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PRACTICE GUIDELINE

2008 Focused Update Incorporated Into the 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)

Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

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PREAMBLE (UPDATED)

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies as they are introduced in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting the absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, whose charge is to develop, update, or revise practice guidelines for important cardiovascular diseases and procedures. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop and update written recommendations for clinical practice.

Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups where appropriate. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of particular tests or therapies are considered, as well as frequency of follow-up. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will be the primary basis for preparing recommendation in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflicts of interest that may arise as a result of an outside relationship or personal interest of a member of the writing committee. Specifically, all members of the writing committee and peer reviewers of the document are asked to provide disclosure statements of all such relationships that may be perceived as real or potential conflicts of interest. Writing committee members are also strongly encouraged to declare a previous relationship with industry that may be perceived as relevant to guideline development. If a writing committee member develops a new relationship with industry during his or her tenure, he or she is required to notify guideline staff in writing. The continued participation of the writing committee member will be reviewed. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at each meeting, and updated and reviewed by the writing committee as changes occur. Please refer to the methodology manual for the ACC/AHA guideline writing committees for further description and the relationships with industry policy (1067). See Appendix 1 for a list of writing committee member relationships with industry and Appendix 2 for a listing of peer reviewer relationships with industry that are pertinent to this guideline.

These practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. See Appendix 3 for a list of abbreviated terms used in this guideline. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all of the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The current document is a republication of the "ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease" (1068), revised to incorporate individual recommendations from a 2008 focused update (1069), which spotlights the 2007 AHA Guidelines for Infective Endocarditis Prophylaxis. For easy reference, this online-only version denotes sections that have been updated. All members of the 2006 Valvular Heart Disease Writing Committee were invited to participate in the writing group; those who agreed were required to disclose all relationships with industry relevant to the data under consideration (1067), as were all peer reviewers of the document. (See Appendixes 4 and 5 for a listing of relationships with industry for the 2008 Focused Update Writing Group and peer reviewers, respectively.) Each recommendation required a confidential vote by the writing group members before and after external review of the document. Any writing group member with a significant (greater than $10 000) relationship with industry relevant to the recommendation was recused from voting on that recommendation.

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Guidelines are reviewed annually by the ACC/AHA Task Force on Practice Guidelines and are considered current unless they are updated or sunsetted and withdrawn from distribution.

Sidney C. Smith, Jr., MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

1. INTRODUCTION

1.1. Evidence Review (UPDATED)

The ACC and the AHA have long been involved in the joint development of practice guidelines designed to assist healthcare providers in the management of selected cardiovascular disorders or the selection of certain cardiovascular procedures. The determination of the disorders or procedures to develop guidelines is based on several factors, including importance to healthcare providers and whether there are sufficient data from which to derive accepted guidelines. One important category of cardiac disorders that affect a large number of patients who require diagnostic procedures and decisions regarding long-term management is valvular heart disease.

During the past 2 decades, major advances have occurred in diagnostic techniques, the understanding of natural history, and interventional cardiology and surgical procedures for patients with valvular heart disease. These advances have resulted in enhanced diagnosis, more scientific selection of patients for surgery or catheter-based intervention versus medical management, and increased survival of patients with these disorders. The information base from which to make clinical management decisions has greatly expanded in recent years, yet in many situations, management issues remain controversial or uncertain. Unlike many other forms of cardiovascular disease, there is a scarcity of large-scale multicenter trials addressing the diagnosis and treatment of patients with valvular disease from which to derive definitive conclusions, and the information available in the literature represents primarily the experiences reported by single institutions in relatively small numbers of patients.

The 1998 Committee on Management of Patients With Valvular Heart Disease reviewed and compiled this information base and made recommendations for diagnostic testing, treatment, and physical activity. For topics for which there was an absence of multiple randomized, controlled trials, the preferred basis for medical decision making in clinical practice (evidence-based medicine), the committee's recommendations were based on data derived from single randomized trials or nonrandomized studies or were based on a consensus opinion of experts. The 2006 writing committee was charged with revising the guidelines published in 1998. The committee reviewed pertinent publications, including abstracts, through a computerized search of the English literature since 1998 and performed a manual search of final articles. Special attention was devoted to identification of randomized trials published since the original document. A complete listing of all publications covering the treatment of valvular heart disease is beyond the scope of this document; the document includes those reports that the committee believes represent the most comprehensive or convincing data that are necessary to support its conclusions. However, evidence tables were updated to reflect major advances over this time period. Inaccuracies or inconsistencies present in the original publication were identified and corrected when possible. Recommendations provided in this document are based primarily on published data. Because randomized trials are unavailable in many facets of valvular heart disease treatment, observational studies, and in some areas, expert opinions form the basis for recommendations that are offered.

All of the recommendations in this guideline revision were converted from the tabular format used in the 1998 guideline to a listing of recommendations that has been written in full sentences to express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document, would still convey the full intent of the recommendation. It is hoped that this will increase the readers' comprehension of the guidelines. Also, the level of evidence, either A, B, or C, for each recommendation is now provided.

Classification of recommendations and level of evidence are expressed in the ACC/AHA format as follows:

- CLASS I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
- CLASS II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- CLASS IIA: Weight of evidence/opinion is in favor of usefulness/efficacy.
- CLASS IIB: Usefulness/efficacy is less well established by evidence/opinion.
- CLASS III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

In addition, the weight of evidence in support of the recommendation is listed as follows:

- Level of Evidence A: Data derived from multiple randomized clinical trials.
- Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

The schema for classification of recommendations and level of evidence is summarized in Figure 1, which also illustrates how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect.

Writing committee membership consisted of cardiovascular disease specialists and representatives of the cardiac surgery and cardiac anesthesiology fields; both the academic

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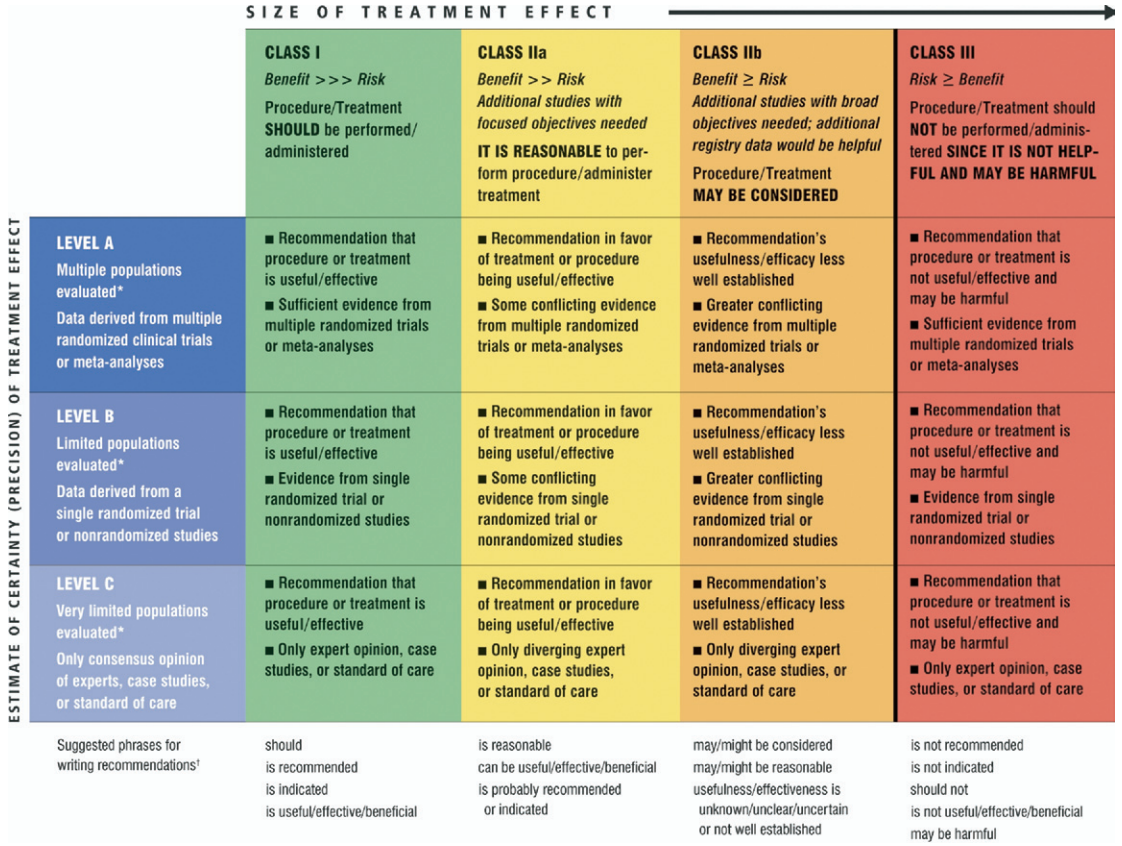

Figure 1. Applying Classification of Recommendations and Level of Evidence

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. †In 2003 the ACC/AHA Task Force on Practice Guidelines recently provided a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

and private practice sectors were represented. The Society of Cardiovascular Anesthesiologists assigned an official representative to the writing committee.

1.2. Scope of the Document (UPDATED)

The guidelines attempt to deal with general issues of treatment of patients with heart valve disorders, such as evaluation of patients with heart murmurs, prevention and treatment of endocarditis, management of valve disease in pregnancy, and treatment of patients with concomitant coronary artery disease (CAD), as well as more specialized issues that pertain to specific valve lesions. The guidelines focus primarily on valvular heart disease in the adult, with a separate section dealing with specific recommendations for valve disorders in adolescents and young adults. The diagnosis and management of infants and young children with congenital valvular abnormalities are significantly different from those of the adolescent or adult and are beyond the scope of these guidelines.

This task force report overlaps with several previously published ACC/AHA guidelines about cardiac imaging and diagnostic testing, including the guidelines for the clinical use of cardiac radionuclide imaging (1), the clinical application of echocardiography (2), exercise testing (3), and percutaneous coronary intervention (4). Although these guidelines are not intended to include detailed information covered in previous guidelines on the use of imaging and diagnostic testing, an essential component of this report is the discussion of indications for these tests in the evaluation and treatment of patients with valvular heart disease.

The committee emphasizes the fact that many factors ultimately determine the most appropriate treatment of individual patients with valvular heart disease within a given community. These include the availability of diagnostic equipment and expert diagnosticians, the expertise of interventional cardiologists and surgeons, and notably, the wishes of well-informed patients. Therefore, deviation from these guidelines may be appropriate in some circumstances. These guidelines are written with the assumption that a diagnostic test can be performed and interpreted with skill levels consistent with previously reported ACC training and

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competency statements and ACC/AHA guidelines, that interventional cardiological and surgical procedures can be performed by highly trained practitioners within acceptable safety standards, and that the resources necessary to perform these diagnostic procedures and provide this care are readily available. This is not true in all geographic areas, which further underscores the committee's position that its recommendations are guidelines and not rigid requirements.

1.3. Review and Approval (NEW)

The 2006 document (1068) was reviewed by 2 official reviewers nominated by the ACC; 2 official reviewers nominated by the AHA; 1 official reviewer from the ACC/AHA Task Force on Practice Guidelines; reviewers nominated by the Society of Cardiovascular Anesthesiologists, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons (STS); and individual content reviewers, including members of the ACCF Cardiac Catheterization and Intervention Committee, ACCF Cardiovascular Imaging Committee, ACCF Cardiovascular Surgery Committee, AHA Endocarditis Committee, AHA Cardiac Clinical Imaging Committee, AHA Cardiovascular Intervention and Imaging Committee, and AHA Cerebrovascular Imaging and Intervention Committee.

As mentioned previously, this document also incorporates a 2008 focused update of the "ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease" (1069), which spotlights the 2007 AHA Guidelines for Infective Endocarditis Prophylaxis (1070). Only recommendations related to infective endocarditis have been revised. This document was reviewed by 2 external reviewers nominated by the ACC and 2 external reviewers nominated by the AHA, as well as 3 reviewers from the ACCF Congenital Heart Disease and Pediatric Committee, 2 reviewers from the ACCF Cardiovascular Surgery Committee, 5 reviewers from the AHA Heart Failure and Transplant Committee, and 3 reviewers from the Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee. All information about reviewers' relationships with industry was collected and distributed to the writing committee and is published in this document (see Appendix 5 for details). This document was approved for publication by the governing bodies of the ACCF and the AHA in May 2008 and endorsed by the Society of Cardiovascular Anesthesiologists, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons.

2. GENERAL PRINCIPLES

2.1. Evaluation of the Patient With a Cardiac Murmur

2.1.1. Introduction (UPDATED)

Cardiac auscultation remains the most widely used method of screening for valvular heart disease (VHD). The production of murmurs is due to 3 main factors:

- high blood flow rate through normal or abnormal orifices
- forward flow through a narrowed or irregular orifice into a dilated vessel or chamber
- backward or regurgitant flow through an incompetent valve

Often, more than 1 of these factors is operative (5–7).

A heart murmur may have no pathological significance or may be an important clue to the presence of valvular, congenital, or other structural abnormalities of the heart (8). Most systolic heart murmurs do not signify cardiac disease, and many are related to physiological increases in blood flow velocity (9). In other instances, a heart murmur may be an important clue to the diagnosis of undetected cardiac disease (e.g., valvular aortic stenosis [AS]) that may be important even when asymptomatic or that may define the reason for cardiac symptoms. In these situations, various noninvasive or invasive cardiac tests may be necessary to establish a firm diagnosis and form the basis for rational treatment of an underlying disorder. Echocardiography is particularly useful in this regard, as discussed in the "ACC/AHA/ASE 2003 Guidelines for the Clinical Application of Echocardiography" (2). Diastolic murmurs virtually always represent pathological conditions and require further cardiac evaluation, as do most continuous murmurs. Continuous "innocent" murmurs include venous hums and mammary souffles.

The traditional auscultation method of assessing cardiac murmurs has been based on their timing in the cardiac cycle, configuration, location and radiation, pitch, intensity (grades 1 through 6), and duration (5–9). The configuration of a murmur may be crescendo, decrescendo, crescendo-decrescendo (diamond-shaped), or plateau. The precise times of onset and cessation of a murmur associated with cardiac pathology depend on the period of time in the cardiac cycle in which a physiologically important pressure difference between 2 chambers occurs (5–9). A classification of cardiac murmurs is listed in Table 1.

Table 1. Classification of Cardiac Murmurs

1. Systolic murmurs
   a. Holosystolic (pansystolic) murmurs
   b. Midsystolic (systolic ejection) murmurs
   c. Early systolic murmurs
   d. Mid to late systolic murmurs
2. Diastolic murmurs
   a. Early high-pitched diastolic murmurs
   b. Middiastolic murmurs
   c. Presystolic murmurs
3. Continuous murmurs

2.1.2. Classification of Murmurs

Holosystolic (pansystolic) murmurs are generated when there is flow between chambers that have widely different pressures throughout systole, such as the left ventricle and either the left atrium or right ventricle. With an abnormal

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regurgitant orifice, the pressure gradient and regurgitant jet begin early in contraction and last until relaxation is almost complete.

Midsystolic (systolic ejection) murmurs, often crescendo-decrescendo in configuration, occur when blood is ejected across the aortic or pulmonic outflow tracts. The murmurs start shortly after S_1, when the ventricular pressure rises sufficiently to open the semilunar valve. As ejection increases, the murmur is augmented, and as ejection declines, it diminishes.

In the presence of normal semilunar valves, this murmur may be caused by an increased flow rate such as that which occurs with elevated cardiac output (e.g., pregnancy, thyrotoxicosis, anemia, and arteriovenous fistula), ejection of blood into a dilated vessel beyond the valve, or increased transmission of sound through a thin chest wall. Most innocent murmurs that occur in children and young adults are midsystolic and originate either from the aortic or pulmonic outflow tracts. Valvular, supravalvular, or subvalvular obstruction (stenosis) of either ventricle may also cause a midsystolic murmur, the intensity of which depends in part on the velocity of blood flow across the narrowed area. Midsystolic murmurs also occur in certain patients with functional mitral regurgitation (MR) or, less frequently, tricuspid regurgitation (TR). Echocardiography is often necessary to separate a prominent and exaggerated (grade 3) benign midsystolic murmur from one due to valvular AS.

Early systolic murmurs are less common; they begin with the first sound and end in midsystole. An early systolic murmur is often due to TR that occurs in the absence of pulmonary hypertension, but it also occurs in patients with acute MR. In large ventricular septal defects with pulmonary hypertension and small muscular ventricular septal defects, the shunting at the end of systole may be insignificant, with the murmur limited to early and midsystole.

Late systolic murmurs are soft or moderately loud, high-pitched murmurs at the left ventricular (LV) apex that start well after ejection and end before or at S_2. They are often due to apical tethering and malcoaptation of the mitral leaflets due to anatomic and functional changes of the annulus and ventricle. Late systolic murmurs in patients with midsystolic clicks result from late systolic regurgitation due to prolapse of the mitral leaflet(s) into the left atrium. Such late systolic murmurs can also occur in the absence of clicks.

Early diastolic murmurs begin with or shortly after S_2, when the associated ventricular pressure drops sufficiently below that in the aorta or pulmonary artery. High-pitched murmurs of aortic regurgitation (AR) or pulmonic regurgitation due to pulmonary hypertension are generally decrescendo, consistent with the rapid decline in volume or rate of regurgitation during diastole. The diastolic murmur of pulmonic regurgitation without pulmonary hypertension is low to medium pitched, and the onset of this murmur is slightly delayed because regurgitant flow is minimal at pulmonic valve closure, when the reverse pressure gradient responsible for the regurgitation is minimal. Such murmurs are common late after repair of tetralogy of Fallot.

Middiastolic murmurs usually originate from the mitral and tricuspid valves, occur early during ventricular filling, and are due to a relative disproportion between valve orifice size and diastolic blood flow volume. Although they are usually due to mitral or tricuspid stenosis, middiastolic murmurs may also be due to increased diastolic blood flow across the mitral or tricuspid valve when such valves are severely regurgitant, across the normal mitral valve (MV) in patients with ventricular septal defect or patent ductus arteriosus, and across the normal tricuspid valve in patients with atrial septal defect. In severe, chronic AR, a low-pitched, rumbling diastolic murmur (Austin-Flint murmur) is often present at the LV apex; it may be either middiastolic or presystolic. An opening snap is absent in isolated AR.

Presystolic murmurs begin during the period of ventricular filling that follows atrial contraction and therefore occur in sinus rhythm. They are usually due to mitral or tricuspid stenosis. A right or left atrial myxoma may cause either middiastolic or presystolic murmurs similar to tricuspid or mitral stenosis (MS).

Continuous murmurs arise from high- to low-pressure shunts that persist through the end of systole and the beginning of diastole. Thus, they begin in systole, peak near S_2, and continue into all or part of diastole. There are many causes of continuous murmurs, but they are uncommon in patients with valvular heart disease (5–9).

2.1.2.1. DYNAMIC CARDIAC AUSCULTATION

Attentive cardiac auscultation during dynamic changes in cardiac hemodynamics often enables the observer to deduce the correct origin and significance of a cardiac murmur (10–13). Changes in the intensity of heart murmurs during various maneuvers are indicated in Table 2.

2.1.2.2. OTHER PHYSICAL FINDINGS

The presence of other physical findings, either cardiac or noncardiac, may provide important clues to the significance of a cardiac murmur and the need for further testing (Fig. 2). For example, a right heart murmur in early to midsystole at the lower left sternal border likely represents TR without pulmonary hypertension in an injection drug user who presents with fever, petechiae, Osler's nodes, and Janeway lesions.

Associated cardiac findings frequently provide important information about cardiac murmurs. Fixed splitting of the second heart sound during inspiration and expiration in a patient with a grade 2/6 midsystolic murmur in the pulmonic area and left sternal border should suggest the possibility of an atrial septal defect. A soft or absent A_2 or reversed splitting of S_2 may denote severe AS. An early aortic systolic ejection sound heard during inspiration and expiration suggests a bicuspid aortic valve, whereas an ejection sound heard only in the pulmonic area and at the left sternal border during expiration usually denotes pulmonic valve stenosis. LV dilatation on precordial palpation

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Table 2. Interventions Used to Alter the Intensity of Cardiac Murmurs

Respiration	Right-sided murmurs generally increase with inspiration. Left-sided murmurs usually are louder during expiration.
Valsalva maneuver	Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva, right-sided murmurs tend to return to baseline intensity earlier than left-sided murmurs.
Exercise	Murmurs caused by blood flow across normal or obstructed valves (e.g., PS and MS) become louder with both isotonic and isometric (handgrip) exercise. Murmurs of MR, VSD, and AR also increase with handgrip exercise.
Positional changes	With standing, most murmurs diminish, 2 exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With brisk squatting, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results as brisk squatting.
Postventricular premature beat or atrial fibrillation	Murmurs originating at normal or stenotic semilunar valves increase in intensity during the cardiac cycle after a VPB or in the beat after a long cycle length in AF. By contrast, systolic murmurs due to atrioventricular valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).
Pharmacological interventions	During the initial relative hypotension after amyl nitrite inhalation, murmurs of MR, VSD, and AR decrease, whereas murmurs of AS increase because of increased stroke volume. During the later tachycardia phase, murmurs of MS and right-sided lesions also increase. This intervention may thus distinguish the murmur of the Austin-Flint phenomenon from that of MS. The response in MVP often is biphasic (softer then louder than control).
Transient arterial occlusion	Transient external compression of both arms by bilateral cuff inflation to 20 mm Hg greater than peak systolic pressure augments the murmurs of MR, VSD, and AR but not murmurs due to other causes.

AF indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PS, pulmonic stenosis; VPB, ventricular premature beat; and VSD, ventricular septal defect.

and bibasilar pulmonary rales favor the diagnosis of severe, chronic MR in a patient with a grade 2/6 holosystolic murmur at the cardiac apex. A slow-rising, diminished arterial pulse suggests severe AS in a patient with a grade 2/6 midsystolic murmur at the second right intercostal space. The typical parvus et tardus pulse may be absent in the elderly, even in those with severe AS, secondary to the effects of aging on the vasculature. Pulsus parvus may also occur with severely reduced cardiac output from any cause. Factors that aid in the differential diagnosis of LV outflow tract obstruction are listed in Table 3 (14). Examination of the jugular venous wave forms may provide additional or corroborative information. For example, regurgitant cv waves are indicative of TR and are often present without an audible murmur.

2.1.2.3. ASSOCIATED SYMPTOMS

An important consideration in the patient with a cardiac murmur is the presence or absence of symptoms (15) (Fig. 2). For example, symptoms of syncope, angina pectoris, or heart failure in a patient with a midsystolic murmur will usually result in a more aggressive diagnostic approach than in a patient with a similar midsystolic murmur who has none of these symptoms. An echocardiogram to rule in or

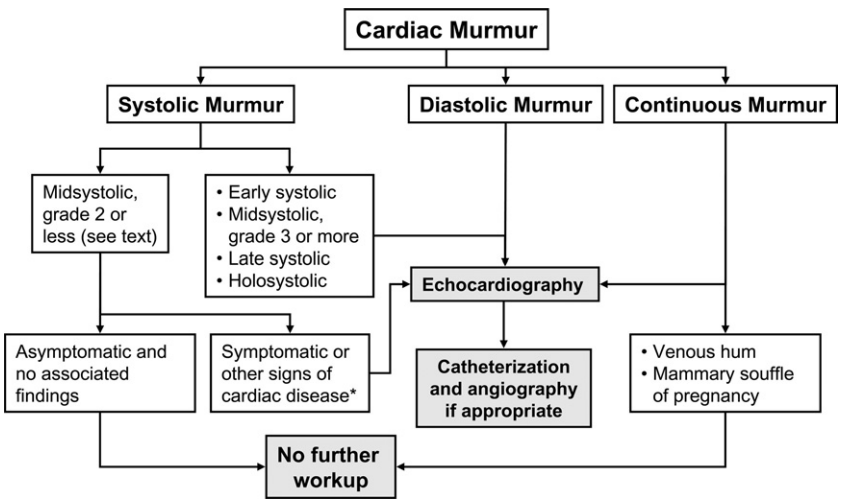

Figure 2. Strategy for Evaluating Heart Murmurs

*If an electrocardiogram or chest X-ray has been obtained and is abnormal, echocardiography is indicated.

