005;**91**:1407–1412.

27. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehaut P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis, operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003;108:319–324.
28. Messika-Zeitoun D, Aubry MC, Detaint D, Bielak LF, Peyser PA, Sheedy PF, Turner ST, Breen JF, Scott C, Tajik AJ, Enriquez-Sarano M. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. *Circulation* 2004;110:356–362.
29. Westenberg JJ, Doornbos J, Versteegh MI, Bax JJ, van der Geest RJ, de Roos A, Dion RA, Reiber JH. Accurate quantitation of regurgitant volume with MRI in patients selected for mitral valve repair. *Eur J Cardiothorac Surg* 2005;27:462–466.
30. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;109:2302–2308.
31. Detaint D, Messika-Zeitoun D, Avierinos JF, Scott C, Chen H, Burnett JC Jr, Enriquez-Sarano M. B-type natriuretic peptide in organic mitral regurgitation. Determinants and impact on outcome. *Circulation* 2005;111:2391–2397.
32. Omran H, Schmidt H, Hackenbroch M, Illien S, Bernhardt P, von der Recke G, Fimmers R, Flacke S, Layer G, Pohl C, Luderitz B, Schild H, Sommer T. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet* 2003;361:1241–1246.
33. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Bärwolf C, Boersma E, Ravaut P, Vahanian A. Decision making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714–2720.
34. Avierinos JF, Gersh BJ, Melton LJ III, Bailey KR, Shub C, Nishimura RA, Tajik AJ, Enriquez-Sarano M. Natural history of mitral valve prolapse in the community. *Circulation* 2002;106:1355–1361.
35. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19 030 patients. *Eur J Cardiothorac Surg* 1999;15:816–823.
36. Edwards FH, Peterson ED, Coombs LP, DeLong ER, Jamieson WR, Shroyer ALW, Grover FL. Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol* 2001;37:885–892.
37. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. *Circulation* 2005;112:224–231.
38. Jin R, Grunkemeier GL, Starr A, the Providence Health System Cardiovascular Study Group. Validation and refinement of mortality risk models for heart valve surgery. *Ann Thorac Surg* 2005;80:471–479.
39. Roques F, Nashef SAM, Michel P, the EuroSCORE Study Group. Risk factors for early mortality after valve surgery in Europe in the 1990s: lessons from the EuroSCORE pilot program. *J Heart Valve Dis* 2001;10:572–578.
40. Judge DP, Dietz HC. Marfan's syndrome. *Lancet* 2005;366:1965–1976.
41. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002;73:17–27.
42. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany Ch J, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol* 1997;30:746–752.
43. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long term follow up study. *Circulation* 1999;99:1851–1857.
44. Borer JS, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D, Devereux RB, Roman MJ, Szulc M, Kligfield P, Isom OW. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. *Circulation* 1998;97:525–534.
45. Tarasoutchi F, Grinberg M, Spina GS, Sampaio RO, Cardoso LF, Rossi EG, Pomerantzeff P, Laurindo F, da Luz PL, Ramirez JA. Ten-year laboratory follow up after application of a symptom-based therapeutic strategy to patients with severe chronic aortic regurgitation of predominant rheumatic etiology. *J Am Coll Cardiol* 2003;41:1316–1324.
46. Borer JS, Bonow RO. Contemporary approach to aortic and mitral regurgitation. *Circulation* 2003;108:2432–2438.
47. Roman MJ, Devereux RB, Niles NW, Hochreiter C, Kligfield P, Sato N, Spitzer MC, Borer JS. Aortic root dilatation as a cause of isolated severe aortic regurgitation. Prevalence, clinical and echocardiographic patterns and relation to left ventricular hypertrophy and function. *Ann Intern Med* 1987;106:800–807.
48. Silverman DI, Gray J, Roman MJ, Bridges A, Burton K, Boxer M, Devereux RB, Tsipouras P. Family history of severe cardiovascular disease in Marfan syndrome is associated with increased aortic diameter and decreased survival. *J Am Coll Cardiol* 1995;26:1062–1067.
49. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, Coe MP, Kopf GS, Elefteriades JA. Novel measurements of relative aortic size predicts rupture of thoracic aortic aneurysm. *Ann Thorac Surg* 2006;81:169–177.
50. Keane MG, Wiegers SE, Plappert T. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. *Circulation* 2000;102(Suppl. III):III35–III39.
51. STS national database: STS U.S. cardiac surgery database: 1997 Aortic valve replacement patients: preoperative risk variables. Chicago, Society of Thoracic Surgeons; 2000. Accessed 10 May 2006. <http://www.ctsnet.org/doc/3031>
52. National Adult Cardiac Surgical Database Report 1999–2000. The United Kingdom Cardiac Surgical Register. Accessed 10 May 2006. <http://www.scts.org/file/NACSDreport2000ukcsr.pdf>
53. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, Enriquez-Sarano M. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation* 2002;106:2687–2693.