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Table 3. Factors That Differentiate the Various Causes of Left Ventricular Outflow Tract Obstruction

Factor	Valvular	Supravalvular	Discrete Subvalvular	Obstructive HCM
Valve calcification	Common after age 40 y	No	No	No
Dilated ascending aorta	Common after age 40 y	Rare	Rare	Rare
PP after VPB	Increased	Increased	Increased	Decreased
Valsalva effect on SM	Decreased	Decreased	Decreased	Increased
Murmur of AR	Common after age 40 y	Rare	Sometimes	No
Fourth heart sound (S_4)	If severe	Uncommon	Uncommon	Common
Paradoxical splitting	Sometimes*	No	No	Rather common*
Ejection click	Most (unless valve calcified)	No	No	Uncommon or none
Maximal thrill and murmur	2nd RIS	1st RIS	2nd RIS	4th LIS
Carotid pulse	Normal to anacrotic* (parvus et tardus)	Unequal	Normal to anacrotic	Brisk, jerky, systolic rebound

*Depends on severity. Modified with permission from Marriott HJL. Bedside cardiac diagnosis. Philadelphia, Pa: Lippincott; 1993:116.
AR indicates aortic regurgitation; HCM, hypertrophic cardiomyopathy; LIS, left intercostal space; PP, pulse pressure; RIS, right intercostal space; SM, systolic murmur; and VPB, ventricular premature beat.

rule out the presence of significant AS should be obtained. A history of thromboembolism will also usually result in a more extensive workup. In patients with cardiac murmurs and clinical findings suggestive of endocarditis, echocardiography is indicated (2).

Conversely, many asymptomatic children and young adults with grade 2/6 midsystolic murmurs and no other cardiac physical findings need no further workup after the initial history and physical examination (Fig. 2). A particularly important group is the large number of asymptomatic older patients, many with systemic hypertension, who have midsystolic murmurs, usually of grade 1 or 2 intensity, related to sclerotic aortic valve leaflets; flow into tortuous, noncompliant great vessels; or a combination of these findings. Such murmurs must be distinguished from those caused by more significant degrees of aortic valve thickening, calcification, and reduced excursion that result in milder or greater degrees of valvular AS. The absence of LV hypertrophy on the electrocardiogram (ECG) may be reassuring, but echocardiography is frequently necessary. Aortic sclerosis can be defined by focal areas of increased echogenicity and thickening of the leaflets without restriction of motion and a peak velocity of less than 2.0 m per second. The recognition of aortic valve sclerosis may prompt the initiation of more aggressive programs of coronary heart disease prevention. In patients with AS, it is difficult to assess the rate and severity of disease progression on the basis of auscultatory findings alone.

2.1.3. Electrocardiography and Chest Roentgenography

Although echocardiography usually provides more specific and often quantitative information about the significance of a heart murmur and may be the only test needed, the ECG and chest X-ray are readily available and may have been obtained previously. The absence of ventricular hypertrophy, atrial enlargement, arrhythmias, conduction abnormalities, prior myocardial infarction, and evidence of active ischemia on the ECG provides useful negative information at a relatively low cost. Abnormal ECG findings in a patient with a heart murmur, such as ventricular hypertrophy or a prior infarction, should lead to a more extensive evaluation that includes echocardiography (Fig. 2).

Posteroanterior and lateral chest roentgenograms often yield qualitative information on cardiac chamber size, pulmonary blood flow, pulmonary and systemic venous pressure, and cardiac calcification in patients with cardiac murmurs. When abnormal findings are present on chest X-ray, echocardiography should be performed (Fig. 2). A normal chest X-ray and ECG are likely in asymptomatic patients with isolated midsystolic murmurs, particularly in younger age groups, when the murmur is grade 2 or less in intensity and heard along the left sternal border (16–18). Routine ECG and chest radiography are not recommended in this setting.

2.1.4. Echocardiography

CLASS I

1. Echocardiography is recommended for asymptomatic patients with diastolic murmurs, continuous murmurs, holosystolic murmurs, late systolic murmurs, murmurs associated with ejection clicks, or murmurs that radiate to the neck or back. *(Level of Evidence: C)*
2. Echocardiography is recommended for patients with heart murmurs and symptoms or signs of heart failure, myocardial ischemia/infarction, syncope, thromboembolism, infective endocarditis, or other clinical evidence of structural heart disease. *(Level of Evidence: C)*
3. Echocardiography is recommended for asymptomatic patients who have grade 3 or louder midpeaking systolic murmurs. *(Level of Evidence: C)*

CLASS IIa

1. Echocardiography can be useful for the evaluation of asymptomatic patients with murmurs associated with other abnormal cardiac physical findings or murmurs associated with an abnormal ECG or chest X-ray. *(Level of Evidence: C)*
2. Echocardiography can be useful for patients whose symptoms and/or signs are likely noncardiac in origin but in whom a cardiac basis cannot be excluded by standard evaluation. *(Level of Evidence: C)*

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CLASS III

Echocardiography is not recommended for patients who have a grade 2 or softer midsystolic murmur identified as innocent or functional by an experienced observer. *(Level of Evidence: C)*

Echocardiography with color flow and spectral Doppler evaluation is an important noninvasive method for assessing the significance of cardiac murmurs. Information regarding valve morphology and function, chamber size, wall thickness, ventricular function, pulmonary and hepatic vein flow, and estimates of pulmonary artery pressures can be readily integrated.

Although echocardiography can provide important information, such testing is not necessary for all patients with cardiac murmurs and usually adds little but expense in the evaluation of asymptomatic younger patients with short grade 1 to 2 midsystolic murmurs and otherwise normal physical findings. At the other end of the spectrum are patients with heart murmurs for whom transthoracic echocardiography proves inadequate. Depending on the specific clinical circumstances, transesophageal echocardiography, cardiac magnetic resonance, or cardiac catheterization may be indicated for better characterization of the valvular lesion.

It is important to note that Doppler ultrasound devices are very sensitive and may detect trace or mild valvular regurgitation through structurally normal tricuspid and pulmonic valves in a large percentage of young, healthy subjects and through normal left-sided valves (particularly the MV) in a variable but lower percentage of patients (16,19–22).

General recommendations for performing echocardiography in patients with heart murmurs are provided. Of course, individual exceptions to these indications may exist.

2.1.5. Cardiac Catheterization

Cardiac catheterization can provide important information about the presence and severity of valvular obstruction, valvular regurgitation, and intracardiac shunting. It is not necessary in most patients with cardiac murmurs and normal or diagnostic echocardiograms, but it provides additional information for some patients in whom there is a discrepancy between the echocardiographic and clinical findings. Indications for cardiac catheterization for hemodynamic assessment of specific valve lesions are given in Section 3, "Specific Valve Lesions," in these guidelines. Specific indications for coronary angiography to screen for the presence of CAD are given in Section 10.2.

2.1.6. Exercise Testing

Exercise testing can provide valuable information in patients with valvular heart disease, especially in those whose symptoms are difficult to assess. It can be combined with echocardiography, radionuclide angiography, and cardiac catheterization. It has a proven track record of safety, even among asymptomatic patients with severe AS. Exercise testing has generally been underutilized in this patient population and should constitute an important component of the evaluation process.

2.1.7. Approach to the Patient

The evaluation of the patient with a heart murmur may vary greatly depending on many of the considerations discussed above (23,24). These include the timing of the murmur in the cardiac cycle, its location and radiation, and its response to various physiological maneuvers (Table 2). Also of importance is the presence or absence of cardiac and noncardiac symptoms and other findings on physical examination that suggest the murmur is clinically significant (Fig. 2).

Patients with diastolic or continuous heart murmurs not due to a cervical venous hum or a mammary souffle during pregnancy are candidates for echocardiography. If the results of echocardiography indicate significant heart disease, further evaluation may be indicated. An echocardiographic examination is also recommended for patients with apical or left sternal edge holosystolic or late systolic murmurs, for patients with midsystolic murmurs of grade 3 or greater intensity, and for patients with softer systolic murmurs in whom dynamic cardiac auscultation suggests a definite diagnosis (e.g., hypertrophic cardiomyopathy).

Echocardiography is also recommended for patients in whom the intensity of a systolic murmur increases during the Valsalva maneuver, becomes louder when the patient assumes the upright position, and decreases in intensity when the patient squats. These responses suggest the diagnosis of either hypertrophic obstructive cardiomyopathy or MV prolapse (MVP). Additionally, further assessment is indicated when a systolic murmur increases in intensity during transient arterial occlusion, becomes louder during sustained handgrip exercise, or does not increase in intensity either in the cardiac cycle that follows a premature ventricular contraction or after a long R-R interval in patients with atrial fibrillation. The diagnosis of MR or ventricular septal defect in these circumstances is likely.

In many patients with grade 1 or 2 midsystolic murmurs, an extensive workup is not necessary. This is particularly true for children and young adults who are asymptomatic, have an otherwise normal cardiac examination, and have no other physical findings associated with cardiac disease.

However, echocardiography is indicated in certain patients with grade 1 or 2 midsystolic murmurs, including patients with symptoms or signs consistent with infective endocarditis, thromboembolism, heart failure, myocardial ischemia/infarction, or syncope. Echocardiography also usually provides an accurate diagnosis in patients with other abnormal physical findings, including widely split second heart sounds, systolic ejection sounds, and specific changes in intensity of the systolic murmur during certain physiological maneuvers (Table 2).

Although echocardiography is an important test for patients with a moderate to high likelihood of a clinically important cardiac murmur, it must be re-emphasized that

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trivial, minimal, or physiological valvular regurgitation, especially affecting the mitral, tricuspid, or pulmonic valves, is detected by color flow imaging techniques in many otherwise normal patients, including many patients who have no heart murmur at all (16,19–22). This observation must be considered when the results of echocardiography are used to guide decisions in asymptomatic patients in whom echocardiography was used to assess the significance of an isolated murmur.

Very few data address the cost-effectiveness of various approaches to the patient undergoing medical evaluation of a cardiac murmur. Optimal auscultation by well-trained examiners who can recognize an insignificant midsystolic murmur with confidence (by dynamic cardiac auscultation as indicated) results in less frequent use of expensive additional testing to define murmurs that do not indicate cardiac pathology.

Characteristics of innocent murmurs in asymptomatic adults that have no functional significance include the following:

- grade 1 to 2 intensity at the left sternal border
- a systolic ejection pattern
- normal intensity and splitting of the second heart sound
- no other abnormal sounds or murmurs
- no evidence of ventricular hypertrophy or dilatation and the absence of increased murmur intensity with the Valsalva maneuver or with standing from a squatting position (12).

Such murmurs are especially common in high-output states such as anemia and pregnancy (25,26). When the characteristic features of individual murmurs are considered together with information obtained from the history and physical examination, the correct diagnosis can usually be established (24). In patients with ambiguous clinical findings, the echocardiogram can often provide a definite diagnosis, rendering a chest X-ray and/or ECG unnecessary.

In the evaluation of heart murmurs, the purposes of echocardiography are to

- define the primary lesion in terms of cause and severity
- define hemodynamics
- define coexisting abnormalities
- detect secondary lesions
- evaluate cardiac chamber size and function
- establish a reference point for future comparisons
- re-evaluate the patient after an intervention.

Throughout these guidelines, treatment recommendations will often derive from specific echocardiographic measurements of LV size and systolic function. Accuracy and reproducibility are critical, particularly when applied to surgical recommendations for asymptomatic patients with MR or AR. Serial measurements over time, or reassessment with a different imaging technology (radionuclide ventriculography or cardiac magnetic resonance), are often helpful for counseling individual patients. Lastly, although handheld echocardiography can be used for screening purposes, it is important to note that its accuracy is highly dependent on the experience of the user. The precise role of handheld echocardiography for the assessment of patients with valvular heart disease has not been elucidated.

As valuable as echocardiography may be, the basic cardiovascular physical examination is still the most appropriate method of screening for cardiac disease and will establish many clinical diagnoses. Echocardiography should not replace the cardiovascular examination but can be useful in determining the cause and severity of valvular lesions, particularly in older and/or symptomatic patients.

2.2. Valve Disease Severity Table

Classification of the severity of valve disease in adults is listed in Table 4 (27). The classification for regurgitant lesions is adapted from the recommendations of the American Society of Echocardiography (27). For full recommendations of the American Society of Echocardiography, please refer to the original document. Subsequent sections of the current guidelines refer to the criteria in Table 4 (27) to define severe valvular stenosis or regurgitation.

2.3. Endocarditis and Rheumatic Fever Prophylaxis (UPDATED)

This updated section deals exclusively with the changes in recommendations for antibiotic prophylaxis against infective endocarditis in patients with valvular heart disease. Treatment considerations in patients with congenital heart disease (CHD) or implanted cardiac devices are reviewed in detail in other publications (1071), and the upcoming ACC/AHA guideline for the management of adult patients with CHD (1072). For an in-depth review of the rationale for the recommended changes in the approach to patients with valvular heart disease, the reader is referred to the AHA guidelines on prevention of infective endocarditis, published online April 2007 (1070).

2.3.1. Endocarditis Prophylaxis (UPDATED)

CLASS IIa

1. Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa (1070):
   - Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. *(Level of Evidence: B)*
   - Patients with previous infective endocarditis. *(Level of Evidence: B)*
   - Patients with CHD. *(Level of Evidence: B)*
     - Unrepaired cyanotic CHD, including palliative shunts and conduits. *(Level of Evidence: B)*
     - Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. *(Level of Evidence: B)*
     - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization). *(Level of Evidence: B)*

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Table 4. Classification of the Severity of Valve Disease in Adults

A. Left-sided valve disease			
	Aortic Stenosis		
Indicator	**Mild**	**Moderate**	**Severe**
Jet velocity (m per s)	Less than 3.0	3.0–4.0	Greater than 4.0
Mean gradient (mm Hg)*	Less than 25	25–40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
Valve area index (cm^2 per m^2)			Less than 0.6
	Mitral Stenosis		
	Mild	**Moderate**	**Severe**
Mean gradient (mm Hg)*	Less than 5	5–10	Greater than 10
Pulmonary artery systolic pressure (mm Hg)	Less than 30	30–50	Greater than 50
Valve area (cm^2)	Greater than 1.5	1.0–1.5	Less than 1.0
	Aortic Regurgitation		
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.6	Greater than 0.6
Quantitative (cath or echo)			
Regurgitant volume (ml per beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.10	0.10–0.29	Greater than or equal to 0.30
Additional essential criteria			
Left ventricular size			Increased
	Mitral Regurgitation		
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (less than 4 cm^2 or less than 20% LA area)	Signs of MR greater than mild present but no criteria for severe MR	Vena contracta width greater than 0.7 cm with large central MR jet (area greater than 40% of LA area) or with a wall-impinging jet of any size, swirling in LA
Doppler vena contracta width (cm)	Less than 0.3	0.3–0.69	Greater than or equal to 0.70
Quantitative (cath or echo)			
Regurgitant volume (ml per beat)	Less than 30	30–59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30–49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.20	0.20–0.39	Greater than or equal to 0.40
Additional essential criteria			
Left atrial size			Enlarged
Left ventricular size			Enlarged
B. Right-sided valve disease	**Characteristic**		
Severe tricuspid stenosis:	Valve area less than 1.0 cm^2		
Severe tricuspid regurgitation:	Vena contracta width greater than 0.7 cm and systolic flow reversal in hepatic veins		
Severe pulmonic stenosis:	Jet velocity greater than 4 m per s or maximum gradient greater than 60 mmHg		
Severe pulmonic regurgitation:	Color jet fills outflow tract; dense continuous wave Doppler signal with a steep deceleration slope		

*Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. Modified from the *Journal of the American Society of Echocardiography, 16,* Zoghbi WA, Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography, 777–802, Copyright 2003, with permission from American Society of Echocardiography (27).

AR indicates aortic regurgitation; cath, catheterization; echo, echocardiography; LA, left atrial/atruim; LVOT, left ventricular outflow tract; and MR, mitral regurgitation.

- Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. *(Level of Evidence: C)*

CLASS III

1. Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. *(Level of Evidence: B)* (1070)

(Table 5 of the 2006 Valvular Heart Disease Guideline [1068] is now obsolete.)

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Table 6. Endocarditis Prophylaxis for Dental Procedures (UPDATED)*

Reasonable	Not Recommended
Endocarditis prophylaxis is reasonable for patients with the highest risk of adverse outcomes who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa.	Endocarditis prophylaxis is not recommended for: • Routine anesthetic injections through noninfected tissue • Dental radiographs • Placement or removal of prosthodontic or orthodontic appliances • Adjustment of orthodontic appliances • Placement of orthodontic brackets • Shedding of deciduous teeth • Bleeding from trauma to the lips or oral mucosa

*This table corresponds to Table 3 in the ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis (1069).
Adapted with permission (28).

Infective endocarditis is a serious illness associated with significant morbidity and mortality. Its prevention by the appropriate administration of antibiotics before a procedure expected to produce bacteremia merits serious consideration. Experimental studies have suggested that endothelial damage leads to platelet and fibrin deposition and the formation of nonbacterial thrombotic endocardial lesions. In the presence of bacteremia, organisms may adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infective vegetation. Valvular and congenital abnormalities, especially those associated with high velocity jets, can result in endothelial damage, platelet fibrin deposition, and a predisposition to bacterial colonization. Since 1955, the AHA has made recommendations for prevention of infective endocarditis with antimicrobial prophylaxis before specific dental, gastrointestinal (GI), and genitourinary (GU) procedures in patients at risk for its development. However, many authorities and societies, as well as the conclusions of published studies, have questioned the efficacy of antimicrobial prophylaxis in most situations.

On the basis of these concerns, a writing group was appointed by the AHA for their expertise in prevention and treatment of infective endocarditis, with liaison members representing the American Dental Association, the Infectious Disease Society of America, and the American Academy of Pediatrics. The writing group reviewed the relevant literature regarding procedure-related bacteremia and infective endocarditis, in vitro susceptibility data of the most common organisms that cause infective endocarditis, results of prophylactic studies of animal models of infective endocarditis, and both retrospective and prospective studies of prevention of infective endocarditis. As a result, major changes were made in the recommendations for prophylaxis against infective endocarditis.

The major changes in the updated recommendations included the following:

- The committee concluded that only an extremely small number of cases of infective endocarditis might be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic therapy were 100 percent effective.
- Infective endocarditis prophylaxis for dental procedures is reasonable only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis.
- For patients with these underlying cardiac conditions, prophylaxis is reasonable for all dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of oral mucosa.
- Prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of infective endocarditis.
- Administration of antibiotics solely to prevent endocarditis is not recommended for patients who undergo GU or GI tract procedure.

Table 7. Regimens for a Dental Procedure (UPDATED)*

Situation	Agent	Regimen: Single Dose 30 to 60 min Before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin†‡	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone‡	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

*This table corresponds to Table 4 in the ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis (1069). †Or use other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage. ‡Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM indicates intramuscular; and IV, intravenous.

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The rationale for these revisions is based on the following:

- Infective endocarditis is more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, GI tract, or GU procedure;
- Prophylaxis may prevent an exceedingly small number of cases of infective endocarditis (if any) in individuals who undergo a dental, GI tract, or GU procedure;
- The risk of antibiotic associated adverse effects exceeds the benefit (if any) from prophylactic antibiotic therapy;
- Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of infective endocarditis.

(Table 8 of the 2006 Valvular Heart Disease Guidelines [1068] is now obsolete.)

The AHA Prevention of Infective Endocarditis Committee recommended that prophylaxis should be given only to the high-risk group of patients prior to dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of oral mucosa. High-risk patients were defined as those patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis, not necessarily those with an increased lifetime risk of acquisition of infective endocarditis. Prophylaxis is no longer recommended for prevention of endocarditis for procedures involving the respiratory tract unless the procedure is performed in a high-risk patient and involves incision of the respiratory tract mucosa, such as tonsillectomy and adenoidectomy. Prophylaxis is no longer recommended for prevention of infective endocarditis for GI or GU procedures, including diagnostic esophagogastroduodenoscopy or colonoscopy. However, in high risk-patients with infections of the GI or GU tract, it is reasonable to administer antibiotic therapy to prevent wound infection or sepsis. For high-risk patients undergoing elective cystoscopy or other urinary tract manipulation who have enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure is reasonable.

These changes are a significant departure from the past AHA (723) and European Society of Cardiology (1073) recommendations for prevention of infective endocarditis, and may violate longstanding expectations in practice patterns of patients and healthcare providers. However, the writing committee for these updated guidelines consisted of experts in the field of infective endocarditis; input was also obtained from experts not affiliated with the writing group. All data to date were thoroughly reviewed, and the current recommendations reflect analysis of all relevant literature. This multidisciplinary team of experts emphasized that previous published guidelines for the prevention of endocarditis contained ambiguities and inconsistencies and relied more on opinion than on data. The writing committee delineated the reasons for which evolutionary refinement in the approach to infective endocarditis prophylaxis can be justified. In determining which patients receive prophylaxis, there is a clear focus on the risk of adverse outcomes after infective endocarditis rather than the lifetime risk of acquisition of infective endocarditis. The current recommendations result in greater clarity for patients, health care providers, and consulting professionals.

Other international societies have published recommendations and guidelines for the prevention of infective endocarditis. New recommendations from the British Society for Antimicrobial Chemotherapy are similar to the current AHA recommendations for prophylaxis before dental procedures. The British Society for Antimicrobial Chemotherapy did differ in continuing to recommend prophylaxis for high-risk patients prior to GI or GU procedures associated with bacteremia or endocarditis (1074).

Therefore, Class IIa indications for prophylaxis against infective endocarditis are reasonable for valvular heart disease patients at highest risk for adverse outcomes from infective endocarditis before dental procedures that involve manipulation of either gingival tissue. This high-risk group includes: 1) patients with a prosthetic heart valve or prosthetic material used for valve repair, 2) patients with a past history of infective endocarditis, and 3) patients with cardiac valvulopathy following cardiac transplantation, as well as 4) specific patients with CHD. Patients with innocent murmurs and those patients who have abnormal echocardiographic findings without an audible murmur should definitely not be given prophylaxis for infective endocarditis. Infective endocarditis prophylaxis is not necessary for nondental procedures which do not penetrate the mucosa, such as transesophageal echocardiography, diagnostic bronchoscopy, esophagogastroscopy, or colonoscopy, in the absence of active infection.

The committee recognizes that decades of previous recommendations for patients with most forms of valvular heart disease and other conditions have been abruptly changed by the new AHA guidelines (1069). Because this may cause consternation among patients, clinicians should be available to discuss the rationale for these new changes with their patients, including the lack of scientific evidence to demonstrate a proven benefit for infective endocarditis prophylaxis. In select circumstances, the committee also understands that some clinicians and some patients may still feel more comfortable continuing with prophylaxis for infective endocarditis, particularly for those with bicuspid aortic valve or coarctation of the aorta, severe mitral valve prolapse, or hypertrophic obstructive cardiomyopathy. In those settings, the clinician should determine that the risks associated with antibiotics are low before continuing a prophylaxis regimen. Over time, and with continuing education, the committee anticipates increasing acceptance of the new guidelines among both provider and patient communities.