54. Corti R, Binggeli C, Turina M, Jenni R, Lüscher TF, Turina J. Predictors of long term survival after valve replacement for chronic aortic regurgitation. *Eur Heart J* 2001;22:866–887.
55. Tornos P, Sambola A, Permyner-Miralda G, Evangelista A, Gomez Z, Soler Soler J. Long term outcome of surgically treated aortic regurgitation: influence of guidelines adherence towards early surgery. *J Am Coll Cardiol* 2006;47:1012–1017.
56. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany Ch, Bailey KR, Seward JB. Aortic regurgitation complicated by extreme left ventricular dilation: long term outcome after surgical correction. *J Am Coll Cardiol* 1996;27:670–677.
57. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic patients with Marfan syndrome. *Circulation* 2005;111:e150–e157.
58. Ergin MA, Spielvogel D, Apaydin A, Lansman SL, McCullough JN, Galla JD, Griep RB. Surgical treatment of the dilated ascending aorta: when and how? *Ann Thorac Surg* 1999;67:1834–1839.
59. Zehr KJ, Orszulak TA, Mullany CJ, Matloobi A, Daly RC, Dearani JA, Sundt TM III, Puga FJ, Danielson GK, Schaff HV. Surgery for aneurysms of the aortic root: a 30-year experience. *Circulation* 2004;110:1364–1371.
60. Enriquez-Sarano M, Tajik AJ. Clinical practice. Aortic regurgitation. *N Engl J Med* 2004;351:1539–1546.
61. Scognamiglio R, Negut C, Palisi M, Fasoli G, Dalla-Volta S. Long-term survival and functional results after aortic valve replacement in asymptomatic patients with chronic severe aortic regurgitation and left ventricular dysfunction. *J Am Coll Cardiol* 2005;45:1025–1030.
62. Evangelista A, Tornos P, Sambola A, Permyner-Miralda G, Soler Soler J. Long term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med* 2005;353:1324–1329.
63. Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;330:1335–1341.
64. Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with Marfan syndrome. *Am J Cardiol* 2005;95:1125–1127.
65. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630–634.
66. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;341:142–147.
67. deFilippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol* 1995;75:191–194.
68. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation* 2002;106:809–813.

69. Feuchtnner GM, Dichtl W, Friedrich GJ, Frick M, Alber H, Schachner T, Bonatti J, Mallouhi A, Frede T, Pachinger O, zur Nedden D, Muller S. Multislice computed tomography for detection of patients with aortic valve stenosis and quantification of severity. *J Am Coll Cardiol* 2006; **47**:1410–1417.
70. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997; **95**:2262–2270.
71. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; **343**:611–617.
72. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation* 2005; **111**:3290–3295.
73. Lund O, Nielsen TT, Emmertsen K, Flo C, Rasmussen B, Jensen FT, Pilegaard HK, Kristensen LH, Hansen OK. Mortality and worsening of prognostic profile during waiting time for valve replacement in aortic stenosis. *Thorac Cardiovasc Surg* 1996; **44**:289–295.
74. Kvidal P, Bergström R, Hörte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000; **35**:747–756.
75. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. *J Am Coll Cardiol* 2000; **36**:1131–1141.
76. Vahanian A, Palacios IF. Percutaneous approaches to valvular disease. *Circulation* 2004; **109**:1572–1579.
77. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006; **47**:1214–1223.
78. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000; **101**:1940–1946.
79. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 2002; **39**:1356–1363.
80. Otto CM. Timing of aortic valve surgery. *Heart* 2000; **84**:211–218.
81. Mohler ER III. Mechanisms of aortic valve calcification. *Am J Cardiol* 2004; **94**:1396–1402.
82. Bellamy MF, Pellikka PA, Klarich KW, Tajik AJ, Enriquez-Sarano M. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 2002; **40**:1723–1730.
83. Rosenhek R, Rader F, Loho N, Gabriel H, Heger M, Klaar U, Schemper M, Binder T, Maurer G, Baumgartner H. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation* 2004; **110**:1291–1295.
84. O'Brien KD, Probstfield JL, Caulfield MT, Nasir K, Takasu J, Shavelle DM, Wu AH, Zhao XQ, Budoff MJ. Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. *Arch Intern Med* 2005; **165**:858–862.
85. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA, Scottish Aortic Stenosis Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005; **352**:2389–2397.
86. Pereira JJ, Balaban K, Lauer MS, Lytle B, Thomas JD, Garcia MJ. Aortic valve replacement in patients with mild or moderate aortic stenosis and coronary bypass surgery. *Am J Med* 2005; **118**:735–742.
87. Byrne JG, Leacche M, Unic D, Rawl JD, Simon DI, Rogers CD, Cohn LH. Staged initial percutaneous coronary intervention followed by valve surgery ('hybrid approach') for patients with complex coronary and valve disease. *J Am Coll Cardiol* 2005; **45**:14–18.
88. Edwards MB, Taylor KM. Outcomes in nanogenarians after valve replacement operation. *Ann Thorac Surg* 2003; **75**:830–834.
89. Borger MA, Preston M, Ivanov J, Fedak PW, Davierwala P, Armstrong S, David TE. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? *J Thorac Cardiovasc Surg* 2004; **128**:677–683.
90. Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ, Krohn MJ, Mays JM. Quantitative Doppler assessment of valvular regurgitation. *Circulation* 1993; **87**:841–848.
91. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005; **352**:875–883.
92. Carpentier A. Cardiac valve surgery—the 'French correction'. *J Thorac Cardiovasc Surg* 1983; **86**:323–337.
93. Enriquez-Sarano M, Freeman WK, Tribouilloy CM, Orszulak TA, Khandheria BK, Seward JB, Bailey KR, Tajik AJ. Functional anatomy of mitral regurgitation: accuracy and outcome implications of TEE. *J Am Coll Cardiol* 1999; **34**:1129–1136.
94. Monin J-L, Dehant P, Roiron C, Monchi M, Tabet J-Y, Clerc P, Fernandez G, Houel R, Garot J, Chauvel C, Gueret P. Functional assessment of mitral regurgitation by transthoracic echocardiography using standardized imaging planes. *J Am Coll Cardiol* 2005; **46**:302–309.
95. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996; **335**:1417–1423.
96. Grigioni F, Enriquez-Sarano M, Ling LH, Bailey KR, Seward JB, Tajik AJ, Frye RL. Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol* 1999; **34**:2078–2085.
97. Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ, Frye RL. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical implications. *Circulation* 1999; **99**:400–405.
98. Lee EM, Shapiro LM, Wells FC. Superiority of mitral valve repair in surgery for degenerative mitral regurgitation. *Eur Heart J* 1997; **18**:655–663.
99. Thamilarasan M, Griffin B. Choosing the most appropriate valve operation and prosthesis. *Cleveland Clin J Med* 2002; **69**:668–703.
100. Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995; **91**:1022–1028.
101. Braunberger E, Deloche A, Berrebi A, Abdallah F, Celestin JA, Meimoun P, Chatellier G, Chauvaud S, Fabiani JN, Carpentier A. Very long-term results (more than 20 years) of valve repair with Carpentier's techniques in nonrheumatic mitral valve insufficiency. *Circulation* 2001; **104**:18–111.
102. Otto CM, Salerno CT. Timing of surgery in asymptomatic mitral regurgitation. *N Engl J Med* 2005; **352**:928–929.
103. Enriquez-Sarano M, Schaff HV, Frye RL. Mitral regurgitation: what causes the leakage is fundamental to the outcome of valve repair. *Circulation* 2003; **108**:253–256.
104. Raanani E, Albage A, David TE, Yau TM, Armstrong S. The efficacy of the Cox/maze procedure combined with mitral valve surgery: a matched control study. *Eur J Cardiothorac Surg* 2001; **19**:438–442.
105. Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, St Goar F, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Condado JA, Foster E. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005; **46**:2134–2140.
106. Webb JG, Harnek J, Munt BI, Kimblad PO, Chandavimol M, Thompson CR, Mayo JR, Solem JO. Percutaneous transvenous mitral annuloplasty: initial human experience with device implantation in the coronary sinus. *Circulation* 2006; **113**:851–855.
107. Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, Schemper M, Maurer G, Baumgartner H. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 2006; **113**:2238–2244.
108. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation—Executive Summary: a report by the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J* 2006; **27**:1976–2030.
109. Grayburn PA. Vasodilator therapy for chronic aortic and mitral regurgitation. *Am J Med Sci* 2000; **320**:202–208.
110. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications

- with quantitative Doppler assessment. *Circulation* 2001;103:1759-1764.
111. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. *Circulation* 2005;112:745-758.
  112. Piérard LA, Lancellotti P. The role of ischaemic mitral regurgitation in the pathogenesis of acute pulmonary edema. *N Engl J Med* 2004;351:1627-1634.
  113. Lebrun F, Lancellotti P, Piérard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. *J Am Coll Cardiol* 2001;38:1685-1692.
  114. Lancellotti P, Gérard P, Piérard L. Long term outcome of patients with heart failure and dynamic mitral regurgitation. *Eur Heart J* 2005;26:1528-1532.