A multicenter randomized controlled trial has never been performed to evaluate the efficacy of infective endocarditis

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Table 9. Primary Prevention of Rheumatic Fever

Agent	Dose	Mode	Duration
Benzathine/Penicillin G	Patients 27 kg (60 lb) or less: 600 000 U	Intramuscular	Once
	Patients greater than 27 kg (60 lb): 1 200 000 U		
or			
Penicillin V (phenoxymethyl penicillin)	Children: 250 mg 2–3 times daily	Oral	10 d
	Adolescents and adults: 500 mg 2–3 times daily		
For individuals allergic to penicillin			
Erythromycin			
Estolate	20–40 mg per kg per day	Oral	10 d
	2–4 times daily (maximum 1 g per day)		
or			
Ethylsuccinate	40 mg per kg per day	Oral	10 d
	2–4 times daily (maximum 1 g per day)		
or			
Azithromycin	500 mg on first day	Oral	5 d
	250 mg per day for the next 4 days		

Reprinted with permission from Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics 1995;96:758–64 (45).

prophylaxis in patients who undergo dental, GI, or GU procedures. On the basis of these new recommendations, fewer patients will receive infective endocarditis prophylaxis. It is hoped that the revised recommendations will stimulate properly designed prospective studies on the prevention of infective endocarditis.

2.3.2. Rheumatic Fever Prophylaxis

2.3.2.1. GENERAL CONSIDERATIONS

Rheumatic fever is an important cause of valvular heart disease. In the United States (and Western Europe), cases of acute rheumatic fever have been uncommon since the 1970s. However, starting in 1987, an increase in cases has been observed (43,44). With the enhanced understanding of the causative organism, group A beta hemolytic streptococcus, its rheumatogenicity is attributed to the prevalence of M-protein serotypes of the offending organism. This finding has resulted in the development of kits that allow rapid detection of group A streptococci with specificity greater than 95% and more rapid identification of their presence in upper respiratory infection. Because the test has a low sensitivity, a negative test requires throat culture confirmation (44). Prompt recognition and treatment comprise primary rheumatic fever prevention. For patients who have had a previous episode of rheumatic fever, continuous antistreptococcal prophylaxis is indicated for secondary prevention.

2.3.2.2. PRIMARY PREVENTION

Rheumatic fever prevention and treatment guidelines have been established previously by the AHA (Table 9) (45).

2.3.2.3. SECONDARY PREVENTION

CLASS I

1. **Patients who have had rheumatic fever with or without carditis (including patients with MS) should receive prophylaxis for recurrent rheumatic fever. *(Level of Evidence: B)***

Patients who have had an episode of rheumatic fever are at high risk of developing recurrent episodes of acute rheumatic fever. Patients who develop carditis are especially prone to similar episodes with subsequent attacks. Secondary prevention of rheumatic fever recurrence is thus of great importance. Continuous antimicrobial prophylaxis has been shown to be effective. Anyone who has had rheumatic fever with or without carditis (including patients with MS) should receive prophylaxis for recurrent rheumatic fever. The 1995 AHA guidelines for secondary prevention are shown in Table 10, and the 1995 AHA guidelines for duration of secondary prevention are shown in Table 11 (45).

Table 10. Secondary Prevention of Rheumatic Fever

Agent	Dose	Mode
Penicillin G benzathine	1 200 000 U every 4 wk (every 3 wk for high-risk* pts such as those with residual carditis)	Intramuscular
or		
Penicillin V	250 mg twice daily	Oral
or		
Sulfadiazine	0.5 g once daily for pts 27 g (60 lb) or less; 1.0 g once daily for pts greater than 27 kg (60 lb)	Oral
For individuals allergic to penicillin and sulfadiazine		
Erythromycin	250 mg twice daily	Oral

*High-risk patients include patients with residual rheumatic carditis and patients from economically disadvantaged populations. Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics 1995;96:758–64 (45).

Pts indicates patients.

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Table 11. Duration of Secondary Rheumatic Fever Prophylaxis

Category	Duration
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 y or greater since last episode and at least until age 40 y; sometimes lifelong prophylaxis*
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 y or well into adulthood, whichever is longer
Rheumatic fever without carditis	5 y or until age 21 y, whichever is longer

*The committee's interpretation of "lifelong" prophylaxis refers to patients who are at high risk and likely to come in contact with populations with a high prevalence of streptococcal infection, that is, teachers and day-care workers. Reprinted with permission from Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics 1995;96:758–64 (45).

3. SPECIFIC VALVE LESIONS

3.1. Aortic Stenosis

3.1.1. Introduction

The most common cause of AS in adults is calcification of a normal trileaflet or congenital bicuspid valve (46–49). This calcific disease progresses from the base of the cusps to the leaflets, eventually causing a reduction in leaflet motion and effective valve area without commissural fusion. Calcific AS is an active disease process characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis (50–60). Rheumatic AS due to fusion of the commissures with scarring and eventual calcification of the cusps is less common and is invariably accompanied by MV disease. A congenital malformation of the valve may also result in stenosis and is the more common cause in young adults. The management of congenital AS in adolescents and young adults is discussed in Section 6.1.

3.1.1.1. GRADING THE DEGREE OF STENOSIS

Although AS is best described as a disease continuum, and there is no single value that defines severity, for these guidelines, we graded AS severity on the basis of a variety of hemodynamic and natural history data (Table 4) (27,61), using definitions of aortic jet velocity, mean pressure gradient, and valve area as follows:

- Mild (area 1.5 cm^2, mean gradient less than 25 mm Hg, or jet velocity less than 3.0 m per second)
- Moderate (area 1.0 to 1.5 cm^2, mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m per second)
- Severe (area less than 1.0 cm^2, mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second).

When stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally greater than 40 mm Hg. However, when cardiac output is low, severe stenosis may be present with a lower transvalvular gradient and velocity, as discussed below. Some patients with severe AS remain asymptomatic, whereas others with only moderate stenosis develop symptoms. Therapeutic decisions, particularly those related to corrective surgery, are based largely on the presence or absence of symptoms. Thus, the absolute valve area (or transvalvular pressure gradient) is not the primary determinant of the need for aortic valve replacement (AVR).

3.1.2. Pathophysiology

In adults with AS, the obstruction develops gradually—usually over decades. During this time, the left ventricle adapts to the systolic pressure overload through a hypertrophic process that results in increased LV wall thickness, while a normal chamber volume is maintained (62–64). The resulting increase in relative wall thickness is usually enough to counter the high intracavitary systolic pressure, and as a result, LV systolic wall stress (afterload) remains within the range of normal. The inverse relation between systolic wall stress and ejection fraction is maintained; as long as wall stress is normal, the ejection fraction is preserved (65). However, if the hypertrophic process is inadequate and relative wall thickness does not increase in proportion to pressure, wall stress increases and the high afterload causes a decrease in ejection fraction (65–67). Depressed contractile state of the myocardium may also be responsible for a low ejection fraction, and it is often difficult clinically to determine whether a low ejection fraction is due to depressed contractility or to excessive afterload (68). When low ejection fraction is caused by depressed contractility, corrective surgery will be less beneficial than in patients with a low ejection fraction caused by high afterload (69).

As a result of increased wall thickness, low volume/mass ratio, and diminished compliance of the chamber, LV end-diastolic pressure increases without chamber dilatation (70–72). Thus, increased end-diastolic pressure usually reflects diastolic dysfunction rather than systolic dysfunction or failure (73). A forceful atrial contraction that contributes to an elevated end-diastolic pressure plays an important role in ventricular filling without increasing mean left atrial or pulmonary venous pressure (74). Loss of atrial contraction such as that which occurs with atrial fibrillation is often followed by serious clinical deterioration.

The development of concentric hypertrophy appears to be an appropriate and beneficial adaptation to compensate for high intracavitary pressures. Unfortunately, this adaptation often carries adverse consequences. The hypertrophied heart may have reduced coronary blood flow per gram of muscle and also exhibit a limited coronary vasodilator reserve, even in the absence of epicardial CAD (75–77). The hemodynamic stress of exercise or tachycardia can produce a maldistribution of coronary blood flow and subendocardial ischemia, which can contribute to systolic or diastolic dysfunction of the left ventricle. Hypertrophied hearts also exhibit an increased sensitivity to ischemic injury, with larger infarcts and higher mortality rates than are seen in the absence of hypertrophy (78–80). Another problem that is particularly common in elderly patients, especially women,

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is an excessive or inappropriate degree of hypertrophy; wall thickness is greater than necessary to counterbalance the high intracavitary pressures (81–84). As a result, systolic wall stress is low and ejection fraction is high; such inappropriate LV hypertrophy has been associated with high perioperative morbidity and mortality (81,83).

3.1.3. Natural History

The natural history of AS in the adult consists of a prolonged latent period during which morbidity and mortality are very low. The rate of progression of the stenotic lesion has been estimated in a variety of invasive and noninvasive studies (85). Once even moderate stenosis is present (jet velocity greater than 3.0 m per second) (Table 4) (27), the average rate of progression is an increase in jet velocity of 0.3 m per second per year, an increase in mean pressure gradient of 7 mm Hg per year, and a decrease in valve area of 0.1 cm^2 per year (86–96). However, there is marked individual variability in the rate of hemodynamic progression. Although it appears that the progression of AS can be more rapid in patients with degenerative calcific disease than in those with congenital or rheumatic disease (96–98), it is not possible to predict the rate of progression in an individual patient. For this reason, regular clinical follow-up is mandatory in all patients with asymptomatic mild to moderate AS. In addition, progression to AS may occur in patients with aortic sclerosis, defined as valve thickening without obstruction to ventricular outflow (99).

Aortic sclerosis, defined as irregular valve thickening without obstruction to LV outflow, is present in about 25% of adults over 65 years of age and is associated with clinical factors such as age, sex, hypertension, smoking, serum low-density lipoprotein and lipoprotein(a) levels, and diabetes mellitus (100). In the Cardiovascular Health Study, the presence of aortic sclerosis on echocardiography in subjects without known coronary disease was also associated with adverse clinical outcome, with an approximately 50% increased risk of myocardial infarction and cardiovascular death compared with subjects with a normal aortic valve (101). This has been confirmed in 2 additional studies (102,103). The association between aortic sclerosis and adverse cardiovascular outcomes persisted even when age, sex, known cardiovascular disease, and cardiovascular risk factors were taken into account. However, the mechanism of this association is unclear and is unlikely to be related to valve hemodynamics. Studies are in progress to evaluate potential mechanisms of this association, including subclinical atherosclerosis, endothelial dysfunction, and systemic inflammation.

In most patients with severe AS, impaired platelet function and decreased levels of von Willebrand factor can be demonstrated. The severity of the coagulation abnormality correlates with the severity of AS and resolves after valve replacement, except when the prosthetic valve area is small for patient size (less than 0.8 cm^2 per m^2). This acquired von Willebrand syndrome is associated with clinical bleeding, most often epistaxis or ecchymoses, in approximately 20% of patients (104).

Eventually, symptoms of angina, syncope, or heart failure develop after a long latent period, and the outlook changes dramatically. After the onset of symptoms, average survival is 2 to 3 years (105–111), with a high risk of sudden death. Thus, the development of symptoms identifies a critical point in the natural history of AS. Management decisions are based largely on these data; most clinicians treat asymptomatic patients conservatively, whereas corrective surgery is generally recommended in patients with symptoms thought to be due to AS. It is important to emphasize that symptoms may be subtle and often are not elicited by the physician in taking a routine clinical history.

Sudden death is known to occur in patients with severe AS and, in older retrospective studies, has been reported to occur without prior symptoms (105,108,112,113). However, in prospective echocardiographic studies, sudden death in previously asymptomatic patients is rare (61,96,109,114–116). Therefore, although sudden death may occur in the absence of preceding symptoms in patients with AS (105,108,112,113,116), it is an uncommon event, estimated at less than 1% per year when patients with known AS are followed up prospectively.

3.1.4. Management of the Asymptomatic Patient

Asymptomatic patients with AS have outcomes similar to age-matched normal adults. However, disease progression with symptom onset is common, as detailed in Table 12 (61,96,109,114–118). In a prospective study of 123 asymptomatic adults with an initial jet velocity of at least 2.6 m per second, the rate of symptom development was 38% at 3 years for the total group. However, clinical outcome was strongly dependent on AS severity, with an event-free survival of 84% at 2 years in those with a jet velocity less than 3 m per second compared with only 21% in those with a jet velocity more than 4 m per second (61,98). In another study of 128 asymptomatic adults with an initial aortic jet velocity of at least 4 m per second, event-free survival was 67% at 1 year and 33% at 4 years, with predictors of outcome that included age and the degree of valve calcification (96). A third study of patients with aortic jet velocities greater than 4 m per second provided similar results, with 33% remaining asymptomatic without surgery at 5 years (116). Therefore, patients with asymptomatic AS require frequent monitoring for development of symptoms and progressive disease.

3.1.4.1. ECHOCARDIOGRAPHY (IMAGING, SPECTRAL, AND COLOR DOPPLER) IN AORTIC STENOSIS

CLASS I

1. Echocardiography is recommended for the diagnosis and assessment of AS severity. *(Level of Evidence: B)*
2. Echocardiography is recommended in patients with AS for the assessment of LV wall thickness, size, and function. *(Level of Evidence: B)*

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Table 12. Clinical Outcomes in Prospective Studies of Asymptomatic Aortic Stenosis in Adults

Study, Year	No. of Patients	Severity of Aortic Stenosis	Age, y	Mean Follow-Up	Group	Event-Free Survival Without Symptoms
Kelly et al., 1988 (109)	51	V_{max} greater than 3.6 m per second	63 ± 8	5–25 mo	Overall	59% at 15 mo
Pellikka et al., 1990 (114)	113	V_{max} 4.0 m per second or greater	40–94	20 mo	Overall Overall	86% at 1 y 62% at 2 y
Kennedy et al., 1991 (115)	66	AVA 0.7–1.2 cm^2	67 ± 10	35 mo	Overall	59% at 4 y
Otto et al., 1997 (61)	123	V_{max} greater than 2.6 m per second	63 ± 16	2.5 ± 1.4 y	Overall	93 ± 5% at 1 y 62 ± 8% at 3 y 26 ± 10% at 5 y
					Subgroups:	
					V_{max} less than 3–4 m per second	84 ± 16% at 2 y
					V_{max} 3–4 m per second	66 ± 13% at 2 y
					V_{max} greater than 3 m per second	21 ± 18% at 2 y
Rosenhek et al., 2000 (96)	128	V_{max} greater than 4.0 m per second	60 ± 18	22 ± 18 mo	Overall	67 ± 5% at 1 y 56 ± 55% at 2 y 33 ± 5% at 4 y
					Subgroups:	
					No or mild Ca^{2+}	75 ± 9% at 4 y
					Moderate-severe Ca^{2+}	20 ± 5% at 4 y
Amato et al., 2001 (117)	66	AVA 1.0 cm^2 or greater	18–80 (50 ± 15)	15 ± 12 mo	Overall	57% at 1 y 38% at 2 y
					Subgroups:	
					AVA 0.7 cm^2 or greater	72% at 2 y
					AVA less than 0.7 cm^2	21% at 2 y
					Negative exercise test	85% at 2 y
					Positive exercise test*	19% at 2 y
Das et al., 2005 (118)	125	AVA less than 1.4 cm^2	56–74 (mean 65)	12 mo	Subgroups: AVA 1.2 cm^2 or greater AVA 0.8 cm^2 or less	100% at 1 y 46% at 1 y
					No symptoms on exercise test	89% at 1 y
					Symptoms on exercise test	49% at 1 y
Pellikka et al., 2005 (116)	622	V_{max} 4.0 m per second or greater	72 ± 11	5.4 ± 4.0 y	Overall	82% at 1 y 67% at 2 y 33% at 5 y

*Positive exercise test indicates symptoms, abnormal ST-segment response, or abnormal blood pressure response (less than 20-mm Hg increase) with exercise.
AVA indicates aortic valve area; Ca^{2+}, aortic valve calcification; and V_{max}, peak instantaneous velocity.

3. **Echocardiography is recommended for re-evaluation of patients with known AS and changing symptoms or signs.** ***(Level of Evidence: B)***
4. **Echocardiography is recommended for the assessment of changes in hemodynamic severity and LV function in patients with known AS during pregnancy.** ***(Level of Evidence: B)***
5. **Transthoracic echocardiography is recommended for re-evaluation of asymptomatic patients: every year for severe AS; every 1 to 2 years for moderate AS; and every 3 to 5 years for mild AS.** ***(Level of Evidence: B)***

Aortic stenosis typically is first suspected on the basis of the finding of a systolic ejection murmur on cardiac auscultation; however, physical examination findings are specific but not sensitive for the diagnosis of AS severity (119). The classic findings of a loud (grade 4/6), late-peaking systolic murmur that radiates to the carotids, a single or paradoxically split second heart sound (S_2), and a delayed and diminished carotid upstroke confirm the presence of severe AS. However, in the elderly, the carotid upstroke may be normal because of the effects of aging on the vasculature, and the murmur may be soft or may radiate to the apex. The only physical examination finding that is reliable in excluding the possibility of severe AS is a normally split second heart sound (119).

Echocardiography is indicated when there is a systolic murmur that is grade 3/6 or greater, a single S_2, or symptoms that might be due to AS. The 2-dimensional (2D) echocardiogram is valuable for evaluation of valve anatomy and function and determining the LV response to pressure overload. In nearly all patients, the severity of the stenotic lesion can be defined with Doppler echocardiographic measurements of maximum jet velocity, mean transvalvular pressure gradient, and continuity equation valve area, as discussed in the "ACC/AHA/ASE 2003 Guidelines for the Clinical Application of Echocardiography" (2). Doppler evaluation of AS severity requires attention to technical details, with the most common error being underestimation of disease severity due to a nonparallel intercept angle between the ultrasound beam and high-velocity jet through the narrowed valve. When measurement

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of LV outflow tract diameter is problematic, the ratio of outflow tract velocity to aortic jet velocity can be substituted for valve area, because this ratio is, in effect, indexed for body size. A ratio of 0.9 to 1.0 is normal, with a ratio less than 0.25 indicating severe stenosis. Echocardiography is also used to assess LV size and function, degree of hypertrophy, and presence of other associated valvular disease.

In some patients, it may be necessary to proceed with cardiac catheterization and coronary angiography at the time of initial evaluation. For example, this is appropriate if there is a discrepancy between clinical and echocardiographic examinations or if symptoms might be due to CAD.

3.1.4.2. EXERCISE TESTING

CLASS IIb

1. **Exercise testing in asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses. *(Level of Evidence: B)***

CLASS III

1. **Exercise testing should not be performed in symptomatic patients with AS. *(Level of Evidence: B)***

Exercise testing in adults with AS has poor diagnostic accuracy for evaluation of concurrent CAD. Presumably, this is due to the presence of an abnormal baseline ECG, LV hypertrophy, and limited coronary flow reserve. Electrocardiographic ST depression during exercise occurs in 80% of adults with asymptomatic AS and has no known prognostic significance.

Exercise testing should not be performed in symptomatic patients owing to a high risk of complications. However, in asymptomatic patients, exercise testing is relatively safe and may provide information that is not uncovered during the initial clinical evaluation (61,117,118,120–124). When the medical history is unclear, exercise testing can identify a limited exercise capacity, abnormal blood pressure responses, or even exercise-induced symptoms (117,118,124). In one series (117), patients manifesting symptoms, abnormal blood pressure (less than 20-mm Hg increase), or ST-segment abnormalities with exercise had a symptom-free survival at 2 years of only 19% compared with 85% symptom-free survival in those with none of these findings with exercise. Four patients died during the course of this study (1.2% annual mortality rate); all had an aortic valve area less than 0.7 cm^2 and an abnormal exercise test. In another series (118), exercise testing brought out symptoms in 29% of patients who where considered asymptomatic before testing; in these patients, spontaneous symptoms developed in 51% over the next year compared with only 11% of patients who had no symptoms on exercise testing. An abnormal hemodynamic response (e.g., hypotension or failure to increase blood pressure with exercise) in a patient with severe AS is considered a poor prognostic finding (117,125). Finally, in selected patients, the observations made during exercise may provide a basis for advice about physical activity. Exercise testing in asymptomatic patients should be performed only under the supervision of an experienced physician with close monitoring of blood pressure and the ECG.

3.1.4.3. SERIAL EVALUATIONS

The frequency of follow-up visits to the physician depends on the severity of the valvular stenosis and on the presence of comorbid conditions. Recognizing that an optimal schedule for repeated medical examinations has not been defined, many physicians perform an annual history and physical examination on patients with asymptomatic AS of any degree. An essential component of each visit is patient education about the expected disease course and symptoms of AS. Periodic echocardiography may be appropriate as discussed below. Patients should be advised to promptly report the development of any change in exercise tolerance, exertional chest discomfort, dyspnea, lightheadedness, or syncope.

Serial echocardiography is an important part of an integrated approach that includes a detailed history, physical examination, and, in some patients, a carefully monitored exercise test. Because the rate of progression varies considerably, clinicians often perform an annual echocardiogram on patients known to have moderate to severe AS. Serial echocardiograms are helpful for assessing changes in stenosis severity, LV hypertrophy, and LV function. Therefore, in patients with severe AS, an echocardiogram every year may be appropriate. In patients with moderate AS, serial studies performed every 1 to 2 years are satisfactory, and in patients with mild AS, serial studies can be performed every 3 to 5 years. Echocardiograms should be performed more frequently if there is a change in signs or symptoms.

3.1.4.4. MEDICAL THERAPY (UPDATED)

Antibiotic prophylaxis against recurrent rheumatic fever is indicated for patients with rheumatic AS. Patients with associated systemic arterial hypertension should be treated cautiously with appropriate antihypertensive agents. With these exceptions, there is no specific medical therapy for patients who have not yet developed symptoms. Patients who develop symptoms require surgery, not medical therapy.

There are no medical treatments proven to prevent or delay the disease process in the aortic valve leaflets. However, the association of AS with clinical factors similar to those associated with atherosclerosis and the mechanisms of disease at the tissue level (50–60,99–103,126–129) have led to the hypothesis that intervention may be possible to slow or prevent disease progression in the valve leaflet (127,130). Specifically, the effect of lipid-lowering therapy on progression of calcific AS has been examined in several small retrospective studies using echocardiography or cardiac computed tomography to measure disease severity (131–136), suggesting a benefit of statins. However, a prospective, randomized, placebo-controlled trial in patients with calcific aortic valve disease failed to demonstrate a benefit of atorvastatin in reducing the progression of aortic

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valve stenosis over a 3-year period (137). It is noteworthy that the patients in this study had high levels of aortic valve calcification by computed tomography and evidence of moderate to severe AS at baseline, based on peak aortic valve gradient (48 to 50 mm Hg), aortic valve area (1.02 to 1.03 cm^2), and peak jet velocity (3.39 to 3.45 m per second). It is possible that the calcific process was too advanced in these patients to be reversed by short-term statin therapy. Thus, further trials in patients with less severe aortic valve calcification, with longer follow-up periods, are needed. In the meanwhile, evaluation and modification of cardiac risk factors is important in patients with aortic valve disease to prevent concurrent CAD.

3.1.4.5. PHYSICAL ACTIVITY AND EXERCISE

Recommendations for physical activity are based on the clinical examination, with special emphasis on the hemodynamic severity of the stenotic lesion. The severity can usually be judged by Doppler echocardiography, but in borderline cases, diagnostic cardiac catheterization may be necessary to accurately define the degree of stenosis.