  115. Pu M, Thomas JD, Gillinov MA, Griffin BP, Brunken RC. Importance of ischaemic and viable myocardium for patients with chronic ischaemic mitral regurgitation and left ventricular dysfunction. *Am J Cardiol* 2003;92:862-864.
  116. Iung B. Management of ischaemic mitral regurgitation. *Heart* 2003;89:459-464.
  117. Glower DD, Tuttle RH, Shaw LK, Orozco RE, Rankin JS. Patient survival characteristics after routine mitral valve repair for ischaemic mitral regurgitation. *J Thorac Cardiovasc Surg* 2005;129:860-868.
  118. Seipelt RG, Schoendube FA, Vazquez-Jimenez JF, Doerge H, Voss M, Messmer BJ. Combined mitral valve and coronary artery surgery: ischaemic versus non-ischaemic mitral valve disease. *Eur J Cardiothorac Surg* 2001;20:270-275.
  119. Bouchard D, Pellerin M, Carrier M, Perrault LP, Page P, Hebert Y, Cartier R, Dyrda I, Pelletier LC. Results following valve replacement for ischaemic mitral regurgitation. *Can J Cardiol* 2001;17:427-431.
  120. Braun J, Bax JJ, Versteegh M, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Preoperative left ventricular dimensions predict reverse remodelling following restrictive mitral annuloplasty in ischaemic mitral regurgitation. *Eur J Cardiothorac Surg* 2005;27:847-853.
  121. Bax JJ, Braun J, Somer ST, Klautz R, Holman ER, Versteegh M, Boersma E, Schalij MJ, van der Wall EE, Dion RA. Restrictive annuloplasty and coronary revascularization in ischaemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation* 2004;110(Suppl.):II103-II108.
  122. Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J, Lytle BW, McCarthy PM. Is repair preferable to replacement for ischaemic mitral regurgitation? *J Thorac Cardiovasc Surg* 2001;122:1125-1141.
  123. Aklog L, Filsoofi F, Flores KQ, Chen RH, Cohn LH, Nathan NS, Byrne JG, Adams DH. Does coronary artery bypass grafting alone correct moderate ischaemic mitral regurgitation? *Circulation* 2001;104:168-175.
  124. Kim YH, Czer LS, Soukiasian HJ, De Robertis M, Magliato KE, Blanche C, Raissi SS, Mirocha J, Siegel RJ, Kass RM, Trento A. Ischemic mitral regurgitation: revascularization alone versus revascularization and mitral valve repair. *Ann Thorac Surg* 2005;79:1895-1901.
  125. Di Donato M, Frigiola A, Menicanti L, Boghdabi A, Badia T, Neagu A, Montericchio V, Ranucci M. Moderate ischaemic mitral regurgitation and coronary artery bypass surgery: effect of mitral repair on clinical outcome. *J Heart Valve Dis* 2003;12:272-279.
  126. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K, ESC Committee for Practice Guideline (CPG). Executive Summary of the Guidelines on the Diagnosis and Treatment of Acute Heart Failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:384-416.
  127. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003;91:538-543.
  128. Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998;115:381-386.
  129. Romano MA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. *J Card Surg* 2004;19:396-400.
  130. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005;45:381-387.
  131. Mehra MR, Griffith BP. Is mitral regurgitation a viable treatment target in heart failure? The plot just thickened. *J Am Coll Cardiol* 2005;45:388-390.
  132. Campos PC, D'Cruz IA, Johnson LS, Malhotra A, Ramanathan KB, Weber KT. Functional valvular incompetence in decompensated heart failure: non-invasive monitoring and response to medical management. *Am J Med Sci* 2005;329:217-221.
  133. Krum H. The Task Force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: full text (update 2005). *Eur Heart J* 2005;26:2472.
  134. Breithardt OA, Sinha AM, Schwammenthal E, Bidaoui N, Markus KU, Franke A, Stellbrink C. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol* 2003;41:765-770.
  135. Iung B, Garbarz E, Michaud P, Helou S, Farah B, Berdah P, Michel PL, Cormier B, Vahanian A. Late results of percutaneous mitral commissurotomy in a series of 1024 patients. Analysis of late clinical deterioration: frequency, anatomic findings, and predictive factors. *Circulation* 1999;99:3272-3278.
  136. Faletra F, Pezzano A Jr, Fusco R, Mantero A, Corno R, Crivellaro W, De Chiara F, Vitali E, Gordini V, Magnani P, Pezzano A Sr. Measurement of mitral valve area in mitral stenosis: four echocardiographic methods compared with direct measurement of anatomic orifices. *J Am Coll Cardiol* 1996;28:1190-1197.
  137. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J* 1988;60:299-308.
  138. Padiol LR, Freitas N, Sagie A, Newell JB, Weyman AE, Levine RA, Palacios IF. Echocardiography can predict which patients will develop severe mitral regurgitation after percutaneous mitral valvulotomy. *J Am Coll Cardiol* 1996;27:1225-1231.
  139. Lev EI, Sagie A, Vaturi M, Sela N, Battler A, Shapira Y. Value of exercise echocardiography in rheumatic mitral stenosis with and without significant mitral regurgitation. *Am J Cardiol* 2004;93:1060-1063.
  140. Diker E, Aydogdu S, Ozdemir M, Kural T, Polat K, Cehreli S, Erdogan A, Goksel S. Prevalence and predictors of atrial fibrillation in rheumatic valvular heart disease. *Am J Cardiol* 1997;77:96-98.
  141. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH. Predictors of systemic embolism in patients with mitral stenosis. A prospective study. *Ann Intern Med* 1998;128:885-889.
  142. Iung B, Cormier B, Ducimetiere P, Porte JM, Nallet O, Michel PL, Acar J, Vahanian A. Immediate results of percutaneous mitral commissurotomy. A predictive model on a series of 1514 patients. *Circulation* 1996;94:2124-2130.
  143. Iung B, Nicoud-Houel A, Fondard O, Akoudad H, Haghghi T, Brochet E, Garbarz E, Cormier B, Baron G, Luxereau P, Vahanian A. Temporal trends in percutaneous mitral commissurotomy over a 15-year period. *Eur Heart J* 2004;25:702-708.
  144. Ben Farhat M, Ayari M, Maatouk F, Betbout F, Gamra H, Jarra M, Tiss M, Hammami S, Thaalbi R, Addad F. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation* 1998;97:245-250.
  145. Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevaluloplasty and postvalvuloplasty variables that predict long-term outcome. *Circulation* 2002;105:1465-1471.
  146. Antunes MJ, Vieira H, Ferrao de Oliveira J. Open mitral commissurotomy: the 'golden standard'. *J Heart Valve Dis* 2000;9:472-477.
  147. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 2000;36:1152-1158.
  148. Silaruks S, Thinkhamrop B, Kiatchoosakun S, Wongvipaporn C, Tatsanavivat P. Resolution of left atrial thrombus after 6 months of anticoagulation in candidates for percutaneous transvenous mitral commissurotomy. *Ann Intern Med* 2004;140:101-105.
  149. Iung B, Garbarz E, Michaud P, Mahdhaoui A, Helou S, Farah B, Berdah P, Michel PL, Makita Y, Cormier B, Luxereau P, Vahanian A. Percutaneous mitral commissurotomy for restenosis after surgical commissurotomy: late efficacy and implications for patient selection. *J Am Coll Cardiol* 2000;35:1295-1302.

150. Iung B, Garbarz E, Doutrelant L, Berdah P, Michaud P, Farah B, Mokhtari M, Makita Y, Michel PL, Luxereau P, Cormier B, Vahanian A. Late results of percutaneous mitral commissurotomy for calcific mitral stenosis. *Am J Cardiol* 2000;**85**:1308–1314.
151. Sutaria N, Elder AT, Shaw TRD. Long term outcome of percutaneous mitral balloon valvotomy in patients aged 70 and over. *Heart* 2000;**83**:433–438.
152. Scully HE, Armstrong CS. Tricuspid valve replacement fifteen years of experience with mechanical prostheses and bio-prostheses. *J Thorac Cardiovasc Surg* 1995;**109**:1035–1041.
153. Filsoofi F, Anyanwu AC, Salzberg SP, Frankel T, Cohn LH, Adams DH. Long-term outcomes of tricuspid valve replacement in the current era. *Ann Thorac Surg* 2005;**80**:845–850.
154. Rizzoli G, Vendramin I, Nesseris G, Bottio T, Guglielmi C, Schiavon L. Biological or mechanical prostheses in tricuspid position? A meta-analysis of intra-institutional results. *Ann Thorac Surg* 2004;**77**:1607–1614.
155. Sancaktar O, Kumbasar SD, Semiz E, Yalcinkaya S. Late results of combined percutaneous balloon valvuloplasty of mitral and tricuspid valves. *Cathet Cardiovasc Diagn* 1998;**45**:246–250.
156. Kar AK, Rath PC, Sinha N, Haridas KK, Dasbiswas A, Kerkar P, Kumar R, Non-Coronary Cardiac Intervention Registry of India, Cardiological Society of India. Noncoronary cardiac interventions. The 3rd report of the Non-Coronary Cardiac Interventions Registry of India. The Cardiological Society of India. *Indian Heart J* 2003;**55**:658–662.
157. Porter A, Shapira Y, Wurzel M, Sulkes J, Vaturi M, Adler Y, Sahar G, Sagie A. Tricuspid regurgitation late after mitral valve replacement: clinical and echocardiographic evaluation. *J Heart Valve Dis* 1999;**8**:57–62.