Recommendations on participation in competitive sports have been published by the Task Force on Acquired Valvular Heart Disease of the 36th Bethesda Conference (138). Physical activity is not restricted in asymptomatic patients with mild AS; these patients can participate in competitive sports. Patients with moderate to severe AS should avoid competitive sports that involve high dynamic and static muscular demands. Other forms of exercise can be performed safely, but it is advisable to evaluate such patients with an exercise test before they begin an exercise or athletic program.

3.1.5. Indications for Cardiac Catheterization

CLASS I

1. Coronary angiography is recommended before AVR in patients with AS at risk for CAD (see Section 10.2). *(Level of Evidence: B)*
2. Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of AS in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS. *(Level of Evidence: C)*
3. Coronary angiography is recommended before AVR in patients with AS for whom a pulmonary autograft (Ross procedure) is contemplated and if the origin of the coronary arteries was not identified by noninvasive technique. *(Level of Evidence: C)*

CLASS III

1. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of severity of AS before AVR when noninvasive tests are adequate and concordant with clinical findings. *(Level of Evidence: C)*
2. Cardiac catheterization for hemodynamic measurements is not recommended for the assessment of LV function and severity of AS in asymptomatic patients. *(Level of Evidence: C)*

In patients with AS, the indications for cardiac catheterization and angiography are essentially the same as in other conditions, namely, to assess the coronary circulation and confirm or clarify the clinical diagnosis. In preparation for AVR, coronary angiography is indicated in patients suspected of having CAD, as discussed in Section 10.2. If the clinical and echocardiographic data are typical of severe isolated AS, coronary angiography may be all that is needed before AVR. A complete left- and right-heart catheterization may be necessary to assess the hemodynamic severity of the AS if there is a discrepancy between clinical and echocardiographic data.

The pressure gradient across a stenotic valve is related to the valve orifice area and the transvalvular flow (139). Thus, in the presence of depressed cardiac output, relatively low pressure gradients may be obtained in patients with severe AS. On the other hand, during exercise or other high-flow states, significant pressure gradients can be measured in minimally stenotic valves. For these reasons, complete assessment of AS requires

- measurement of transvalvular flow
- determination of the mean transvalvular pressure gradient
- calculation of the effective valve area.

Attention to detail with accurate measurements of pressure and flow is important, especially in patients with low cardiac output or a low transvalvular pressure gradient.

3.1.6. Low-Flow/Low-Gradient Aortic Stenosis

CLASS IIa

1. Dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and LV dysfunction. *(Level of Evidence: B)*
2. Cardiac catheterization for hemodynamic measurements with infusion of dobutamine can be useful for evaluation of patients with low-flow/low-gradient AS and LV dysfunction. *(Level of Evidence: C)*

Patients with severe AS and low cardiac output often present with a relatively low transvalvular pressure gradient (i.e., mean gradient less than 30 mm Hg). Such patients can be difficult to distinguish from those with low cardiac output and only mild to moderate AS. In the former (true anatomically severe AS), the stenotic lesion contributes to an elevated afterload, decreased ejection fraction, and low stroke volume. In the latter, primary contractile dysfunction is responsible for the decreased ejection fraction and low stroke volume; the problem is further complicated by reduced valve opening forces that contribute to limited valve mobility and apparent stenosis. In both situations, the low-flow state and low-pressure gradient contribute to a calculated effective valve area that can meet criteria for severe AS. Alternate measures of AS severity have been proposed as being less flow dependent than gradients or valve area. These include valve resistance and stroke work loss. However, all of these measures are flow dependent, have not been shown to predict clinical outcome, and have not gained widespread clinical use (140).

In selected patients with low-flow/low-gradient AS and LV dysfunction, it may be useful to determine the transvalvular pressure gradient and to calculate valve area during a

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baseline state and again during exercise or low-dose pharmacological (i.e., dobutamine infusion) stress, with the goal of determining whether stenosis is severe or only moderate in severity (123,141–147). Such studies can be performed in the echocardiography laboratory or in the cardiac catheterization laboratory. This approach is based on the notion that patients who do not have true anatomically severe stenosis will exhibit an increase in the valve area and little change in gradient during an increase in stroke volume (141,142). Thus, if a dobutamine infusion produces an increment in stroke volume and an increase in valve area greater than 0.2 cm^2 and little change in gradient, it is likely that baseline evaluation overestimated the severity of stenosis. In contrast, patients with severe AS will have a fixed valve area with an increase in stroke volume and an increase in gradient. These patients are likely to respond favorably to surgery. Patients who fail to show an increase in stroke volume with dobutamine (less than 20%), referred to as "lack of contractile reserve," appear to have a very poor prognosis with either medical or surgical therapy (2,148). Dobutamine stress testing in patients with AS should be performed only in centers with experience in pharmacological stress testing and with a cardiologist in attendance.

The clinical approach to the patient with low-output AS relies on integration of multiple sources of data. In addition to measurement of Doppler velocity, gradient, and valve area, the extent of valve calcification should be assessed. Severe calcification suggests that AVR may be beneficial. When transthoracic images are suboptimal, transesophageal imaging or fluoroscopy may be used to assess the degree of valve calcification and orifice area. The risk of surgery and patient comorbidities also are taken into account. Although patients with low-output severe AS have a poor prognosis, in those with contractile reserve, outcome is still better with AVR than with medical therapy (148). Some patients without contractile reserve may also benefit from AVR, but decisions in these high-risk patients must be individualized because there are no data indicating who will have a better outcome with surgery.

3.1.7. Indications for Aortic Valve Replacement

CLASS I

1. AVR is indicated for symptomatic patients with severe AS.* *(Level of Evidence: B)*
2. AVR is indicated for patients with severe AS* undergoing coronary artery bypass graft surgery (CABG). *(Level of Evidence: C)*
3. AVR is indicated for patients with severe AS* undergoing surgery on the aorta or other heart valves. *(Level of Evidence: C)*
4. AVR is recommended for patients with severe AS* and LV systolic dysfunction (ejection fraction less than 0.50). *(Level of Evidence: C)*

CLASS IIa

1. AVR is reasonable for patients with moderate AS* undergoing CABG or surgery on the aorta or other heart valves (see Section 3.7 on combined multiple valve disease and Section 10.4 on AVR in patients undergoing CABG). *(Level of Evidence: B)*

*See Table 4 (27).

CLASS IIb

1. AVR may be considered for asymptomatic patients with severe AS* and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension). *(Level of Evidence: C)*
2. AVR may be considered for adults with severe asymptomatic AS* if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset. *(Level of Evidence: C)*
3. AVR may be considered in patients undergoing CABG who have mild AS* when there is evidence, such as moderate to severe valve calcification, that progression may be rapid. *(Level of Evidence: C)*
4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area less than 0.6 cm^2, mean gradient greater than 60 mm Hg, and jet velocity greater than 5.0 m per second) when the patient's expected operative mortality is 1.0% or less. *(Level of Evidence: C)*

CLASS III

1. AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the CLASS IIa/IIb recommendations. *(Level of Evidence: B)*

In adults with severe, symptomatic, calcific AS, AVR is the only effective treatment. Younger patients with congenital or rheumatic AS may be candidates for valvotomy (see Section 6.1 under management of adolescents and young adults). Although there is some lack of agreement about the optimal timing of surgery in asymptomatic patients, it is possible to develop rational guidelines for most patients. A proposed management strategy for patients with severe AS is shown in Figure 3 (149). Particular consideration should be given to the natural history of asymptomatic patients and to operative risks and outcomes after surgery. See also Section 7.2.

3.1.7.1. SYMPTOMATIC PATIENTS

In symptomatic patients with AS, AVR improves symptoms and improves survival (106,150–155). These salutary results of surgery are partly dependent on LV function. The outcome is similar in patients with normal LV function and in those with moderate depression of contractile function. The depressed ejection fraction in many patients in this latter group is caused by excessive afterload (afterload mismatch) (66), and LV function improves after AVR in such patients. If LV dysfunction is not caused by afterload mismatch, survival is still improved, but improvement in LV function and resolution of symptoms might not be complete after AVR (150,154,156–158). Therefore, in the absence of serious comorbid conditions, AVR is indicated in virtually all symptomatic patients with severe AS. Because of the risk of sudden death, AVR should be performed promptly after the onset of symptoms. Age is not a contraindication to surgery, with several series showing outcomes similar to age-matched normal subjects in the very elderly. The operative risks can be estimated with readily available and well-validated online risk calculators from the Society of Thoracic Surgeons (www.sts.org) and the European System for Cardiac Operative Risk Evaluation (www.euroscore.org)

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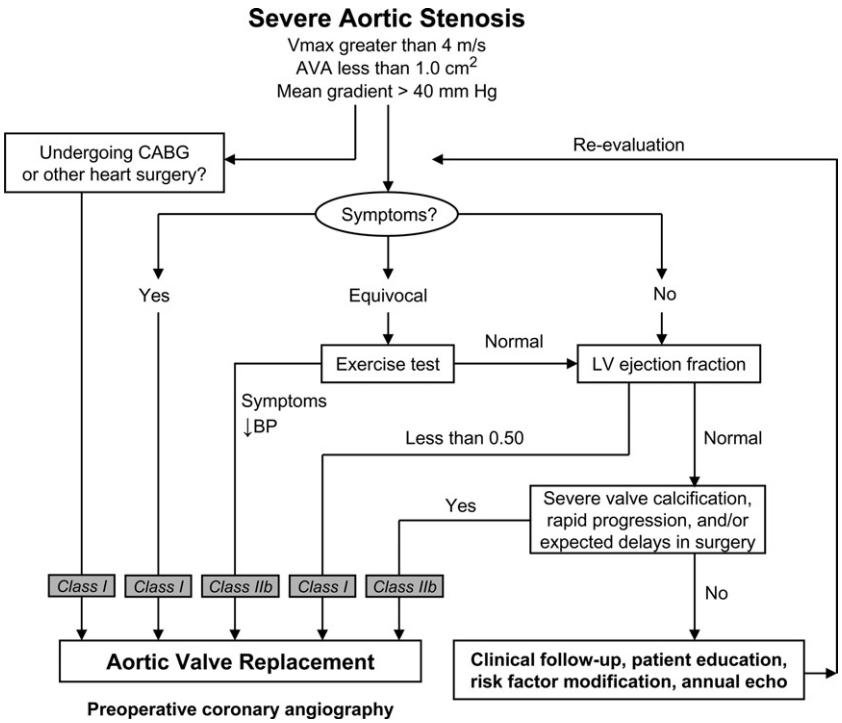

Figure 3. Management Strategy for Patients With Severe Aortic Stenosis

Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. Modified from CM Otto. Valvular aortic stenosis: disease severity and timing of intervention. J Am Coll Cardiol 2006;47:2141–51 (149). AVA indicates aortic valve area; BP, blood pressure; CABG, coronary artery bypass graft surgery; echo, echocardiography; LV, left ventricular; and Vmax, maximal velocity across aortic valve by Doppler echocardiography.

(159–161), as well as the risk calculator developed specifically for valvular heart surgery by Ambler et al. (162).

3.1.7.2. ASYMPTOMATIC PATIENTS

Many clinicians are reluctant to proceed with AVR in an asymptomatic patient (163), whereas others are concerned about caring for a patient with severe AS without surgery. Although AVR is associated with low perioperative morbidity and mortality in many centers, the average perioperative mortality in the STS database is 3.0% to 4.0% for isolated AVR and 5.5% to 6.8% for AVR plus CABG (164,165). These rates are 33% higher in centers with low volume than in centers with the highest surgical volume (166). A review of Medicare data (167), involving 684 US hospitals and more than 142 000 patients, indicates that the average in-hospital mortality for AVR in patients over the age of 65 years is 8.8% (13.0% in low-volume centers and 6.0% in high-volume centers). In addition, despite improved longevity of current-generation bioprosthetic valves (168,169), AVR in young patients subjects them to the risks of structural valve deterioration of bioprostheses (168,170–174) and the appreciable morbidity and mortality of mechanical valves (172,174–178). Thus, the combined risk of surgery in older patients and the late complications of a prosthesis in younger patients needs to be balanced against the possibility of preventing sudden death, which, as noted above, occurs at a rate of less than 1.0% per year.

Despite these considerations, some difference of opinion persists among clinicians regarding the indications for AVR in asymptomatic patients with severe AS, because the probability of remaining free of cardiac symptoms without surgery is less than 50% at 5 years (61,96,116). Some argue that irreversible myocardial depression or fibrosis might develop during a prolonged asymptomatic stage and that this might preclude an optimal outcome. Such irreversibility has not been proved, but this concept has been used to support early surgery (152,179). Still others attempt to identify patients who are at especially high risk of sudden death without surgery, although data supporting this approach are limited. Currently, there is general agreement that the risk of AVR exceeds any potential benefit in patients with severe AS who are truly asymptomatic with normal LV systolic function. However, as improved valve substitutes are developed and methods of valve replacement become safer, the risk-benefit balance may change to favor earlier intervention in AS.

Studies suggest that patients at risk of rapid disease progression and impending symptom onset can be identified on the basis of clinical and echocardiographic parameters. The rate of hemodynamic progression is faster in patients with asymptomatic severe (96) or mild to moderate (98) AS when patient age is over 50 years and severe valve calcification or concurrent CAD is present. Adverse clinical outcomes are more likely in patients with a more rapid rate

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of hemodynamic progression, defined as an annual increase in aortic jet velocity greater than 0.3 m per second per year or a decrease in valve area greater than 0.1 cm^2 per year (61,96). The presence of left ventricular hypertrophy by ECG and smaller aortic valve area by Doppler echocardiography predict the development of symptoms (61,116). In addition, serum levels of B-type natriuretic peptide may provide important prognostic information (180). In situations in which there is delay between symptom onset and surgical intervention, patients are at high risk of adverse outcomes during the waiting period. These higher-risk patients might warrant more frequent echocardiography or earlier consideration of valve replacement.

In the 1998 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease, consideration was given to performing AVR in patients with AS and severe LV hypertrophy and those with ventricular tachycardia (Class IIb). The current committee determined that there was insufficient evidence to support those recommendations, which are not carried forward in the current document.

3.1.7.3. PATIENTS UNDERGOING CORONARY ARTERY BYPASS OR OTHER CARDIAC SURGERY

Patients with severe AS, with or without symptoms, who are undergoing CABG should undergo AVR at the time of the revascularization procedure. Similarly, patients with severe AS undergoing surgery on other valves (such as MV repair) or the aortic root should also undergo AVR as part of the surgical procedure. In patients with moderate AS, it is generally accepted practice to perform AVR at the time of CABG (181–185). Many clinicians also recommend AVR for moderate AS at the time of MV or aortic root surgery (for further detail, see Section 3.7, "Multiple Valve Disease"). However, there are no data to support a policy of AVR for mild AS at the time of CABG, with the exception of those patients with moderate to severe valvular calcification (98,181,182,185–187). Recommendations for AVR at the time of CABG are discussed in Section 10.4.

3.1.8. Aortic Balloon Valvotomy

CLASS IIb

1. Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR. *(Level of Evidence: C)*
2. Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions. *(Level of Evidence: C)*

CLASS III

1. Aortic balloon valvotomy is not recommended as an alternative to AVR in adult patients with AS; certain younger adults without valve calcification may be an exception (see Section 6.1.3). *(Level of Evidence: B)*

Percutaneous balloon aortic valvotomy is a procedure in which 1 or more balloons are placed across a stenotic valve and inflated to decrease the severity of AS (188–190). This procedure has an important role in treating adolescents and young adults with AS (see Section 6.1.) but a very limited role in older adults. The mechanism underlying relief of the stenotic lesion in older adults is fracture of calcific deposits within the valve leaflets and, to a minor degree, stretching of the annulus and separation of the calcified or fused commissures (191–193). Immediate hemodynamic results include a moderate reduction in the transvalvular pressure gradient, but the postvalvotomy valve area rarely exceeds 1.0 cm^2. Despite the modest change in valve area, an early symptomatic improvement is usually seen. However, serious acute complications occur with a frequency greater than 10% (194–200), and restenosis and clinical deterioration occur within 6 to 12 months in most patients (195,200–204). Therefore, in adults with AS, balloon valvotomy is not a substitute for AVR (204–207).

Some clinicians contend that despite the procedural morbidity and mortality and limited long-term results, balloon valvotomy can have a temporary role in the management of some symptomatic patients who are not initially candidates for AVR (207). For example, patients with severe AS and refractory pulmonary edema or cardiogenic shock might benefit from aortic valvuloplasty as a "bridge" to surgery; an improved hemodynamic state may reduce the risks of surgery. However, most clinicians recommend proceeding directly to AVR in these cases. The indications for palliative valvotomy in patients in whom AVR cannot be recommended because of serious comorbid conditions are even less well established, with no data to suggest improved longevity, although some patients do report a decrease in symptoms. Most asymptomatic patients with severe AS who require urgent noncardiac surgery can undergo surgery at a reasonably low risk with monitoring of anesthesia and attention to fluid balance (208–212). Balloon aortic valvotomy is not recommended for these patients. If preoperative correction of AS is needed, they should be considered for AVR.

3.1.9. Medical Therapy for the Inoperable Patient

Comorbid conditions (e.g., malignancy) or, on occasion, patient preferences might preclude AVR for severe AS. Under such circumstances, there is no therapy that prolongs life, and only limited medical therapies are available to alleviate symptoms. Patients with evidence of pulmonary congestion can benefit from cautious treatment with digitalis, diuretics, and angiotensin converting enzyme (ACE) inhibitors. Indeed, a cautious reduction in central blood volume and LV preload can be efficacious in some patients with heart failure symptoms. It should be recognized, however, that excessive preload reduction can depress cardiac output and reduce systemic arterial pressure; patients with severe AS are especially subject to this untoward effect due to a small hypertrophied ventricle. In patients with acute pulmonary edema due to AS, nitroprusside infusion may be used to reduce congestion and improve LV performance. Such therapy should be performed in an intensive

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care unit under the guidance of invasive hemodynamic monitoring (213). Digitalis should be reserved for patients with depressed systolic function or atrial fibrillation. Atrial fibrillation and other atrial arrhythmias have an adverse effect on atrial pump function and ventricular rate; if prompt cardioversion is unsuccessful, pharmacological control of the ventricular rate is essential. If angina is the predominant symptom, cautious use of nitrates and beta blockers can provide relief. There is no specific medical therapy for syncope unless it is caused by a bradyarrhythmia or tachyarrhythmia.

3.1.10. Evaluation After Aortic Valve Replacement

Considering the known complications of prosthetic aortic valves (168,170–178,214), patients require periodic clinical and selected laboratory examinations after AVR. A complete history and physical examination should be performed at least once a year. Indications for echocardiography are discussed in Section 9.3.

3.1.11. Special Considerations in the Elderly

Because there is no effective medical therapy and balloon valvotomy is not an acceptable alternative to surgery, AVR must be considered in all elderly patients who have symptoms caused by AS. Valve replacement is technically possible at any age (215), but the decision to proceed with such surgery depends on many factors, including the patient's wishes and expectations. Older patients with symptoms due to severe AS, normal coronary arteries, and preserved LV function can expect a better outcome than those with CAD or LV dysfunction (110). Certainly advanced cancer and permanent neurological defects as a result of stroke or dementia make cardiac surgery inappropriate. Deconditioned and debilitated patients often do not return to an active existence, and the presence of the other comorbid disorders could have a major impact on outcome.

In addition to the confounding effects of CAD and the potential for stroke, other considerations are peculiar to older patients. For example, a narrow LV outflow tract and a small aortic annulus sometimes present in elderly women could require enlargement of the annulus. Heavy calcification of the valve, annulus, and aortic root may require debridement. Occasionally, a composite valve-aortic graft is needed. Likewise, excessive or inappropriate hypertrophy associated with valvular stenosis can be a marker for perioperative morbidity and mortality (81,83). Preoperative recognition of elderly patients with marked LV hypertrophy followed by appropriate perioperative management can reduce this morbidity and mortality substantially. There is no perfect method for weighing all of the relevant factors and identifying specifically high- and low-risk elderly patients, but this risk can be estimated well in individual patients (159–162,216). The decision to proceed with AVR depends on an imprecise analysis that considers the balance between the potential for improved symptoms and survival and the morbidity and mortality of surgery (217–219).

3.2. Aortic Regurgitation

3.2.1. Etiology

There are a number of common causes of AR. These include idiopathic dilatation of the aorta, congenital abnormalities of the aortic valve (most notably bicuspid valves), calcific degeneration, rheumatic disease, infective endocarditis, systemic hypertension, myxomatous degeneration, dissection of the ascending aorta, and Marfan syndrome. Less common causes include traumatic injuries to the aortic valve, ankylosing spondylitis, syphilitic aortitis, rheumatoid arthritis, osteogenesis imperfecta, giant cell aortitis, Ehlers-Danlos syndrome, Reiter's syndrome, discrete subaortic stenosis, and ventricular septal defects with prolapse of an aortic cusp. Recently, anorectic drugs have also been reported to cause AR (see Section 3.9.). The majority of these lesions produce chronic AR with slow, insidious LV dilation and a prolonged asymptomatic phase (Table 4) (27). Other lesions, in particular infective endocarditis, aortic dissection, and trauma, more often produce acute severe AR, which can result in sudden catastrophic elevation of LV filling pressures and reduction in cardiac output.

3.2.2. Acute Aortic Regurgitation

3.2.2.1. PATHOPHYSIOLOGY

In acute severe AR, the sudden large regurgitant volume is imposed on a left ventricle of normal size that has not had time to accommodate the volume overload. With an abrupt increase in end-diastolic volume, the ventricle operates on the steep portion of a normal diastolic pressure-volume relationship, and LV end-diastolic and left atrial pressures may increase rapidly and dramatically. The Frank-Starling mechanism is used, but the inability of the ventricle to develop compensatory chamber dilatation acutely results in a decrease in forward stroke volume. Although tachycardia develops as a compensatory mechanism to maintain cardiac output, this is often insufficient. Hence, patients frequently present with pulmonary edema or cardiogenic shock. Acute AR creates especially marked hemodynamic changes in patients with pre-existing pressure overload hypertrophy, in whom the small, noncompliant LV cavity is set on an even steeper diastolic pressure-volume relationship and has reduced preload reserve. Examples of this latter situation include aortic dissection in patients with systemic hypertension, infective endocarditis in patients with pre-existing AS, and acute regurgitation after balloon valvotomy or surgical commissurotomy for congenital AS. Patients may also present with signs and symptoms of myocardial ischemia. As the LV end-diastolic pressure approaches the diastolic aortic and coronary artery pressures, myocardial perfusion pressure in the subendocardium is diminished. LV dilation and thinning of the LV wall result in increased afterload, and this combines with tachycardia to increase myocardial oxygen demand. Therefore, ischemia and its consequences, including sudden death, occur commonly in acute severe AR.

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3.2.2.2. DIAGNOSIS

Many of the characteristic physical findings of chronic AR are modified or absent when valvular regurgitation is acute, which can lead to underestimation of its severity. LV size may be normal on physical examination, and cardiomegaly may be absent on chest X-ray. Pulse pressure may not be increased because systolic pressure is reduced and the aortic diastolic pressure equilibrates with the elevated LV diastolic pressure. Because this diastolic pressure equilibration between aorta and ventricle can occur before the end of diastole, the diastolic murmur may be short and/or soft and therefore poorly heard. The elevated LV diastolic pressure can close the MV prematurely, reducing the intensity of the first heart sound. An apical diastolic rumble can be present, but it is usually brief and without presystolic accentuation. Tachycardia is invariably present.

Echocardiography is indispensable in confirming the presence and severity of the valvular regurgitation, determining its cause, estimating the degree of pulmonary hypertension (if TR is present), and determining whether there is rapid equilibration of aortic and LV diastolic pressure. Evidence for rapid pressure equilibration includes a short AR diastolic half-time (less than 300 ms), a short mitral deceleration time (less than 150 ms), or premature closure of the MV.