158. Sugiimoto T, Okada M, Ozaki N, Hatakeyama T, Kawahira T. Long-term evaluation of treatment for functional tricuspid regurgitation with regurgitant volume: characteristic differences based on primary cardiac lesion. *J Thorac Cardiovasc Surg* 1999;**117**:463–471.
159. Moss R, Munt B. Injection drug use and right-sided endocarditis. *Heart* 2003;**89**:577–581.
160. Tribouilloy CM, Enriquez-Sarano M, Bailey KR, Tajik AJ, Seward JB. Quantification of tricuspid regurgitation by measuring the width of the vena contracta with Doppler color flow imaging: a clinical study. *J Am Coll Cardiol* 2000;**36**:472–478.
161. Colombo T, Russo C, Ciliberto GR, Lanfranco M, Bruschi G, Agati S, Vitali E. Tricuspid regurgitation secondary to mitral valve disease: tricuspid annulus function as guide to tricuspid valve repair. *Cardiovasc Surg* 2001;**9**:369–377.
162. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? *Ann Thorac Surg* 2005;**79**:127–132.
163. Rivera R, Duran E, Ajuria M. Carpentier's flexible ring versus De Vega's annuloplasty. A prospective randomized study. *J Thorac Cardiovasc Surg* 1985;**89**:196–203.
164. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, Miller HC. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine prostheses. *Heart* 2003;**89**:715–721.
165. Lund O, Bland M. Age and risk corrected impact of mechanical versus biological valves on long-term mortality after aortic valve replacement. *J Thorac Cardiovasc Surg* 2006;**132**:20–26.
166. Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. *Curr Probl Cardiol* 2000;**25**:73–156.
167. Rahimtoola SJ. Choice of prosthetic heart valve for adult patients. *J Am Coll Cardiol* 2003;**41**:893–904.
168. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. *J Thorac Cardiovasc Surg* 2002;**123**:715–723.
169. O'Brien MF, Hancock S, Stafford EG. The homograft aortic valve: a 29-year, 99.3% follow-up of 1,022 valve replacements. *J Heart Valve Dis* 2001;**10**:334–344.
170. Elkins RC, Knott-Craig CJ, Ward KE. Pulmonary autograft in children: realized growth potential. *Ann Thorac Surg* 1994;**57**:1387–1392.
171. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Arch Intern Med* 2001;**161**:2125–2128.
172. Poli D, Antonucci E, Lombardi A, Boddi V, Gensini GF, Abbate R, Prisco D. Low rate of bleeding and thrombotic complications of oral anticoagulant therapy independent of age in the real-practice of an anticoagulation clinic. *Blood Coagul Fibrinolysis* 2003;**14**:269–275.
173. Grunkemeier GL, Jamieson WRE, Miller DC, Starr A. Actuarial versus actual risk of porcine structural valve deterioration. *J Thorac Cardiovasc Surg* 1994;**108**:709–718.
174. Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? *Circulation* 2002;**105**:1336–1341.
175. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. *Circulation* 2003;**107**:1240–1246.
176. Fitzmaurice DA, Machin SJ, British Society of Haematology Task Force for Haemostasis Thrombosis. Recommendations for patients undertaking self management of oral anticoagulation. *BMJ* 2001;**323**:985–989.
177. Butchart EG, Ionescu A, Payne N, Giddings J, Grunkemeier GL, Fraser AG. A new scoring system to determine thromboembolic risk after heart valve replacement. *Circulation* 2003;**108**(Suppl. II):68–74.
178. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, Pauker SG. Antithrombotic therapy in valvular heart disease—native and prosthetic. *Chest* 2004;**126**(Suppl.):457S–482S.
179. Gherli T, Colli A, Fragnito C, Nicolini F, Borrello B, Sacconi S, D'Amico R, Beghi C. Comparing warfarin with aspirin after biological aortic valve replacement: a prospective study. *Circulation* 2004;**110**:496–500.
180. Laplace G, Lafitte S, Labeque JN, Perron JM, Baudet E, Deville C, Roques X, Roudaut R. Clinical significance of early thrombosis after prosthetic mitral valve replacement: a postoperative monocentric study of 680 patients. *J Am Coll Cardiol* 2004;**43**:1283–1290.
181. Acar J, Iung B, Boissel JP, Samama MM, Michel PL, Teppe JP, Pony JC, Breton HL, Thomas D, Isnard R, de Gevigny G, Viguiet E, Sfihi A, Hanania G, Ghannem M, Mirode A, Nemoz C. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation* 1996;**94**:2107–2112.