Acute AR caused by aortic root dissection is a surgical emergency that requires particularly prompt identification and management. Transesophageal echocardiography is indicated when aortic dissection is suspected (220–222). In some settings, computed tomographic imaging or magnetic resonance imaging should be performed if this will lead to a more rapid diagnosis than can be achieved by transesophageal echocardiography (220,221,223). Cardiac catheterization, aortography, and coronary angiography are rarely required, are associated with increased risk, and might delay urgent surgery unnecessarily (221,224–227). Angiography should be considered only when the diagnosis cannot be determined by noninvasive imaging and when patients have known CAD, especially those with previous CABG (see Section 10.2).

3.2.2.3. TREATMENT

Death due to pulmonary edema, ventricular arrhythmias, electromechanical dissociation, or circulatory collapse is common in acute severe AR, even with intensive medical management. Urgent surgical intervention is recommended. Nitroprusside, and possibly inotropic agents such as dopamine or dobutamine to augment forward flow and reduce LV end-diastolic pressure, may be helpful to manage the patient temporarily before surgery. Intra-aortic balloon counterpulsation is contraindicated. Although beta blockers are often used in treating aortic dissection, these agents should be used very cautiously, if at all, in the setting of acute AR because they will block the compensatory tachycardia. In patients with acute severe AR resulting from infective endocarditis, surgery should not be delayed, especially if there is hypotension, pulmonary edema, or evidence of low output. In patients with mild acute AR, antibiotic treatment may be all that is necessary if the patient is hemodynamically stable. Exceptions to this latter recommendation are discussed in Section 4.6.1.

3.2.3. Chronic Aortic Regurgitation

3.2.3.1. PATHOPHYSIOLOGY

The left ventricle responds to the volume load of chronic AR with a series of compensatory mechanisms, including an increase in end-diastolic volume, an increase in chamber compliance that accommodates the increased volume without an increase in filling pressures, and a combination of eccentric and concentric hypertrophy. The greater diastolic volume permits the ventricle to eject a large total stroke volume to maintain forward stroke volume in the normal range. This is accomplished through rearrangement of myocardial fibers with the addition of new sarcomeres and development of eccentric LV hypertrophy (228). As a result, preload at the sarcomere level remains normal or near normal, and the ventricle retains its preload reserve. The enhanced total stroke volume is achieved through normal performance of each contractile unit along the enlarged circumference (229). Thus, LV ejection performance is normal, and ejection phase indexes such as ejection fraction and fractional shortening remain in the normal range. However, the enlarged chamber size, with the associated increase in systolic wall stress, also results in an increase in LV afterload and is a stimulus for further hypertrophy (228,230). Thus, AR represents a condition of combined volume overload and pressure overload (231). As the disease progresses, recruitment of preload reserve and compensatory hypertrophy permit the ventricle to maintain normal ejection performance despite the elevated afterload (232,233). The majority of patients remain asymptomatic throughout this compensated phase, which may last for decades. Vasodilator therapy has the potential to reduce the hemodynamic burden in such patients.

For purposes of the subsequent discussion, patients with normal LV systolic function will be defined as those with normal LV ejection fraction at rest. It is recognized that other indices of LV function may not be "normal" in chronic severe AR and that the hemodynamic abnormalities noted above may be considerable. It is also recognized that the transition to LV systolic dysfunction represents a continuum and that there is no single hemodynamic measurement that represents the absolute boundary between normal LV systolic function and LV systolic dysfunction.

In a large subset of patients, the balance between afterload excess, preload reserve, and hypertrophy cannot be maintained indefinitely. Preload reserve may be exhausted (233), and/or the hypertrophic response may be inadequate (63), so that further increases in afterload result in a reduction in ejection fraction, first into the low normal range and then below normal. Impaired myocardial contractility may also contribute to this process. Patients often

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Table 13. Preoperative Predictors of Surgical Outcome in Aortic Regurgitation

Study, Year	Study Design	No. of Patients	Outcome Assessed	Findings
Forman et al., 1980 (251)	Retrospective	90	Survival	High-risk group identified by preoperative angiographic LV EF less than 0.50
Henry et al., 1980 (257)	Prospective	50	Survival	High-risk group identified by preoperative echocardiographic LV FS less than 0.25 and/or ESD greater than 55 mm
Cunha et al., 1980 (250)	Retrospective	86	Survival	High-risk group identified by preoperative echocardiographic LV FS less than 0.30. Mortality also significantly associated with preoperative ESD. Among patients with FS less than 0.30, mortality higher in NYHA FC III-IV than in FC I-II.
Greves et al., 1981 (252)	Retrospective	45	Survival	High-risk group identified by preoperative angiographic LV EF less than 0.45 and/or CI less than 2.5 L/mm. Among patients with EF less than 0.45, mortality higher in NYHA FC III-IV than in FC I–II.
Kumpuris et al., 1982 (258)	Prospective	43	Survival, heart failure, LV function	Persistent LV dilatation after AVR predicted by preoperative echocardiographic LV ESD, radius/thickness mean and end-systolic wall stress. All deaths occurred in patients with persistent LV dilatation.
Gaasch et al., 1983 (253)	Prospective	32	Symptoms, LV function	Persistent LV dilatation after AVR predicted by echocardiographic LV ESD greater than 2.6 cm/m^2 and radius/thickness ratio greater than 3.8. Trend toward worse survival in patients with persistent LV dilatation.
Fioretti et al., 1983 (259)	Retrospective	47	LV function	Persistent LV dysfunction predicted by preoperative EDD 75 mm or greater and/or ESD 55 mm or greater
Stone et al., 1984 (260)	Prospective	113	LV function	Normal LV function after AVR predicted by preoperative LV FS greater than 0.26, ESD less than 55 mm, and EDD less than 80 mm. No preoperative variable predicted postoperative LV function.
Bonow et al., 1985, 1988 (254, 245)	Prospective	80	Survival, LV function	Postoperative survival and LV function predicted by preoperative LV EF, FS, and ESD. High-risk group identified by subnormal EF at rest. Among patients with subnormal EF, poor exercise tolerance and prolonged duration of LV dysfunction identified the highest-risk group.
Daniel et al., 1985 (261)	Retrospective	84	Survival, symptoms, LV function	Outcome after AVR predicted by preoperative LV FS and ESD. Survival at 2.5 years was 90.5% with FS greater than 0.25 and ESD 55 mm or less but only 70% with ESD greater than 55 mm and FS 25% or less.
Cormier et al., 1986 (262)	Prospective	73	Survival	High-risk group identified by preoperative LV EF less than 0.40 and ESD 55 mm or greater
Sheiban et al., 1986 (263)	Retrospective	84	Survival	High-risk group identified by preoperative LV EF less than 0.50 and ESD greater than 55 mm
Carabello et al., 1987 (243)	Retrospective	14	LV function	Postoperative LV EF predicted by preoperative ESD, FS, EDD, and radius/thickness ratio
Taniguchi et al., 1987 (244)	Retrospective	62	Survival	High-risk group identified by preoperative ESV greater than 200 ml/m^2 and/or EF less than 0.40
Michel et al., 1995 (256)	Retrospective	286	LV function	Postoperative LV dysfunction predicted by preoperative LV EF, FS, ESD, and EDD
Klodas et al., 1996, 1997 (264, 265)	Retrospective	289	Survival	High-risk group identified by symptom severity and preoperative EF less than 0.50
Turina et al., 1998 (266)	Retrospective	192	Survival	High-risk group identified by symptom severity, low EF, and elevated end-diastolic volume

AVR indicates aortic valve replacement; CI, cardiac index; EDD, end-diastolic dimension; EF, ejection fraction; ESD, end-systolic dimension; ESV, end-systolic volume; FC, functional class; FS, fractional shortening; LV, left ventricular; NYHA, New York Heart Association.

develop dyspnea at this point in the natural history. In addition, diminished coronary flow reserve in the hypertrophied myocardium may result in exertional angina (234). However, this transition may be much more insidious, and it is possible for patients to remain asymptomatic until severe LV dysfunction has developed.

LV systolic dysfunction (defined as an ejection fraction below normal at rest) is initially a reversible phenomenon related predominantly to afterload excess, and full recovery of LV size and function is possible with AVR (235–246). With time, during which the ventricle develops progressive chamber enlargement and a more spherical geometry, depressed myocardial contractility predominates over excessive loading as the cause of progressive systolic dysfunction. This can progress to the extent that the full benefit of surgical correction of the regurgitant lesion, in terms of recovery of LV function and improved survival, can no longer be achieved (244,247–256).

A large number of studies have identified LV systolic function and end-systolic size as the most important determinants of survival and postoperative LV function in patients undergoing AVR for chronic AR (235,237–267). Studies of predictors of surgical outcome are listed in Table 13.

Among patients undergoing valve replacement for chronic AR with preoperative LV systolic dysfunction (defined as an ejection fraction below normal at rest), several

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Table 14. Factors Predictive of Reduced Postoperative Survival and Recovery of Left Ventricular Function in Patients With Aortic Regurgitation and Preoperative Left Ventricular Systolic Dysfunction

Severity of preoperative symptoms or reduced exercise tolerance
Severity of depression of left ventricular ejection fraction
Duration of preoperative left ventricular systolic dysfunction

factors are associated with worse functional and survival results after operation. These are listed in Table 14.

3.2.3.2. NATURAL HISTORY

3.2.3.2.1. ASYMPTOMATIC PATIENTS WITH NORMAL LEFT VENTRICULAR FUNCTION. There are no truly large-scale studies evaluating the natural history of asymptomatic patients in whom LV systolic function was known to be normal (as determined by invasive or noninvasive testing). The current recommendations are derived from 9 published series (268–277) involving a total of 593 such patients (range, 27 to 104 patients/series) with a mean follow-up period of 6.6 years (Table 15). This analysis is subject to the usual limitations of comparisons of different clinical series with different patient selection factors and different end points. For example, 1 series (270) represents patients receiving placebo in a randomized drug trial (278) that included some patients with "early" New York Heart Association (NYHA) functional class II symptoms (although none had "limiting" symptoms), and another (272) represents patients receiving

Table 15. Studies of the Natural History of Asymptomatic Patients With Aortic Regurgitation

Study, Year	No. of Patients	Mean Follow-Up, y	Progression to Symptoms, Death, or LV Dysfunction, Rate per y (%)	Progression to Asymptomatic LV Dysfunction		Mortality, No. of Patients	Comments
				n	Rate per y (%)		
Bonow et al., 1983, 1991 (268, 271)	104	8.0	3.8	4	0.5	2	Outcome predicted by LV ESD, EDD, change in EF with exercise, and rate of change in ESD and EF at rest with time.
Scognamiglio et al., 1986* (269)	30	4.7	2.1	3	2.1	0	3 Patients who developed asymptomatic LV dysfunction initially had lower PAP/ESV ratios and trended toward higher LV ESD and EDD and lower FS
Siemienczuk et al., 1989 (270)	50	3.7	4.0	1	0.5	0	Patients included those receiving placebo and medical dropouts in a randomized drug trial; included some patients with NYHA FC II symptoms; outcome predicted by LV ESV, EDV, change in EF with exercise, and end-systolic wall stress
Scognamiglio et al., 1994* (272)	74	6.0	5.7	15	3.4	0	All patients received digoxin as part of a randomized trial
Tornos et al., 1995 (273)	101	4.6	3.0	6	1.3	0	Outcome predicted by pulse pressure, LV ESD, EDD, and EF at rest
Ishii et al., 1996 (274)	27	14.2	3.6	—	—	0	Development of symptoms predicted by systolic BP, LV ESD, EDD, mass index, and wall thickness. LV function not reported in all patients
Borer et al., 1998 (275)	104	7.3	6.2	7	0.9	4	20% Of patients in NYHA FC II; outcome predicted by initial FC II symptoms, change in LV EF with exercise, LV ESD, and LV FS
Tarasoutchi et al., 2003 (276)	72	10	4.7	1	0.1	0	Development of symptoms predicted by LV ESD and EDD. LV function not reported in all patients
Evangelista et al., 2005 (277)	31	7	3.6	—	—	1	Placebo control group in 7-year vasodilator clinical trial
Average	593	6.6	4.3	37	1.2	0.18% per y	

A dash indicates that data were not available. *Two studies by the same authors involved separate patient groups.

BP indicates blood pressure; EDD, end-diastolic dimension; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic dimension; ESV, end-systolic volume; FC, functional class; FS, fractional shortening; LV, left ventricular; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.

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Table 16. Natural History of Aortic Regurgitation

Asymptomatic patients with normal LV systolic function (268–277)	
Progression to symptoms and/or LV dysfunction	Less than 6% per y
Progression to asymptomatic LV dysfunction	Less than 3.5% per y
Sudden death	Less than 0.2% per y
Asymptomatic patients with LV dysfunction (281–283)	
Progression to cardiac symptoms	Greater than 25% per y
Symptomatic patients (284–288)	
Mortality rate	Greater than 10% per y

LV indicates left ventricular.

digoxin in a long-term study comparing the effects of nifedipine with digoxin. In 2 studies (274,276), LV function was not reported in all patients, and it is unclear whether all had normal LV systolic function at baseline. In another study (275), 20% of patients were not asymptomatic but had "early" NYHA functional class II symptoms, and the presence of these symptoms was a significant predictor of death, LV dysfunction, or development of more severe symptoms. Some patients in this latter series had evidence of LV systolic dysfunction (fractional shortening as low as 18%).

The results of these 9 studies are summarized in Tables 15 and 16. The rate of progression to symptoms and/or LV systolic dysfunction averaged 4.3% per year. Sudden death occurred in 7 of the 593 patients, for an average mortality rate of less than 0.2% per year. Seven of the 9 studies reported the rate of development of asymptomatic LV dysfunction, defined as an ejection fraction at rest below normal (269–273,275,276); 37 of a total of 535 patients developed depressed systolic function at rest without symptoms during a mean 5.9-year follow-up period, a rate of 1.2% per year.

Despite the low likelihood of patients developing asymptomatic LV dysfunction, it should also be emphasized that more than one fourth of patients who die or develop systolic dysfunction do so before the onset of warning symptoms (269–271,275). Thus, thorough questioning of patients regarding symptomatic status is not sufficient in the serial evaluation of asymptomatic patients; quantitative evaluation of LV function is also indispensable. Moreover, patients at risk of future symptoms, death, or LV dysfunction can also be identified on the basis of noninvasive testing. Five of the natural history studies provide concordant information on the variables associated with higher risk (270–272,275,276). These variables are age, LV end-systolic dimension (or volume), LV end-diastolic dimension (or volume), and the LV ejection fraction during exercise. In 1 study (275), the LV ejection fraction during exercise was an independent risk factor. However, the direction and magnitude of change in ejection fraction from rest to exercise is related not only to myocardial contractility (279) but also to severity of volume overload (271,278–280) and exercise-induced changes in preload and peripheral resistance (280). In 2 multivariate analyses (271,276), only age and end-systolic dimension on initial study were independent predictors of outcome, as were the rate of increase in end-systolic dimension and decrease in resting ejection fraction during serial longitudinal studies (271). During a mean follow-up period of 8 years, patients with initial end-systolic dimensions greater than 50 mm had a likelihood of death, symptoms, and/or LV dysfunction of 19% per year. In those with end-systolic dimensions of 40 to 50 mm, the likelihood was 6% per year, and when the dimension was less than 40 mm, it was zero (271).

3.2.3.2.2. ASYMPTOMATIC PATIENTS WITH DEPRESSED SYSTOLIC FUNCTION. The limited data in asymptomatic patients with depressed LV ejection fraction indicate that the majority develop symptoms that warrant AVR within 2 to 3 years (281–283). The average rate of symptom onset in such patients is greater than 25% per year (Table 16) (268–277,281–288).

3.2.3.2.3. SYMPTOMATIC PATIENTS. There are no contemporary large-scale studies of the natural history of symptomatic patients with chronic AR, because the onset of angina or significant dyspnea is usually an indication for valve replacement. The data developed in the presurgical era indicate that patients with dyspnea, angina, or overt heart failure have a poor outcome with medical therapy, analogous to that of patients with symptomatic AS. Mortality rates of greater than 10% per year have been reported in patients with angina pectoris and greater than 20% per year in those with heart failure (284–286). LV function was not measured in these patients, so it is unclear whether symptomatic patients with normal ejection fractions have the same adverse outcome as symptomatic patients with LV dysfunction; however, subsequent data indicate a poor outcome for symptomatic patients with medical therapy, even among those with preserved LV systolic function (274,287,288).

3.2.3.3. DIAGNOSIS AND INITIAL EVALUATION

CLASS I

1. Echocardiography is indicated to confirm the presence and severity of acute or chronic AR. *(Level of Evidence: B)*
2. Echocardiography is indicated for diagnosis and assessment of the cause of chronic AR (including valve morphology and aortic root size and morphology) and for assessment of LV hypertrophy, dimension (or volume), and systolic function. *(Level of Evidence: B)*
3. Echocardiography is indicated in patients with an enlarged aortic root to assess regurgitation and the severity of aortic dilatation. *(Level of Evidence: B)*
4. Echocardiography is indicated for the periodic re-evaluation of LV size and function in asymptomatic patients with severe AR. *(Level of Evidence: B)*
5. Radionuclide angiography or magnetic resonance imaging is indicated for the initial and serial assessment of LV volume and function at rest in patients with AR and suboptimal echocardiograms. *(Level of Evidence: B)*
6. Echocardiography is indicated to re-evaluate mild, moderate, or severe AR in patients with new or changing symptoms. *(Level of Evidence: B)*

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CLASS IIa

1. Exercise stress testing for chronic AR is reasonable for assessment of functional capacity and symptomatic response in patients with a history of equivocal symptoms. *(Level of Evidence: B)*
2. Exercise stress testing for patients with chronic AR is reasonable for the evaluation of symptoms and functional capacity before participation in athletic activities. *(Level of Evidence: C)*
3. Magnetic resonance imaging is reasonable for the estimation of AR severity in patients with unsatisfactory echocardiograms. *(Level of Evidence: B)*

CLASS IIb

1. Exercise stress testing in patients with radionuclide angiography may be considered for assessment of LV function in asymptomatic or symptomatic patients with chronic AR. *(Level of Evidence: B)*

The diagnosis of chronic severe AR can usually be made on the basis of the diastolic murmur, displaced LV impulse, wide pulse pressure, and characteristic peripheral findings that reflect wide pulse pressure. A third heart sound is often heard as a manifestation of the volume load and is not necessarily an indication of heart failure. An Austin-Flint rumble is a specific finding for severe AR (289,290). In many patients with more mild to moderate AR, the physical examination will identify the regurgitant lesion but will be less accurate in determining its severity. When the diastolic murmur of AR is louder in the third and fourth right intercostal spaces than in the third and fourth left intercostal spaces, the AR likely results from aortic root dilatation rather than from a deformity of the leaflets alone (291). The chest X-ray and ECG are helpful in evaluating overall heart size and rhythm, evidence of LV hypertrophy, and evidence of conduction disorders.

Echocardiography is indicated:

- to confirm the diagnosis of AR if there is an equivocal diagnosis based on physical examination
- to assess the cause of AR and to assess valve morphology
- to provide a semiquantitative estimate of the severity of AR
- to assess LV dimension, mass, and systolic function
- to assess aortic root size.

In asymptomatic patients with preserved systolic function, these initial measurements represent the baseline information with which future serial measurements can be compared. In addition to semiquantitative assessment of the severity of AR by color flow jet area and width by Doppler echocardiography, quantitative measurement of regurgitant volume, regurgitant fraction, and regurgitant orifice area can be performed in experienced laboratories (Table 4) (27). Indirect measures of severity of AR are helpful, using the rate of decline in regurgitant gradient measured by the slope of diastolic flow velocity, the degree of reversal in pulse wave velocity in the descending aorta, and the magnitude of LV outflow tract velocity (2,292,293). Comparison of stroke volumes at the aortic valve compared with another uninvolved valve may provide a quantitative measurement of regurgitant fraction (294), but this measurement is more technically demanding.

LV wall stress may also be estimated from blood pressure and echocardiographic measurements. However, such wall stress measurements are difficult to reproduce, have methodological and conceptual problems, and should not be used for diagnosis or management decision making in clinical practice.

For purposes of the subsequent discussion of management of patients with AR, severe AR is defined as clinical and Doppler evidence of severe regurgitation (Table 4) (27) in addition to LV cavity dilatation. If the patient is asymptomatic and leads an active lifestyle and the echocardiogram is of good quality, no other testing is necessary. If the patient has severe AR and is sedentary or has equivocal symptoms, exercise testing is helpful to assess functional capacity, symptomatic responses, and hemodynamic effects of exercise (Fig. 4). If the echocardiogram is of insufficient quality to assess LV function, radionuclide angiography or cardiac magnetic resonance should be used in asymptomatic patients to measure LV ejection fraction at rest and estimate LV volumes. In patients who are symptomatic on initial evaluation, it is reasonable to proceed directly to transesophageal echocardiography or cardiac catheterization and angiography if the echocardiogram is of insufficient quality to assess LV function or severity of AR.

The exercise ejection fraction and the change in ejection fraction from rest to exercise are often abnormal, even in asymptomatic patients (268,270–272,275,283,295–303); however, these have not been proved to have independent diagnostic or prognostic value when LV function at rest and severity of LV volume overload by echocardiography are already known. One study that did identify the LV ejection fraction response to exercise as a predictor of symptomatic deterioration or LV dysfunction (275) included many patients with NYHA functional class II symptoms, LV systolic dysfunction (fractional shortening as low as 18%), and severe LV dilatation (end-diastolic and end-systolic dimensions as high as 87 and 65 mm, respectively). Hence, the predictive nature of this response in asymptomatic patients with normal LV systolic function and without severe LV dilatation has not been fully demonstrated.

3.2.3.4. MEDICAL THERAPY

CLASS I

1. Vasodilator therapy is indicated for chronic therapy in patients with severe AR who have symptoms or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors. *(Level of Evidence: B)*

CLASS IIa

1. Vasodilator therapy is reasonable for short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction before proceeding with AVR. *(Level of Evidence: C)*

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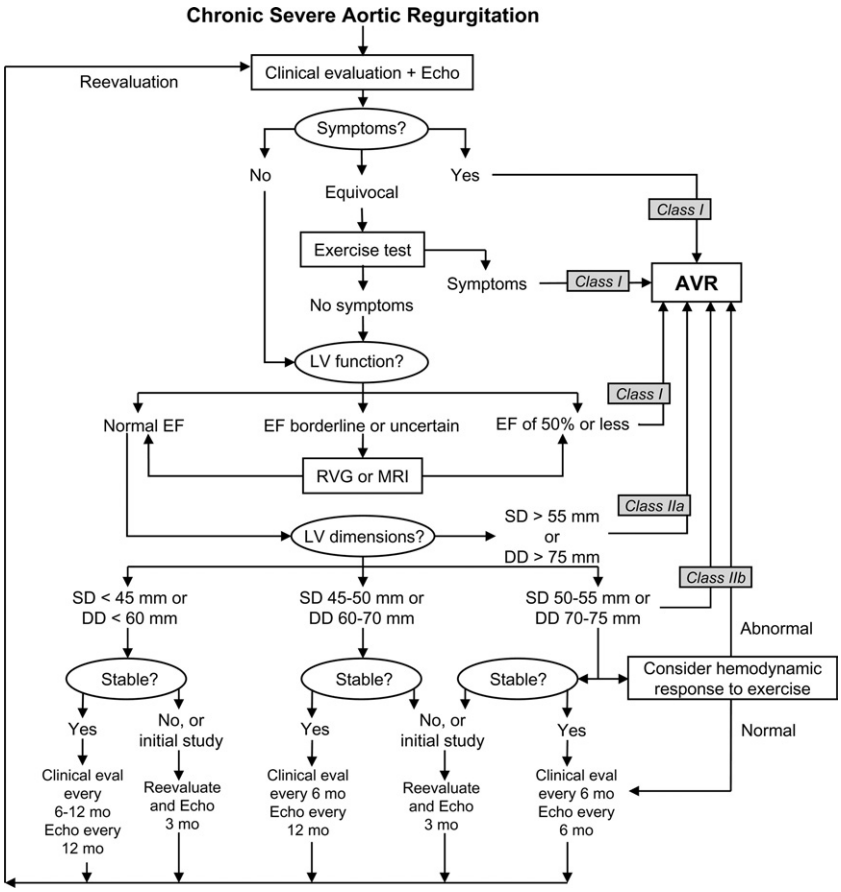

Figure 4. Management Strategy for Patients With Chronic Severe Aortic Regurgitation

Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. "Stable" refers to stable echocardiographic measurements. In some centers, serial follow-up may be performed with radionuclide ventriculography (RVG) or magnetic resonance imaging (MRI) rather than echocardiography (Echo) to assess left ventricular (LV) volume and systolic function. AVR indicates aortic valve replacement; DD, end-diastolic dimension; EF, ejection fraction; eval, evaluation; and SD, end-systolic dimension.