182. Huth C, Friedl A, Rost A, for the GELIA study investigator group. Intensity of oral anticoagulation after implantation of St Jude Medical aortic prosthesis: analysis of the GELIA database (GELIA 4). *Eur Heart J* 2001;**3**(Suppl. Q):Q33–Q38.
183. Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. *Ann Intern Med* 2001;**135**:393–400.
184. Makris M, Watson HG. The management of coumarin-induced over-anticoagulation. *Br J Haematol* 2001;**114**:271–280.
185. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
186. Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, Klimek M, Hirsh J. A comparison of aspirin with placebo in patients treated with warfarin after heart valve replacement. *N Engl J Med* 1993;**329**:524–529.
187. Chesebro J, Fuster V, Elveback LR. Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: danger of aspirin compared with dipyridamole. *Am J Cardiol* 1983;**51**:1537–1541.
188. Pouleur H, Buyse M. Effects of dipyridamole in combination with anti-coagulant therapy on survival and thromboembolic events in patients with prosthetic heart valves. A meta-analysis of the randomized trials. *J Thorac Cardiovasc Surg* 1995;**110**:463–472.
189. Cappelleri JC, Fiore LD, Brophy MT, Deykin D, Lau J. Efficacy and safety of combined anticoagulant and antiplatelet therapy versus anticoagulant monotherapy after mechanical heart valve replacement: a meta-analysis. *Am Heart J* 1995;**130**:547–552.
190. Laffort P, Roudaut R, Roques X, Lafitte S, Deville C, Bonnet J, Baudet E. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transeophageal echocardiographic study. *J Am Coll Cardiol* 2001;**35**:739–746.
191. Massel D, Little SH. Risks and benefits of adding antiplatelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. *J Am Coll Cardiol* 2001;**37**:569–578.
192. Orford JL, Fasseas P, Melby S, Burger K, Steinhilb SR, Holmes DR, Berger PB. Safety and efficacy of aspirin, clopidogrel and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J* 2004;**147**:463–467.
193. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W, Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary

- interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–847.
194. Lengyel M, Fuster V, Keltai M, Roudaut R, Schulte HD, Seward JB, Chesebro JH, Turpie AG. Guidelines for management of left-sided prosthetic valve thrombosis: a role for thrombolytic therapy. *J Am Coll Cardiol* 1997;**30**:1521–1526.
  195. Gohlke-Bärwolf C. Anticoagulation in valvar heart disease: new aspects and management during non-cardiac surgery. *Heart* 2000;**84**:567–572.
  196. Dunn AS, Turpie AGG. Perioperative management of patients receiving oral anticoagulants. A systematic review. *Arch Intern Med* 2003;**163**:901–908.
  197. Wahl MJ. Dental surgery in anticoagulated patients. *Arch Intern Med* 1998;**158**:1610–1616.
  198. Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. *Br J Haematol* 2003;**123**:676–682.
  199. Meurin P, Tabet JY, Weber H, Renaud N, Ben Driss A. Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement. *Circulation* 2006;**113**:564–569.
  200. Seshadri N, Goldhaber SZ, Elkayam U, Grimm RA, Groce JB III, Heit JA, Spinler SA, Turpie AG, Bosker G, Klein AL. The clinical challenge of bridging anticoagulation with low-molecular-weight heparin in patients with mechanical prosthetic heart valves: an evidence-based comparative review focusing on anticoagulation options in pregnant and nonpregnant patients. *Am Heart J* 2005;**150**:27–34.
  201. Ferreira I, Dos L, Tornos P, Nicolau I, Permyer-Miralda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocoumarol. *Heart* 2003;**89**:527–530.
  202. Tong AT, Roudaut R, Ozkan M, Sagie A, Shahid MS, Pontes Junior SC, Carreras F, Girard SE, Arnaout S, Stainback RF, Thadhani R, Zoghbi WA, Prosthetic Valve Thrombolysis—Role of Transesophageal Echocardiography (PRO-TEE) Registry Investigators. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. *J Am Coll Cardiol* 2004;**43**:77–84.
  203. Montorsi P, De Bernardi F, Muratori M, Cavoretto D, Pepi M. Role of cine-fluoroscopy, transthoracic, and TEE in patients with suspected prosthetic heart valve thrombosis. *Am J Cardiol* 2000;**85**:58–64.
  204. Roudaut R, Lafitte S, Roudaut MF, Courtaut C, Perron JM, Jais C, Pillois X, Coste P, DeMaria A. Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003;**41**:653–658.
  205. Lengyel M, Horstkotte D, Voller H, Mistiaen WP, Working Group Infection, Thrombosis, Embolism Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis* 2005;**14**:567–575.
  206. Rizzoli G, Guglielmi C, Toscano G, Pistorio V, Vendramin I, Bottio T, Thiene G, Casarotto D. Reoperations for acute prosthetic thrombosis and pannus: an assessment of rates, relationship and risk. *Eur J Cardiothorac Surg* 1999;**16**:74–80.