CLASS IIb

1. Vasodilator therapy may be considered for long-term therapy in asymptomatic patients with severe AR who have LV dilatation but normal systolic function. *(Level of Evidence: B)*

CLASS III

1. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with mild to moderate AR and normal LV systolic function. *(Level of Evidence: B)*
2. Vasodilator therapy is not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for AVR. *(Level of Evidence: C)*
3. Vasodilator therapy is not indicated for long-term therapy in symptomatic patients with either normal LV function or mild to moderate LV systolic dysfunction who are otherwise candidates for AVR. *(Level of Evidence: C)*

Therapy with vasodilating agents is designed to improve forward stroke volume and reduce regurgitant volume. These effects should translate into reductions in LV end-diastolic volume, wall stress, and afterload, resulting in preservation of LV systolic function and reduction in LV mass. The acute administration of sodium nitroprusside, hydralazine, nifedipine, or felodipine reduces peripheral vascular resistance and results in an immediate augmentation in forward cardiac output and a decrease in regurgitant volume (304–313). With nitroprusside and hydralazine, these acute hemodynamic changes lead to a consistent reduction in end-diastolic volume and an increase in ejection fraction (304–306,312). This is an inconsistent finding with a single oral dose of nifedipine (308–311). Reduced end-diastolic volume and increased ejection fraction have also been observed in small numbers of patients receiving long-term oral therapy with hydralazine and nifedipine for periods of 1 to 2 years (278,314); with nifedipine, these effects are associated with a reduction in LV mass (272,314). Less consistent results have been reported with ACE inhibitors, depending on the degree of reduction in arterial pressure and end-diastolic volume (315–317). Reduced blood pressure with enalapril and quinapril has been associated with decreases in end-diastolic volume and mass but no change in ejection fraction (316,317).

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There are 3 potential uses of vasodilating agents in chronic AR. It should be emphasized that these criteria apply only to patients with severe AR. The first is long-term treatment of patients with severe AR who have symptoms and/or LV dysfunction who are considered poor candidates for surgery because of additional cardiac or noncardiac factors. The second is improvement in the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction with short-term vasodilator therapy before proceeding with AVR. In such patients, vasodilating agents with negative inotropic effects should be avoided. The third is prolongation of the compensated phase of asymptomatic patients who have volume-loaded left ventricles but normal systolic function.

Whether this latter effect can be achieved has been investigated in only 2 studies. The first study compared long-acting nifedipine versus digoxin in a prospective randomized trial (272). Over a 6-year period, fewer patients randomized to nifedipine required AVR because of symptoms or development of LV dysfunction (ejection fraction less than 0.50). This study enrolled a relatively small number of patients (143 patients); there were relatively few end points (20 patients in the digoxin group and 6 in the nifedipine group underwent AVR); and there was no placebo control group. A more recent study compared placebo, long-acting nifedipine, and enalapril in 95 consecutive patients, who were followed for 7 years (277). Neither nifedipine nor enalapril reduced the development of symptoms or LV dysfunction warranting AVR compared with placebo. Moreover, neither drug significantly altered LV dimension, ejection fraction, or mass over the course of time compared with placebo. Thus, definitive recommendations regarding the indications for long-acting nifedipine or ACE inhibitors cannot be made at this time.

If vasodilator therapy is used, the goal is to reduce systolic blood pressure, and drug dosage should be increased until there is a measurable decrease in systolic blood pressure or the patient develops side effects. It is rarely possible to decrease systolic blood pressure to normal because of the increased LV stroke volume, and drug dosage should not be increased excessively in an attempt to achieve this goal. Vasodilator therapy is of unknown benefit and is not indicated in patients with normal blood pressure or normal LV cavity size.

Vasodilator therapy is not recommended for asymptomatic patients with mild or moderate AR and normal LV function in the absence of systemic hypertension, because these patients have an excellent outcome with no therapy. In patients with severe AR, vasodilator therapy is not an alternative to surgery in asymptomatic or symptomatic patients with LV systolic dysfunction; such patients should be considered surgical candidates rather than candidates for long-term medical therapy unless AVR is not recommended because of additional cardiac or noncardiac factors. Whether symptomatic patients who have preserved systolic function can be treated safely with aggressive medical management and whether aggressive medical management is as good or better than AVR have not been determined. It is recommended that symptomatic patients undergo surgery rather than long-term medical therapy.

There is scant information about long-term therapy with drugs other than vasodilators in asymptomatic patients with severe AR and normal LV function. Thus, there are no data to support the long-term use of digoxin, diuretics, nitrates, or positive inotropic agents in asymptomatic patients and no data with regard to any drug in patients with mild or moderate AR.

3.2.3.5. PHYSICAL ACTIVITY AND EXERCISE

There are no data suggesting that exercise, particularly strenuous periodic exercise, will contribute to or accelerate the progression of LV dysfunction in AR. Asymptomatic patients with normal LV systolic function may participate in all forms of normal daily physical activity, including mild forms of exercise and in some cases competitive athletics. Isometric exercise should be avoided. Recommendations regarding participation in competitive athletics were published by the Task Force on Acquired Valvular Heart Disease of the 36th Bethesda Conference (138). Before participation in athletics, exercise testing to at least the level of exercise required by the proposed activity is recommended so that the patient's tolerance for this degree of exercise can be evaluated. This does not necessarily evaluate the long-term effects of strenuous exercise, which are unknown.

3.2.3.6. SERIAL TESTING

The aim of serial evaluation of asymptomatic patients with chronic AR is to detect the onset of symptoms and objectively assess changes in LV size and function that can occur in the absence of symptoms. In general, the stability and chronicity of the regurgitant lesion and the LV response to volume load need to be established when the patient first presents to the physician, especially if AR is moderate to severe. If the chronic nature of the lesion is uncertain and the patient does not present initially with one of the indications for surgery, repeat physical examination and echocardiography should be performed within 2 to 3 months after the initial evaluation to ensure that a subacute process with rapid progression is not under way. Once the chronicity and stability of the process has been established, the frequency of clinical re-evaluation and repeat noninvasive testing depends on the severity of the valvular regurgitation, the degree of LV dilatation, the level of systolic function, and whether previous serial studies have revealed progressive changes in LV size or function (Fig. 4). In most patients, serial testing during the long-term follow-up period should include a detailed history, physical examination, and echocardiography. Serial chest X-rays and ECGs have less value but are helpful in selected patients.

Asymptomatic patients with mild AR, little or no LV dilatation, and normal LV systolic function can be seen on a yearly basis, with instructions to alert the physician if symptoms develop in the interim. Yearly echocardiography

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is not necessary unless there is clinical evidence that regurgitation has worsened. Routine echocardiography can be performed every 2 to 3 years in such patients.

Asymptomatic patients with normal systolic function but severe AR and significant LV dilatation (end-diastolic dimension greater than 60 mm) require more frequent and careful re-evaluation, with a history and physical examination every 6 months and echocardiography every 6 to 12 months, depending on the severity of dilatation and stability of measurements. If patients are stable, echocardiographic measurements are not required more frequently than every 12 months. In patients with more advanced LV dilatation (end-diastolic dimension greater than 70 mm or end-systolic dimension greater than 50 mm), for whom the risk of developing symptoms or LV dysfunction ranges between 10% and 20% per year (271,272), it is reasonable to perform serial echocardiograms as frequently as every 4 to 6 months. Serial chest X-rays and ECGs have less value but are helpful in selected patients.

Chronic AR may develop from disease processes that involve the proximal ascending aorta. In patients with aortic root dilatation, serial echocardiograms are indicated to evaluate aortic root size, as well as LV size and function. This is discussed in Section 3.2.4.

Repeat echocardiograms are also recommended when the patient has onset of symptoms, there is an equivocal history of changing symptoms or changing exercise tolerance, or there are clinical findings that suggest worsening regurgitation or progressive LV dilatation. Patients with echocardiographic evidence of progressive ventricular dilatation or declining systolic function have a greater likelihood of developing symptoms or LV dysfunction (271) and should have more frequent follow-up examinations (every 6 months) than those with stable LV function.

In some centers with expertise in nuclear cardiology, serial radionuclide ventriculograms to assess LV volume and function at rest may be an accurate and cost-effective alternative to serial echocardiograms. However, there is no justification for routine serial testing with both an echocardiogram and a radionuclide ventriculogram. Serial radionuclide ventriculograms are also recommended in patients with suboptimal echocardiograms, patients with suggestive but not definite echocardiographic evidence of LV systolic dysfunction, and patients for whom there is discordance between clinical assessment and echocardiographic data. In centers with specific expertise in cardiac magnetic resonance imaging, serial magnetic resonance imaging may be performed in place of radionuclide angiography for the indications listed above. In addition to accurate assessment of LV volume, mass, wall thickness, and systolic function (318–322), cardiac magnetic resonance imaging may be used to quantify the severity of valvular regurgitation (323–327).

Serial exercise testing is also not recommended routinely in asymptomatic patients with preserved systolic function; however, exercise testing may be invaluable to assess functional capacity and symptomatic responses in patients with equivocal changes in symptomatic status. Serial exercise imaging studies to assess LV functional reserve are not indicated in asymptomatic patients or those in whom symptoms develop.

3.2.3.7. INDICATIONS FOR CARDIAC CATHETERIZATION

CLASS I

1. Cardiac catheterization with aortic root angiography and measurement of LV pressure is indicated for assessment of severity of regurgitation, LV function, or aortic root size when noninvasive tests are inconclusive or discordant with clinical findings in patients with AR. *(Level of Evidence: B)*
2. Coronary angiography is indicated before AVR in patients at risk for CAD. *(Level of Evidence: C)*

CLASS III

1. Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function, aortic root size, or severity of regurgitation before AVR when noninvasive tests are adequate and concordant with clinical findings and coronary angiography is not needed. *(Level of Evidence: C)*
2. Cardiac catheterization with aortic root angiography and measurement of LV pressure is not indicated for assessment of LV function and severity of regurgitation in asymptomatic patients when noninvasive tests are adequate. *(Level of Evidence: C)*

Cardiac catheterization is not required in patients with chronic AR unless there are questions about the severity of AR, hemodynamic abnormalities, or LV systolic dysfunction that persist despite physical examination and noninvasive testing, or unless AVR is contemplated and there is a need to assess coronary anatomy. The indications for coronary arteriography are discussed in Section 10.2. In some patients undergoing left-heart catheterization for coronary angiography, additional aortic root angiography and hemodynamic measurements may provide useful supplementary data.

Hemodynamic and angiographic assessment of the severity of AR and LV function may be necessary in some patients being considered for surgery when there are conflicting data between clinical assessment and noninvasive tests. Less commonly, asymptomatic patients who are not being considered for surgery may also require invasive measurement of hemodynamics and/or determination of severity of AR when this information cannot be obtained accurately from noninvasive tests.

Hemodynamic measurements during exercise are occasionally helpful for determining the effect of AR on LV function or making decisions regarding medical or surgical therapy. In selected patients with severe AR, borderline or normal LV systolic function, and LV chamber enlargement that is approaching the threshold for surgery (defined below), measurement of cardiac output and LV filling pressures at rest and during exercise with a right-heart catheter may be valuable for identifying patients with severe hemodynamic abnormalities in whom surgery is warranted.

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3.2.3.8. INDICATIONS FOR AORTIC VALVE REPLACEMENT OR AORTIC VALVE REPAIR

The majority of patients with severe AR requiring surgery undergo valve replacement (see Section 7.2.). However, in several surgical centers, there is increasing experience in performing aortic valve replacement in selected patients (see Section 7.2.6.). In the discussion that follows, the term "AVR" applies to both aortic valve replacement and aortic valve repair, with the understanding that aortic valve repair should be considered only in those surgical centers that have developed the appropriate technical expertise, gained experience in patient selection, and demonstrated outcomes equivalent to those of valve replacement. The indications for valve replacement and repair do not differ.

In patients with pure, chronic AR, AVR should be considered only if AR is severe (Table 4) (27). Patients with only mild AR are not candidates for AVR, and if such patients have symptoms or LV dysfunction, other causes should be considered, such as CAD, hypertension, or cardiomyopathic processes. If the severity of AR is uncertain after a review of clinical and echocardiographic data, additional information may be needed, such as invasive hemodynamic and angiographic data. The following discussion applies only to those patients with pure, severe AR.

CLASS I

1. AVR is indicated for symptomatic patients with severe AR irrespective of LV systolic function. *(Level of Evidence: B)*
2. AVR is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfunction (ejection fraction 0.50 or less) at rest. *(Level of Evidence: B)*
3. AVR is indicated for patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves. *(Level of Evidence: C)*

CLASS IIa

1. AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (ejection fraction greater than 0.50) but with severe LV dilatation (end-diastolic dimension greater than 75 mm or end-systolic dimension greater than 55 mm).* *(Level of Evidence: B)*

CLASS IIb

1. AVR may be considered in patients with moderate AR while undergoing surgery on the ascending aorta. *(Level of Evidence: C)*
2. AVR may be considered in patients with moderate AR while undergoing CABG. *(Level of Evidence: C)*
3. AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function at rest (ejection fraction greater than 0.50) when the degree of LV dilatation exceeds an end-diastolic dimension of 70 mm or end-systolic dimension of 50 mm, when there is evidence of progressive LV dilatation, declining exercise tolerance, or abnormal hemodynamic responses to exercise.* *(Level of Evidence: C)*

CLASS III

1. AVR is not indicated for asymptomatic patients with mild, moderate, or severe AR and normal LV systolic function at rest (ejection fraction greater than 0.50) when degree of dilatation is not moderate or severe (end-diastolic dimension less than 70 mm, end-systolic dimension less than 50 mm).* *(Level of Evidence: B)*

*Consider lower threshold values for patients of small stature of either gender.

3.2.3.8.1. SYMPTOMATIC PATIENTS WITH NORMAL LEFT VENTRICULAR SYSTOLIC FUNCTION. AVR is indicated in patients with normal LV systolic function (defined as ejection fraction greater than 0.50 at rest) who have NYHA functional class III or IV symptoms. Patients with Canadian Heart Association functional class II to IV angina pectoris should also be considered for surgery. In many patients with NYHA functional class II dyspnea, the cause of symptoms is often unclear, and clinical judgment is required. Patients with well-compensated AR often have chronic mild dyspnea or fatigue, and it may be difficult to differentiate the effects of deconditioning or aging from true cardiac symptoms. In such patients, exercise testing may be valuable. If the cause of these mild symptoms is uncertain and they are not severe enough to interfere with the patient's lifestyle, a period of observation may be reasonable. However, new onset of mild dyspnea has different implications in severe AR, especially in patients with increasing LV chamber size or evidence of declining LV systolic function into the low normal range. Thus, even if patients have not achieved the threshold values of LV size and function recommended for surgery in asymptomatic patients, development of mild symptoms is an indication for AVR in a patient who is nearing these values.

3.2.3.8.2. SYMPTOMATIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION. Patients with NYHA functional class II, III, or IV symptoms and with mild to moderate LV systolic dysfunction (ejection fraction 0.25 to 0.50) should undergo AVR. Patients with NYHA functional class IV symptoms have worse postoperative survival rates and lower likelihood of recovery of systolic function than patients with less severe symptoms (245,250,252,254), but AVR will improve ventricular loading conditions and expedite subsequent management of LV dysfunction (238).

Severely symptomatic patients (NYHA functional class IV) with advanced LV dysfunction (ejection fraction less than 0.25 and/or end-systolic dimension greater than 60 mm) present difficult management issues. Some patients will manifest meaningful recovery of LV function after AVR, but many will have developed irreversible myocardial changes. The mortality associated with valve replacement approaches 10%, and postoperative mortality over the subsequent few years is high. Valve replacement should be considered more strongly in patients with NYHA functional class II and III symptoms, especially if

- symptoms and evidence of LV dysfunction are of recent onset;
- intensive short-term therapy with vasodilators and diuretics results in symptomatic improvement;
- intravenous positive inotropic agents result in substantial improvement in hemodynamics or systolic function.

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However, even in patients with NYHA functional class IV symptoms and ejection fraction less than 0.25, the high risks associated with AVR and subsequent medical management of LV dysfunction are usually a better alternative than the higher risks of long-term medical management alone (328).

3.2.3.8.3. ASYMPTOMATIC PATIENTS. AVR in asymptomatic patients remains a controversial topic, but it is generally agreed (233,329–335) that AVR is indicated in patients with LV systolic dysfunction. As noted previously, for the purposes of these guidelines, LV systolic dysfunction is defined as an ejection fraction below normal at rest. The lower limit of normal will be assumed to be 0.50, with the realization that this lower limit is technique dependent and may vary among institutions. The committee also realizes that there may be variability in any given measurement of LV dimension or ejection fraction. Therefore, the committee recommends that 2 consecutive measurements be obtained before one proceeds with a decision to recommend surgery in the asymptomatic patient. These consecutive measurements could be obtained with the same test repeated in a short time period (such as a second echocardiogram after an initial echocardiogram) or with a separate, independent test (e.g., radionuclide ventriculography, magnetic resonance imaging, or contrast left ventriculography after an initial echocardiogram).

AVR is also recommended in patients with severe LV dilatation (end-diastolic dimension greater than 75 mm or end-systolic dimension greater than 55 mm), even if ejection fraction is normal. The majority of patients with this degree of dilatation will have already developed systolic dysfunction because of afterload mismatch and will thus be candidates for valve replacement on the basis of the depressed ejection fraction. The elevated end-systolic dimension in this regard is often a surrogate for systolic dysfunction. The relatively small number of asymptomatic patients with preserved ejection fraction despite severe increases in end-systolic and end-diastolic chamber size should be considered for surgery, because they appear to represent a high-risk group with an increased incidence of sudden death (271,336), and the results of valve replacement in such patients have thus far been excellent (264). In contrast, postoperative mortality is considerable once patients with severe LV dilatation develop symptoms or LV systolic dysfunction (264). The recommendations regarding the risk of sudden death and postoperative outcome with severe LV dilatation were based on reports of sudden death in 2 of 3 patients with an LV end-diastolic dimension greater than 80 mm (271) and 2 patients with an LV end-diastolic volume index greater than 200 ml/m^2 (336). It should be recognized, however, that LV end-diastolic dimension, whether examined as a continuous or as a dichotomous variable (less than 80 vs. greater than 80 mm), has not been found to be predictive of postoperative survival or LV function, whereas ejection fraction is predictive. Conservatively managed patients with an end-diastolic dimension exceeding 70 mm likewise exhibit a favorable clinical outcome (276). These data do not strongly support the use of extreme LV enlargement as an indication for AVR, unless cardiac symptoms or systolic dysfunction is present (337). However, the committee recommends surgery before the left ventricle achieves an extreme degree of dilatation and recommends AVR for patients with LV end-diastolic dimension greater than 75 mm.

Anthropometric normalization of LV end-diastolic dimension (or volume) should be considered, but unfortunately, there is lack of agreement as to whether or not normalization based on body surface area or body mass index is predictive of outcome (288,338). Normalization of end-diastolic dimension for body surface area tends to mask the diagnosis of LV enlargement, especially in patients who are overweight (339). The use of height and a consideration of gender are likely to be more appropriate than body surface area (340).

Patients with severe AR in whom the degree of LV dilatation has not reached but is approaching these threshold values (e.g., LV end-diastolic dimension of 70 to 75 mm or end-systolic dimension of 50 to 55 mm) should be followed with frequent echocardiograms every 4 to 6 months, as noted previously (Fig. 4). In addition, AVR may be considered in such patients if there is evidence of declining exercise tolerance or abnormal hemodynamic responses to exercise, for example, an increase in pulmonary artery wedge pressure greater than 25 mm Hg with exercise.

Several patient subgroups develop LV systolic dysfunction with less marked LV dilatation than observed in the majority of patients with uncomplicated AR. These include patients with long-standing hypertension in whom the pressure-overloaded ventricle has reduced compliance and a limited potential to increase its chamber size; patients with concomitant CAD, in whom myocardial ischemia may develop with increasing myocardial wall stress, resulting in LV dysfunction; and patients with concomitant MS, in whom the left ventricle will not dilate to the same extent as in patients with pure AR (341). In such patients, it is particularly important that LV ejection fraction and not merely systolic dimension be monitored. Women also tend to develop symptoms and LV dysfunction with less LV dilatation than men (338); this appears to be related to body size, because these differences are not apparent when LV dimensions are corrected for body surface area. Hence, LV dimensions alone may be misleading in small patients of either gender, and the threshold values of end-diastolic and end-systolic dimension recommended above for AVR in asymptomatic patients (75 and 55 mm, respectively) may need to be reduced in such patients. There are no data with which to derive guidelines for LV dimensions corrected for body size, and clinical judgment is required.

A decrease in ejection fraction during exercise should not be used as the only indication for AVR in asymptomatic patients with normal LV systolic function at rest, because the exercise ejection fraction response is multifactorial, and

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the strength of evidence is limited. The ejection fraction response to exercise has not proved to have independent prognostic value in patients undergoing surgery (254). The change in ejection fraction with exercise is a relatively nonspecific response related to both severity of volume load (271,296,300,301) and exercise-induced changes in preload and peripheral resistance (280) that develop early in the natural history of AR. AVR should also not be recommended in asymptomatic patients with normal systolic function merely because of evidence of LV dilatation as long as the dilatation is not severe (end-diastolic dimension less than 75 mm or end-systolic dimension less than 55 mm).

Patients who demonstrate progression of LV dilatation or progressive decline in ejection fraction on serial studies represent a higher-risk group who require careful monitoring (271), but such patients often reach a new steady state and may do well for extended periods of time. Hence, AVR is not recommended until the threshold values noted above are reached or symptoms or LV systolic dysfunction develop. However, prompt referral to AVR once patients develop symptoms, subnormal ejection fraction, or progressive LV dilatation results in significantly better postoperative survival than if AVR is delayed until symptoms or LV systolic function becomes more severe (254,265,267).

The surgical options for treating AR are expanding, with growing experience in aortic homografts, pulmonary autografts, unstented tissue valves, and aortic valve repair. If these techniques are ultimately shown to improve long-term survival or reduce postoperative valve complications, it is conceivable that the thresholds for recommending AVR may be reduced. Until such data are available, the indications for surgery for AR should not vary with the operative technique to be used.

3.2.4. Concomitant Aortic Root Disease

In addition to causing acute AR, diseases of the proximal aorta may also contribute to chronic AR. Dilatation of the ascending aorta is among the most common causes of isolated AR (342). In such patients, the valvular regurgitation may be less important in decision making than the primary disease of the aorta, such as Marfan syndrome, dissection, or chronic dilatation of the aortic root related to hypertension or a bicuspid aortic valve (see Section 3.3). In such patients, if the AR is mild or the left ventricle is only mildly dilated, management should focus on treating the underlying aortic root disease. In many patients, however, AR may be severe and associated with severe LV dilatation or systolic dysfunction, in which case decisions regarding medical therapy and timing of the operation must consider both conditions. In general, AVR and aortic root reconstruction are indicated in patients with disease of the aortic root or proximal aorta and AR of any severity when the degree of dilatation of the aorta or aortic root reaches or exceeds 5.0 cm by echocardiography (343). However, some have recommended surgery at a lower level of dilatation (4.5 cm) or based on a rate of increase of 0.5 cm per year or greater in surgical centers with established expertise in repair of the aortic root and ascending aorta (344). Aortic root and ascending aorta dilation in patients with bicuspid aortic valves is discussed in greater detail in Section 3.3.

3.2.5. Evaluation of Patients After Aortic Valve Replacement

After AVR, close follow-up is necessary during the early and long-term postoperative course to evaluate prosthetic valve function and assess LV function, as discussed in Sections 9.3. to 9.3.3. An echocardiogram should be performed soon after surgery to assess the results of surgery on LV size and function and to serve as a baseline against which subsequent echocardiograms may be compared. This could be performed either before hospital discharge or preferably at the first outpatient re-evaluation. Within the first few weeks of surgery, there is little change in LV systolic function, and ejection fraction may even deteriorate compared with preoperative values because of the reduced preload (345), even though ejection fraction may increase over the subsequent several months. Thus, persistent or more severe systolic dysfunction early after AVR is a poor predictor of subsequent improvement in LV function in patients with preoperative LV dysfunction. A better predictor of subsequent LV systolic function is the reduction in LV end-diastolic dimension, which declines significantly within the first week or 2 after AVR (240,245,346). This is an excellent marker of the functional success of valve replacement, because 80% of the overall reduction in end-diastolic dimension observed during the long-term postoperative course occurs within the first 10 to 14 days after AVR (240,245,346), and the magnitude of reduction in end-diastolic dimension after surgery correlates with the magnitude of increase in ejection fraction (245).

After the initial postoperative re-evaluation, the patient should be seen and examined again at 6 and 12 months and then on a yearly basis if the clinical course is uncomplicated. If the patient is asymptomatic, the early postoperative echocardiogram demonstrates substantial reduction in LV end-diastolic dimension, and LV systolic function is normal, serial postoperative echocardiograms after the initial early postoperative study are usually not indicated. However, repeat echocardiography is warranted at any point at which there is evidence of a new murmur, questions of prosthetic valve integrity, or concerns about LV function. Patients with persistent LV dilatation on the initial postoperative echocardiogram should be treated as would any other patient with symptomatic or asymptomatic LV dysfunction, including treatment with ACE inhibitors and beta-adrenergic blocking agents. In such patients, repeat echocardiography to assess LV size and systolic function is warranted at the 6- and 12-month re-evaluations. If LV dysfunction persists beyond this time frame, repeat echocardiograms should be performed as clinically indicated. Management of patients after AVR is discussed in greater detail in Section 9.3.

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3.2.6. Special Considerations in the Elderly

The vast majority of elderly patients with aortic valve disease have AS or combined AS and AR, and pure AR is uncommon (347). Elderly patients with AR generally fare less well than patients who are young or middle-aged. Patients older than 75 years are more likely to develop symptoms or LV dysfunction at earlier stages of LV dilatation, have more persistent ventricular dysfunction and heart failure symptoms after surgery, and have worse postoperative survival rates than their younger counterparts. Many such patients have concomitant CAD, which must be considered in the evaluation of symptoms, LV dysfunction, and indications for surgery. Because the goal of therapy is to improve the quality of life rather than longevity, symptoms are the most important guide to determining whether or not AVR should be performed. Nonetheless, asymptomatic or mildly symptomatic patients who develop LV dysfunction (as defined previously) should be considered for AVR if the risks of surgery are balanced in otherwise healthy patients against the expected improvement in long-term outcome.

3.3. Bicuspid Aortic Valve With Dilated Ascending Aorta

CLASS I

1. Patients with known bicuspid aortic valves should undergo an initial transthoracic echocardiogram to assess the diameters of the aortic root and ascending aorta. *(Level of Evidence: B)*
2. Cardiac magnetic resonance imaging or cardiac computed tomography is indicated in patients with bicuspid aortic valves when morphology of the aortic root or ascending aorta cannot be assessed accurately by echocardiography. *(Level of Evidence: C)*
3. Patients with bicuspid aortic valves and dilatation of the aortic root or ascending aorta (diameter greater than 4.0 cm* should undergo serial evaluation of aortic root/ascending aorta size and morphology by echocardiography, cardiac magnetic resonance, or computed tomography on a yearly basis. *(Level of Evidence: C)*
4. Surgery to repair the aortic root or replace the ascending aorta is indicated in patients with bicuspid aortic valves if the diameter of the aortic root or ascending aorta is greater than 5.0 cm* or if the rate of increase in diameter is 0.5 cm per year or more. *(Level of Evidence: C)*
5. In patients with bicuspid valves undergoing AVR because of severe AS or AR (see Sections 3.1.7 and 3.2.3.8), repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm.* *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable to give beta-adrenergic blocking agents to patients with bicuspid valves and dilated aortic roots (diameter greater than 4.0 cm*) who are not candidates for surgical correction and who do not have moderate to severe AR. *(Level of Evidence: C)*
2. Cardiac magnetic resonance imaging or cardiac computed tomography is reasonable in patients with bicuspid aortic valves when aortic root dilatation is detected by echocardiography to further quantify severity of dilatation and involvement of the ascending aorta. *(Level of Evidence: B)*

*Consider lower threshold values for patients of small stature of either gender.

There is growing awareness that many patients with bicuspid aortic valves have disorders of vascular connective tissue, involving loss of elastic tissue (348,349), which may result in dilatation of the aortic root or ascending aorta even in the absence of hemodynamically significant AS or AR (350–353). Aortic root or ascending aortic dilatation can progress with time in this condition (354). These patients have a risk of aortic dissection that is related to the severity of dilatation (349,355–357). Recommendations for athletic participation in patients with bicuspid valve disease and associated dilatation of the aortic root or ascending aorta from the 36th Bethesda Conference (138) are based on limited data but with the understanding that aortic dissection can occur in some patients with aortic root or ascending aorta diameters less than 50 mm (344,356,358). Therapy with beta-adrenergic blocking agents might be effective in slowing the progression of aortic dilatation, but the available data have been developed in patients with Marfan syndrome (359) and not in patients with bicuspid aortic valves.

Echocardiography remains the primary imaging technique for identifying those patients in whom the aortic root or ascending aorta is enlarged. In many cases, echocardiography, including transesophageal imaging, provides all of the necessary information required to make management decisions. More accurate quantification of the diameter of the aortic root and ascending aorta, as well as full assessment of the degree of enlargement, can be obtained with cardiac magnetic resonance imaging or computed tomography. These techniques also allow for an accurate depiction of the size and contour of the aorta in its arch, descending thoracic, and abdominal segments. When the findings on transthoracic echocardiography relative to the aortic root and ascending aorta are concordant with those of either cardiac magnetic resonance or computed tomographic imaging, then transthoracic echocardiography can be used for annual surveillance. The dimensions of the aortic root and ascending aorta show considerable variability in normal populations. Regression formulas and nomograms have been developed for adolescents and adults that account for age and body surface area (360). An upper limit of 2.1 cm per m^2 has been established at the level of the aortic sinuses. Dilatation is considered an increase in diameter above the norm for age and body surface area, and an aneurysm has been defined as a 50% increase over the normal diameter (361).

Surgery to repair the aortic root or replace the ascending aorta has been recommended for those patients with greatly enlarged aortic roots or ascending aortas (344,349,357,358). In recommending elective surgery for this condition, a number of factors must be considered, including the patient's age, the relative size of the aorta and aortic root, the structure and function of the aortic valve, and the experience of the surgical team. Aortic valve-sparing operations are feasible in most patients with dilatation of the aortic root or ascending aorta who do not have significant AR or aortic valve calcification (362–364). It is recommended that patients with bicuspid valves should undergo elective repair of

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the aortic root or replacement of the ascending aorta if the diameter of these structures exceeds 5.0 cm. Such surgery should be performed by a surgical team with established expertise in these procedures. Others have recommended a value of 2.5 cm per m^2 or greater as the indication for surgery (365). If patients with bicuspid valves and associated aortic root enlargement undergo AVR because of severe AS or AR (Sections 3.1.7. and 3.2.3.8.), it is recommended that repair of the aortic root or replacement of the ascending aorta be performed if the diameter of these structures is greater than 4.5 cm (366).

3.4. Mitral Stenosis

3.4.1. Pathophysiology and Natural History

MS is an obstruction to LV inflow at the level of the MV as a result of a structural abnormality of the MV apparatus, which prevents proper opening during diastolic filling of the left ventricle. The predominant cause of MS is rheumatic carditis. Isolated MS occurs in 40% of all patients presenting with rheumatic heart disease, and a history of rheumatic fever can be elicited from approximately 60% of patients presenting with pure MS (367,368). The ratio of women to men presenting with isolated MS is 2:1 (367–369). Congenital malformation of the MV occurs rarely and is observed mainly in infants and children (370). Acquired causes of MV obstruction, other than rheumatic heart disease, are rare. These include left atrial myxoma, ball valve thrombus, mucopolysaccharidosis, and severe annular calcification.

In patients with MS due to rheumatic fever, the pathological process causes leaflet thickening and calcification, commissural fusion, chordal fusion, or a combination of these processes (370,371). The result is a funnel-shaped mitral apparatus in which the orifice of the mitral opening is decreased in size. Interchordal fusion obliterates the secondary orifices, and commissural fusion narrows the principal orifice (370,371).

The normal MV area is 4.0 to 5.0 cm^2. Narrowing of the valve area to less than 2.5 cm^2 typically occurs before the development of symptoms (139). With a reduction in valve area by the rheumatic process, blood can flow from the left atrium to the left ventricle only if propelled by a pressure gradient. This diastolic transmitral gradient is the fundamental expression of MS (372) and results in elevation of left atrial pressure, which is reflected back into the pulmonary venous circulation. Decreased pulmonary venous compliance that results in part from an increased pulmonary endothelin-1 spillover rate may also contribute to increased pulmonary venous pressure (373). Increased pressure and distension of the pulmonary veins and capillaries can lead to pulmonary edema as pulmonary venous pressure exceeds that of plasma oncotic pressure. In patients with chronic MV obstruction, however, even when it is severe and pulmonary venous pressure is very high, pulmonary edema may not occur owing to a marked decrease in pulmonary microvascular permeability. The pulmonary arterioles may react with vasoconstriction, intimal hyperplasia, and medial hypertrophy, which lead to pulmonary arterial hypertension.

An MV area greater than 1.5 cm^2 usually does not produce symptoms at rest (374). However, if there is an increase in transmitral flow or a decrease in the diastolic filling period, there will be a rise in left atrial pressure and development of symptoms. From hydraulic considerations, at any given orifice size, the transmitral gradient is a function of the square of the transvalvular flow rate and is dependent on the diastolic filling period (139). Thus, the first symptoms of dyspnea in patients with mild MS are usually precipitated by exercise, emotional stress, infection, pregnancy, or atrial fibrillation with a rapid ventricular response (374). As the obstruction across the MV increases, decreasing effort tolerance occurs.

As the severity of stenosis increases, cardiac output becomes subnormal at rest (374) and fails to increase during exercise (375). The degree of pulmonary vascular disease is also an important determinant of symptoms in patients with MS (373,374,376). A second obstruction to flow develops from increased pulmonary arteriolar resistance (376,377), which may protect the lungs from pulmonary edema (376,377). In some patients, an additional reversible obstruction develops at the level of the pulmonary veins (378,379). The low cardiac output and increased pulmonary arteriolar resistance, which results from functional and structural changes (alveolar basement membrane thickening, adaptation of neuroreceptors, increased lymphatic drainage, and increased transpulmonary endothelin spillover rate), contribute to the ability of a patient with severe MS to remain minimally symptomatic for prolonged periods of time (374,376,377).

The natural history of patients with untreated MS has been defined from studies in the 1950s and 1960s (367–369). Mitral stenosis is a continuous, progressive, lifelong disease, usually consisting of a slow, stable course in the early years followed by a progressive acceleration later in life (367–369,380). In developed countries, there is a long latent period of 20 to 40 years from the occurrence of rheumatic fever to the onset of symptoms. Once symptoms develop, there is another period of almost a decade before symptoms become disabling (367). Overall, the 10-year survival of untreated patients presenting with MS is 50% to 60%, depending on symptoms at presentation (368,369). In the asymptomatic or minimally symptomatic patient, survival is greater than 80% at 10 years, with 60% of patients having no progression of symptoms (368,369,380). However, once significant limiting symptoms occur, there is a dismal 0% to 15% 10-year survival rate (367–369,380,381). Once there is severe pulmonary hypertension, mean survival drops to less than 3 years (382). The mortality of untreated patients with MS is due to progressive pulmonary and systemic congestion in 60% to 70%, systemic embolism in 20% to 30%, pulmonary embolism in 10%, and infection in 1% to 5% (369,370). In North America and Europe, this classic history of MS has been replaced by an even milder delayed

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course with the decline in incidence of rheumatic fever (380,383). The mean age of presentation is now in the fifth to sixth decade (380,383); more than one third of patients undergoing valvotomy are older than 65 years (384). In some geographic areas, MS progresses more rapidly, presumably due to either a more severe rheumatic insult or repeated episodes of rheumatic carditis due to new streptococcal infections, resulting in severe symptomatic MS in the late teens and early 20s (380). Serial hemodynamic and Doppler-echocardiographic studies have reported annual loss of MV area ranging from 0.09 to 0.32 cm^2 (385,386).

Although MS is best described as a disease continuum, and there is no single value that defines severity, for these guidelines, MS severity is based on a variety of hemodynamic and natural history data (Table 4) (27) using mean gradient, pulmonary artery systolic pressure, and valve area as follows: mild (area greater than 1.5 cm^2, mean gradient less than 5 mm Hg, or pulmonary artery systolic pressure less than 30 mm Hg), moderate (area 1.0 to 1.5 cm^2, mean gradient 5 to 10 mm Hg, or pulmonary artery systolic pressure 30 to 50 mm Hg), and severe (area less than 1.0 cm^2, mean gradient greater than 10 mm Hg, or pulmonary artery systolic pressure greater than 50 mm Hg).

3.4.2. Indications for Echocardiography in Mitral Stenosis

CLASS I

1. Echocardiography should be performed in patients for the diagnosis of MS, assessment of hemodynamic severity (mean gradient, MV area, and pulmonary artery pressure), assessment of concomitant valvular lesions, and assessment of valve morphology (to determine suitability for percutaneous mitral balloon valvotomy). *(Level of Evidence: B)*
2. Echocardiography should be performed for re-evaluation in patients with known MS and changing symptoms or signs. *(Level of Evidence: B)*
3. Echocardiography should be performed for assessment of the hemodynamic response of the mean gradient and pulmonary artery pressure by exercise Doppler echocardiography in patients with MS when there is a discrepancy between resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. *(Level of Evidence: C)*
4. Transesophageal echocardiography in MS should be performed to assess the presence or absence of left atrial thrombus and to further evaluate the severity of MR in patients considered for percutaneous mitral balloon valvotomy. *(Level of Evidence: C)*
5. Transesophageal echocardiography in MS should be performed to evaluate MV morphology and hemodynamics in patients when transthoracic echocardiography provides suboptimal data. *(Level of Evidence: C)*

CLASS IIa

1. Echocardiography is reasonable in the re-evaluation of asymptomatic patients with MS and stable clinical findings to assess pulmonary artery pressure (for those with severe MS, every year; moderate MS, every 1 to 2 years; and mild MS, every 3 to 5 years). *(Level of Evidence: C)*

CLASS III

1. Transesophageal echocardiography in the patient with MS is not indicated for routine evaluation of MV morphology and hemodynamics when complete transthoracic echocardiographic data are satisfactory. *(Level of Evidence: C)*

The diagnosis of MS should be made on the basis of the history, physical examination, chest X-ray, and ECG (Fig. 5). Patients may present with no symptoms but have an abnormal physical examination (380,383). Although some patients may present with fatigue, dyspnea, or frank pulmonary edema, in others, the initial manifestation of MS is the onset of atrial fibrillation or an embolic event (367). Rarely, patients may present with hemoptysis, hoarseness, or dysphagia. The characteristic auscultatory findings of rheumatic MS are accentuated first heart sound (S_1), opening snap (OS), low-pitched middiastolic rumble, and a presystolic murmur. These findings, however, may also be present in patients with nonrheumatic MV obstruction (e.g., left atrial myxoma) and may be absent with severe pulmonary hypertension, low cardiac output, and a heavily calcified immobile MV. A shorter A2-OS interval and longer duration of diastolic rumble indicates more severe MS. An A2-OS interval of less than 0.08 seconds implies severe MS (387). Physical findings of pulmonary hypertension, such as a loud P_2 or right ventricular (RV) heave, also suggest severe MS.

The diagnostic tool of choice in the evaluation of a patient with MS is 2D and Doppler echocardiography (388–393). Echocardiography is able to identify restricted diastolic opening of the MV leaflets due to "doming" of the anterior leaflet and immobility of the posterior leaflet (388,390,392,393). Other entities that can simulate the clinical features of rheumatic MS, such as left atrial myxoma, mucopolysaccharidosis, nonrheumatic calcific MS, cor triatriatum, and a parachute MV, can be readily identified by 2D echocardiography. Planimetry of the orifice area may be possible from the short-axis view. Two-dimensional echocardiography can be used to assess the morphological appearance of the MV apparatus, including leaflet mobility and flexibility, leaflet thickness, leaflet calcification, subvalvular fusion, and the appearance of commissures (391,394–398). These features may be important when one considers the timing and type of intervention to be performed (394–400). Patients with mobile noncalcified leaflets, no commissural calcification, and little subvalvular fusion may be candidates for either balloon catheter or surgical commissurotomy/valvotomy (394–399). There are several methods used to assess suitability for valvotomy, including a Wilkins score (Table 17) (400), an echocardiographic grouping (based on valve flexibility, subvalvular fusion, and leaflet calcification) (397), and the absence or presence of commissural calcium (398). Chamber size and function and other structural valvular, myocardial, or pericardial abnormalities can be assessed with the 2D echocardiographic study.

Doppler echocardiography can be used to assess the hemodynamic severity of the obstruction (389,391,401). The mean transmitral gradient can be accurately and repro-

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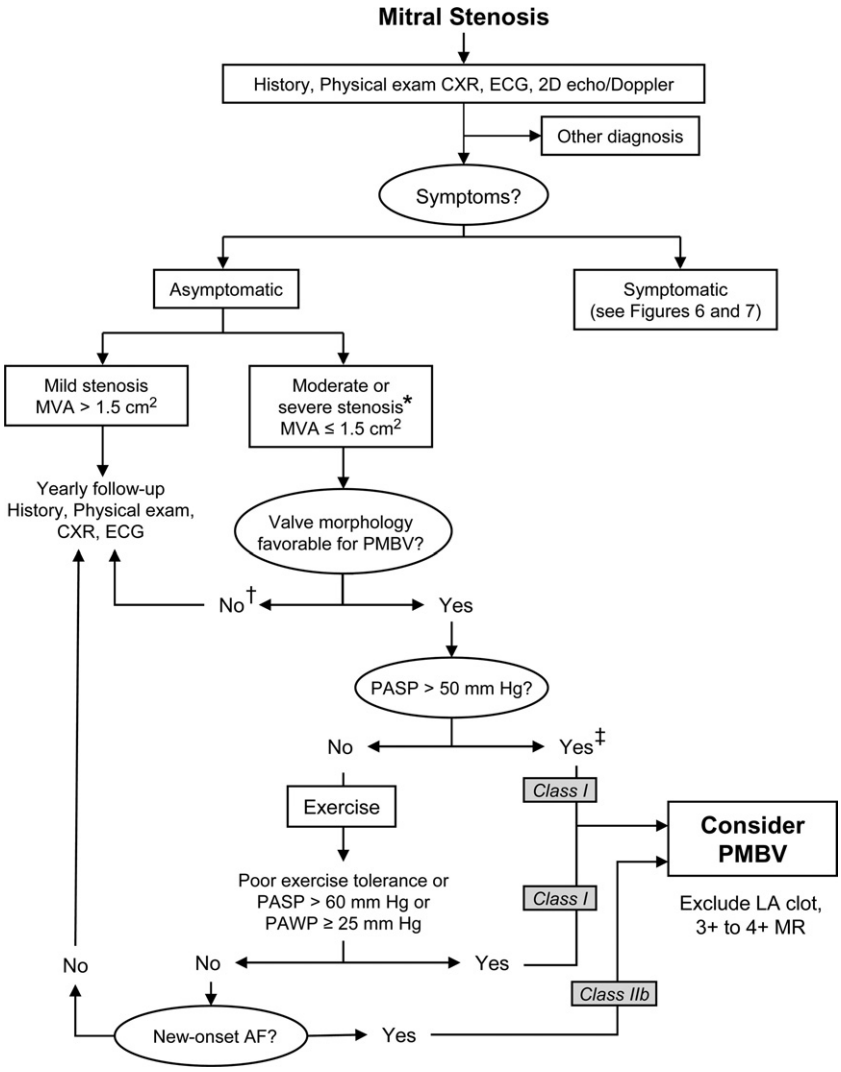

Figure 5. Management Strategy for Patients With Mitral Stenosis

*The writing committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradients, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PP) should also be taken into consideration. †There is controversy as to whether patients with severe mitral stenosis (MVA less than 1.0 cm^2) and severe pulmonary hypertension (pulmonary artery pressure greater than 60 mm Hg) should undergo percutaneous mitral balloon valvotomy (PMBV) or mitral valve replacement to prevent right ventricular failure. ‡Assuming no other cause for pulmonary hypertension is present. AF indicates atrial fibrillation; CXR, chest X-ray; ECG, electrocardiogram; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; and 2D, 2-dimensional.

Table 17. Determinants of the Echocardiographic Mitral Valve Score

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 to 5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one third of the chordal length	Midleaflets normal, considerable thickening of margins (5 to 8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5 to 8 mm)	Brightness extending into the midportion 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 (greater than 8 to 10 mm)	Extensive brightness throughout much of the leaflet tissue

Reprinted with permission from 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 (400).

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ducibly measured from the continuous-wave Doppler signal across the MV with the modified Bernoulli equation (391,401). The MV area can be noninvasively derived from Doppler echocardiography with either the diastolic pressure half-time method (401–404) or the continuity equation (402). The half-time method may be inaccurate in patients with abnormalities of left atrial or LV compliance, those with associated AR, and those who have had mitral valvotomy (403,404). Doppler echocardiography may also be used to estimate pulmonary artery systolic pressure from the TR velocity signal (405) and to assess severity of concomitant MR or AR. Formal hemodynamic exercise testing can be done noninvasively with either a supine bicycle or upright treadmill with Doppler recordings of transmitral and tricuspid velocities (406–409). This allows measurement of both the transmitral gradient (407–409) and pulmonary artery systolic pressure (406,408) at rest and with exercise (410). The criteria for the assessment of the severity of MS are summarized in Table 4 (27). These criteria are applicable when the heart rate is between 60 and 90 bpm.