  207. Iung B, Cormier B, Dadez E, Drissi MF, Tsezana R, Viguier E, Cavielz B, Michel PL, Samama M, Vahanian A, Acar J. Small abnormal echos after mitral valve replacement with bileaflet mechanical prostheses: predisposing factors and effect on thromboembolism. *J Heart Valve Dis* 1993;**2**:259–266.
  208. Gueret P, Vignon P, Fournier P, Chabernaude JM, Gomez M, LaCroix P, Bensaïd J. TEE for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prosthesis. *Circulation* 1995;**91**:103–110.
  209. Butchart EG, Moreno de la Santa P, Rooney SJ, Lewis PA. Arterial risk factors and cerebrovascular events following aortic valve replacement. *J Heart Valve Dis* 1995;**4**:1–8.
  210. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using TEE. *Heart* 2003;**89**:1316–1321.
  211. Hussain ST, Devagourou V, Sampath Kumar A. Management of mitral paravalvular leak: therapy or misadventure? *J Thorac Cardiovasc Surg* 2003;**126**:879–880.
  212. Vogt PR, Brunner-LaRocca H, Sidler P, Zund G, Truniger K, Lachat M, Turina J, Turina M. Reoperative surgery for degenerated aortic bioprostheses: predictors for emergency surgery and reoperative mortality. *Eur J Cardiothorac Surg* 2000;**17**:134–139.
  213. Akins CW, Buckley MJ, Daggett WM, Hilgenberg AD, Vlahakes GJ, Torchiana DF, Madsen JC. Risk of reoperative valve replacement for failed mitral and aortic bioprostheses. *Ann Thorac Surg* 1998;**65**:1545–1551.
  214. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr, American College of Cardiology, American Heart Association. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery—Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2002;**39**:542–553.
  215. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;**100**:1043–1049.
  216. O’Keefe JH Jr, Shub C, Rettke SR. Risk of noncardiac surgical procedures in patients with aortic stenosis. *Mayo Clin Proc* 1989;**64**:400–405.
  217. Raymer K, Yang H. Patients with aortic stenosis: cardiac complications in non-cardiac surgery. *Can J Anaesth* 1998;**45**:855–859.
  218. Torsher LC, Shub C, Rettke SR, Brown DL. Risk of patients with severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol* 1998;**81**:448–452.
  219. Kertai MD, Bountiokos M, Boersma E, Bax JJ, Thomson IR, Sozzi F, Klein J, Roelandt JR, Poldermans D. Aortic stenosis: an underestimated risk factor for perioperative complications in patients undergoing non-cardiac surgery. *Am J Med* 2004;**116**:8–13.
  220. Boon NA, Bloomfield P. The medical management of valvar heart disease. *Heart* 2002;**87**:395–400.
  221. Bradley D, Creswell LL, Hoghe ChW, Epstein AE, Prystowsky EN, Daoud EG. Pharmacologic prophylaxis. American College of Chest Physicians Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery. *Chest* 2005;**128**:395–475.
  222. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;**341**:1789–1794.
  223. Thorne SA. Pregnancy in heart disease. *Heart* 2004;**90**:450–456.
  224. Oakley C, Child A, Iung B, Presbitero P, Tornos P. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003;**24**:761–781.
  225. Siu SC, Sermer M, Harrison DA, Grigoriadis E, Liu G, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Colman JM. Risk and predictors for pregnancy-related complications in women with heart disease. *Circulation* 1997;**96**:2789–2794.
  226. Hameed A, Karaalp IS, Tummala PP, Wani OR, Canetti M, Akhter MW, Goodwin I, Zapadinsky N, Elkayam U. The effect of valvular heart disease on maternal and fetal outcome during pregnancy. *J Am Coll Cardiol* 2001;**37**:893–899.
  227. Malhotra M, Sharma JB, Tripathii R, Arora P, Arora R. Maternal and fetal outcome in valvular heart disease. *Int J Gynaecol Obstet* 2004;**84**:11–16.
  228. Rossiter JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;**173**:1599–1606.
  229. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;**160**:191–196.
  230. Elkayam U. Valvular heart disease and pregnancy. Part II: Prosthetic valves. *J Am Coll Cardiol* 2005;**46**:403–410.
  231. Arnoni RT, Arnoni AS, Bonini RC, de Almeida AF, Neto CA, Dinkhuysen JJ, Issa M, Chaccor P, Paulista PP. Risk factors associated with cardiac surgery during pregnancy. *Ann Thorac Surg* 2003;**76**:1605–1608.
  232. Presbitero P, Prever SB, Brusca A. Interventional cardiology in pregnancy. *Eur Heart J* 1996;**17**:182–188.