In all patients with MS, an initial clinical history, physical examination, ECG, and chest X-ray should be performed. 2D and Doppler echocardiography should also be performed to confirm the diagnosis of MS and rule out other causes of MV obstruction and concomitant problems that would require further therapy, that is, myocardial or other valvular heart disease. The morphology of the MV apparatus and suitability for valvotomy should be assessed. The severity of MS should be determined using both the mean transmitral gradient and valve area from the Doppler echocardiogram, and pulmonary artery pressure should be estimated when possible. A transesophageal echocardiogram is not required unless a question about diagnosis remains after transthoracic echocardiography.

In the asymptomatic patient who has documented mild MS (valve area greater than 1.5 cm^2 and mean gradient less than 5 mm Hg), no further investigations are needed on the initial workup (Fig. 5). These patients usually remain stable for years (368,369,380). If there is more significant MS, a decision to proceed further should be based on the suitability of the patient for mitral valvotomy. In patients with pliable, noncalcified valves with no or little subvalvular fusion, no calcification in the commissures, and no left atrial thrombus, percutaneous mitral valvotomy can be performed with a low complication rate and may be indicated if symptoms develop. Because of the slowly progressive course of MS, patients may remain "asymptomatic" with severe stenosis merely by readjusting their lifestyles to a more sedentary level. Elevated pulmonary vascular resistance and/or low cardiac output may also play an adaptive role in preventing congestive symptoms from occurring in patients with severe MS (374,376,377). Elevation of pulmonary vascular resistance is an important physiological event in MS (377), and the level of pulmonary pressure is an indicator of the overall hemodynamic consequence. Patients with moderate pulmonary hypertension at rest (pulmonary artery systolic pressure greater than 50 mm Hg) and pliable MV leaflets may be considered for percutaneous mitral valvotomy even if they deny symptoms. In patients who lead a sedentary lifestyle, a hemodynamic exercise test with Doppler echocardiography is useful (406–409). Objective limitation of exercise tolerance with a rise in transmitral gradient greater than 15 mm Hg and a rise in pulmonary artery systolic pressure greater than 60 mm Hg may be an indication for percutaneous valvotomy if the MV morphology is suitable. There is a subset of asymptomatic patients with severe MS (valve area less than 1.0 cm^2) and severe pulmonary hypertension (pulmonary artery systolic pressure greater than 75% of systemic pressure either at rest or with exercise). If these patients do not have a valve morphology favorable for percutaneous mitral balloon valvotomy or surgical valve repair, it is controversial whether MV replacement should be performed in the absence of symptoms to prevent RV failure, but surgery is generally recommended in such patients. However, the patient (and the family) should be involved in the decision regarding intervention.

3.4.3. Medical Therapy

3.4.3.1. MEDICAL THERAPY: GENERAL (UPDATED)

In the patient with MS, the major problem is mechanical obstruction to inflow at the level of the MV, and no medical therapy will specifically relieve the fixed obstruction. The LV is protected from a volume or pressure overload, and thus, no specific medical therapy is required in the asymptomatic patient in normal sinus rhythm who has mild MS. Because rheumatic fever is the primary cause of MS, prophylaxis against rheumatic fever is recommended.

In the patient who has more than a mild degree of MS, counseling on avoidance of unusual physical stresses is advised. Increased flow and a shortening of the diastolic filling period by tachycardia increase left atrial pressure against an obstructed MV. Agents with negative chronotropic properties, such as beta blockers or heart rate–regulating calcium channel blockers, may be of benefit in patients in sinus rhythm who have exertional symptoms if these symptoms occur with high heart rates (411,412). The greater efficacy of a beta blocker compared with a heart rate–regulating calcium channel blocker has been reported (413). Some patients with MS have increased bronchial reactivity that may improve with inhaled corticosteroids (414). Salt restriction and intermittent administration of a diuretic are useful if there is evidence of pulmonary vascular congestion. Digitalis does not benefit patients with MS in sinus rhythm unless there is LV or RV dysfunction (415).

Although MS is a slowly progressive condition, acute pulmonary edema can occur suddenly in asymptomatic patients with severe MS, especially with the onset of rapid atrial fibrillation, and this can be rapidly fatal. Thus, patients should be counseled to seek medical attention immediately if they experience a sudden marked increase in shortness of breath.

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3.4.3.2. MEDICAL THERAPY: ATRIAL FIBRILLATION

Patients with MS are prone to developing atrial arrhythmias, particularly atrial fibrillation and atrial flutter. Thirty to forty percent of patients with symptomatic MS develop atrial fibrillation (367,368). Structural changes from the pressure and volume overload alter the electrophysiological properties of the left atrium (380), and the rheumatic process itself may lead to fibrosis of the internodal and interatrial tracts and damage to the sinoatrial node. There may be significant hemodynamic consequences resulting from the acute development of atrial fibrillation, primarily from the rapid ventricular rate, which shortens the diastolic filling period and causes elevation of left atrial pressure. Atrial fibrillation occurs more commonly in older patients (367) and is associated with a poorer prognosis, with a 10-year survival rate of 25% compared with 46% in patients who remain in sinus rhythm (369). The risk of arterial embolization, especially stroke, is significantly increased in patients with atrial fibrillation (367,368,416–418).

Treatment of an acute episode of rapid atrial fibrillation consists of anticoagulation with heparin and control of the heart rate response. Intravenous digoxin, heart rate–regulating calcium channel blockers, or beta blockers should be used to control ventricular response by slowing conduction through the atrioventricular node. Intravenous or oral amiodarone can also be used when beta blockers or heart rate-regulating calcium channel blockers cannot be used. If there is hemodynamic instability, electrical cardioversion should be undertaken urgently, with intravenous heparin before, during, and after the procedure. In selected patients, chemical cardioversion may also be attempted. Patients who have been in atrial fibrillation longer than 24 to 48 h without anticoagulation are at an increased risk for embolic events after cardioversion, but embolization may occur with less than 24 h of atrial fibrillation. The decision to proceed with elective cardioversion is dependent on multiple factors, including duration of atrial fibrillation, hemodynamic response to the onset of atrial fibrillation, a documented history of prior episodes of atrial fibrillation, and a history of prior embolic events. If the decision has been made to proceed with elective cardioversion in a patient who has had documented atrial fibrillation for longer than 24 to 48 h and who has not been on long-term anticoagulation, 1 of 2 approaches is recommended based on data from patients with nonrheumatic atrial fibrillation. The first is anticoagulation with warfarin for more than 3 weeks, followed by elective cardioversion (419). The second is anticoagulation with heparin and transesophageal echocardiography to look for left atrial thrombus. In the absence of left atrial thrombus, cardioversion is performed with intravenous heparin before, during, and after the procedure (420). It is important to continue long-term anticoagulation after cardioversion.

Recurrent paroxysmal atrial fibrillation may be treated for maintenance of sinus rhythm in selected patients with Class IC antiarrhythmic drugs (in conjunction with negative dromotropic agent) or Class III antiarrhythmic drugs; however, eventually, the atrial fibrillation becomes resistant to prevention or cardioversion (376), and control of ventricular response becomes the mainstay of therapy. Digoxin slows the heart rate response in patients with atrial fibrillation and MS (415). However, heart rate–regulating calcium channel blockers or beta blockers are more effective for preventing exercise-induced increases in heart rate. Patients with either paroxysmal or sustained atrial fibrillation should be treated with long-term anticoagulation with warfarin to prevent embolic events if they do not have a strong contraindication to anticoagulation (417,421). It is controversial whether percutaneous mitral valvotomy should be performed in patients with new-onset atrial fibrillation and moderate to severe MS who are otherwise asymptomatic.

Successful percutaneous balloon mitral commissurotomy may not prevent the development of atrial fibrillation. Advanced age and left atrial dimension appear to be the important predictors of development of atrial fibrillation (422).

3.4.3.3. MEDICAL THERAPY: PREVENTION OF SYSTEMIC EMBOLIZATION

CLASS I

1. Anticoagulation is indicated in patients with MS and atrial fibrillation (paroxysmal, persistent, or permanent). *(Level of Evidence: B)*
2. Anticoagulation is indicated in patients with MS and a prior embolic event, even in sinus rhythm. *(Level of Evidence: B)*
3. Anticoagulation is indicated in patients with MS with left atrial thrombus. *(Level of Evidence: B)*

CLASS IIb

1. Anticoagulation may be considered for asymptomatic patients with severe MS and left atrial dimension greater than or equal to 55 mm by echocardiography.* *(Level of Evidence: B)*
2. Anticoagulation may be considered for patients with severe MS, an enlarged left atrium, and spontaneous contrast on echocardiography. *(Level of Evidence: C)*

Systemic embolization may occur in 10% to 20% of patients with MS (367,368,416). The risk of embolization is related to age and the presence of atrial fibrillation (367,368,416–418). One third of embolic events occur within 1 month of the onset of atrial fibrillation, and two thirds occur within 1 year. The frequency of embolic events does not seem to be related to the severity of MS, cardiac output, size of the left atrium, or even the presence or absence of heart failure symptoms (368,417,424). An embolic event may thus be the initial manifestation of MS (367). In patients who have experienced an embolic event, the frequency of recurrence is as high as 15 to 40 events per 100 patient-months (417–421).

There are no randomized trials examining the efficacy of anticoagulation in preventing embolic events specifically in patients with MS. Retrospective studies have shown a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation in these patients (417,421). This benefit applies to both systemic and pulmonary embolism. Most

*This recommendation is based on a grade C level of evidence given by the American College of Chest Physicians Fourth Consensus Conference on Antithrombotic Therapy (423).

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trials involved patients who had 1 embolus before the onset of anticoagulation therapy (421). However, large randomized trials have demonstrated a significant reduction in embolic events by treatment with anticoagulation in subsets of patients with atrial fibrillation not associated with MS (425,426). In these randomized trials, the subset of patients who benefited most from anticoagulation were those with the highest risk of embolic events (353,354). Patients with MS at the highest risk for future embolic events are those with prior embolic events and those with paroxysmal or persistent atrial fibrillation (367,368,416–418,421). Paroxysmal atrial fibrillation may be difficult to detect; ambulatory ECG monitoring is valuable in patients with palpitations. There are no data to support the concept that oral anticoagulation is beneficial in patients with MS who have not had atrial fibrillation or an embolic event. It is controversial whether patients without atrial fibrillation or an embolic event who might be at higher risk for future embolic events (i.e., those with severe MS or an enlarged left atrium) should be considered for long-term warfarin therapy (423,427).

Although embolic events are thought to originate from left atrial thrombi (417,418), the presence or absence of a left atrial thrombus does not appear to correlate with embolic events (367,418). Left atrial thrombi are found during surgery in 15% to 20% of patients with prior embolic events and a similar number of patients without embolic events (367,416). However, in clinical practice, anticoagulation is frequently used if obvious left atrial thrombi are detected.

It has been suggested that surgical commissurotomy reduces the incidence of future embolic events (381). There are no randomized trial data to support this hypothesis, and the retrospective studies that have been reported were performed before the availability of standardized anticoagulation regimens. Other retrospective studies have concluded that surgery does not decrease the incidence of systemic emboli (380,428,429). One prospective study has reported decreased risk for arterial embolism after mitral commissurotomy (430).

3.4.4. Recommendations Regarding Physical Activity and Exercise

Many patients with mild MS will remain asymptomatic even with strenuous exercise. In more severe MS, exercise can cause sudden marked increases in pulmonary venous pressure from the increase in heart rate and cardiac output, at times resulting in pulmonary edema (375,376). The long-term effects of repeated exertion-related increases in pulmonary venous and pulmonary artery pressures on the lung or right ventricle remain unknown. MS rarely causes sudden death (367–369). These factors must be considered when recommending physical activity and exercise for the patient with MS.

In the majority of patients with MS, recommendations for exercise are symptom limited. Patients should be encouraged to pursue a low-level aerobic exercise program for maintenance of cardiovascular fitness. Exertional symptoms of dyspnea are the limiting factors in terms of exercise tolerance. However, there is a subset of asymptomatic patients who wish to participate in competitive athletics who may deny symptoms. The 36th Bethesda Conference on Recommendations for Determining Eligibility for Competition in Athletes with Cardiovascular Abnormalities published guidelines for patients with MS who wish to engage in competitive athletics (138).

3.4.5. Serial Testing

Serial follow-up testing of a patient with MS should be based on whether the results of a test will dictate either a change in therapy or a recommendation for a procedure. Patients with MS usually have years without symptoms before the onset of deterioration (367,380). All patients should be informed that any change in symptoms warrants re-evaluation. In the asymptomatic patient, yearly re-evaluation is recommended (Fig. 5). At the time of the yearly evaluation, a history, physical examination, chest X-ray, and ECG should be obtained. Physical examination is useful to assess the progression of the severity of MS. A shortening of the A2-OS interval, longer duration of the middiastolic murmur, and the presence of findings of pulmonary hypertension indicates more severe MS. An echocardiogram is not recommended yearly unless there is a change in clinical status or the patient has severe MS. Ambulatory ECG monitoring (Holter or event recorder) to detect paroxysmal atrial fibrillation is indicated in patients with palpitations.

3.4.6. Evaluation of the Symptomatic Patient

Patients who develop symptoms should undergo evaluation with a history, physical examination, ECG, chest X-ray, and echocardiogram (Figs. 6 and 7). Two-dimensional and Doppler echocardiography are indicated to evaluate MV morphology, MV hemodynamics, and pulmonary artery pressure. Patients with NYHA functional class II symptoms and moderate or severe MS (MV area less than or equal to 1.5 cm^2 or mean gradient greater than 5 mm Hg) may be considered for mitral balloon valvotomy if they have suitable MV morphology and no left atrial thrombi. Patients who have NYHA functional class III or IV symptoms and evidence of severe MS have a poor prognosis if left untreated (367–369) and should be considered for intervention with either balloon valvotomy or surgery.

A subset of patients have significant limiting symptoms, yet clinical and Doppler echocardiographic evaluation do not indicate moderate or severe MS. In such patients, formal exercise testing or dobutamine stress may be useful to differentiate symptoms due to MS from other causes of symptoms. Exercise tolerance, heart rate and blood pressure response, transmitral gradient, and pulmonary artery pressure can be obtained at rest and during exercise. This can usually be accomplished with either supine bicycle or up-

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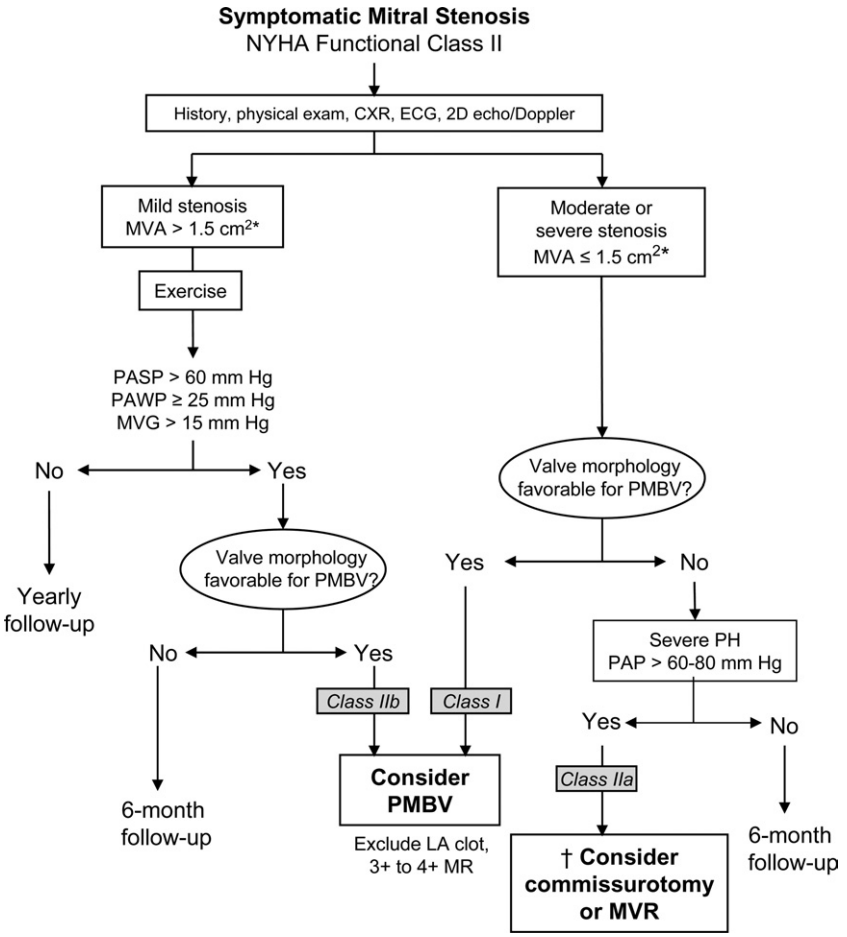

Figure 6. Management Strategy for Patients With Mitral Stenosis and Mild Symptoms

*The committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradient, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PP) should also be taken into consideration. †There is controversy as to whether patients with severe mitral stenosis (MVA less than 1.0 cm^2) and severe pulmonary hypertension (PH; PP greater than 60 to 80 mm Hg) should undergo percutaneous mitral balloon valvotomy (PMBV) or mitral valve replacement to prevent right ventricular failure. CXR indicates chest X-ray; ECG, electrocardiogram; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; MVG, mean mitral valve pressure gradient; NYHA, New York Heart Association; PAP, pulmonary artery pressure; and 2D, 2-dimensional.

right exercise testing with Doppler recording of TR and transmitral velocities (406–409). Right- and left-heart catheterization with exercise may be helpful and occasionally necessary (431). Patients who are symptomatic with a significant elevation of pulmonary artery pressure (greater than 60 mm Hg), mean transmitral gradient (greater than 15 mm Hg), or pulmonary artery wedge pressure (greater than 25 mm Hg) during exercise (375,407–409,432,433) have hemodynamically significant MS and should be considered for further intervention. Alternatively, patients who do not manifest elevation in either pulmonary artery, pulmonary artery wedge, or transmitral pressures coincident with development of exertional symptoms most likely would not benefit from intervention on the MV.

3.4.7. Indications for Invasive Hemodynamic Evaluation

CLASS I

1. Cardiac catheterization for hemodynamic evaluation should be performed for assessment of severity of MS when noninvasive tests are inconclusive or when there is discrepancy between noninvasive tests and clinical findings regarding severity of MS. *(Level of Evidence: C)*
2. Catheterization for hemodynamic evaluation including left ventriculography (to evaluate severity of MR) for patients with MS is indicated when there is a discrepancy between the Doppler-derived mean gradient and valve area. *(Level of Evidence: C)*

CLASS IIa

1. Cardiac catheterization is reasonable to assess the hemodynamic response of pulmonary artery and left atrial pressures to exercise when clinical symptoms and resting hemodynamics are discordant. *(Level of Evidence: C)*
2. Cardiac catheterization is reasonable in patients with MS to assess the cause of severe pulmonary arterial hypertension when out of proportion to severity of MS as determined by noninvasive testing. *(Level of Evidence: C)*

CLASS III

1. Diagnostic cardiac catheterization is not recommended to assess the MV hemodynamics when 2D and Doppler echocardiographic data are concordant with clinical findings. *(Level of Evidence: C)*

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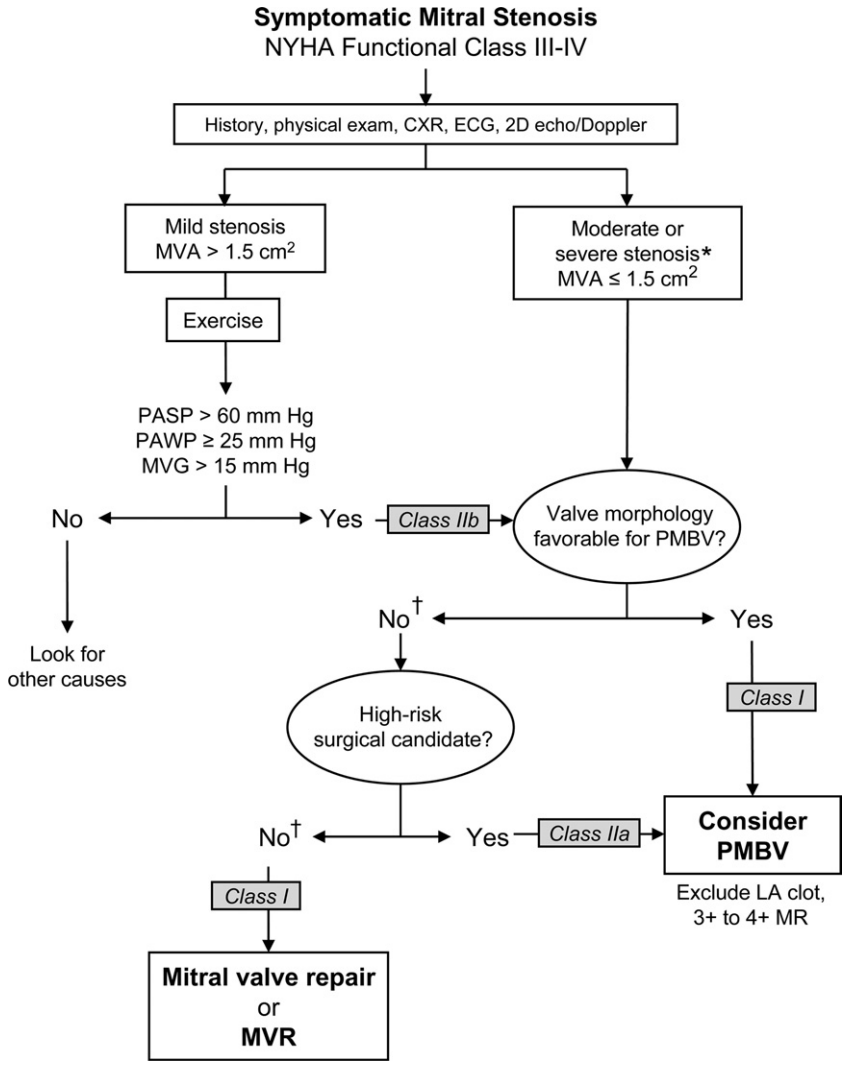

Figure 7. Management Strategy for Patients With Mitral Stenosis and Moderate to Severe Symptoms

*The writing committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradient, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PP) should also be taken into consideration. †It is controversial as to which patients with less favorable valve morphology should undergo percutaneous mitral balloon valvotomy (PMBV) rather than mitral valve surgery (see text). CXR, chest X-ray; ECG, electrocardiography; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; MVG, mean mitral valve pressure gradient; MVR, mitral valve replacement; NYHA, New York Heart Association; and 2D, 2-dimensional.

Hemodynamic measurements by cardiac catheterization can be used to determine the severity of MS. Direct measurements of left atrial and LV pressure determine the transmitral gradient, which is the fundamental expression of severity of MS (372). Because the severity of obstruction is dependent on both flow and gradient (376), the hydraulic Gorlin equation has been used in the catheterization laboratory to derive a calculated valve area (139). Pulmonary artery pressure and pulmonary vascular resistance can be measured to determine the effect of MS on the pulmonary circulation.

With the advent of Doppler echocardiography, cardiac catheterization is no longer required for assessment of hemodynamics in the majority of patients with isolated MS. Reliable measurements of the transmitral gradient may be obtained with the modified Bernoulli equation (389,391). The potential problems of angle dependence, pressure recovery, proximal acceleration, and inadequate velocity signals that occur in the evaluation of other valve lesions are not present with MS. There is often overestimation of the transmitral gradient when catheterization is performed with pulmonary artery wedge pressure as a substitute for left atrial pressure, even after correction for phase delay. Thus, the transmitral gradient derived by Doppler echocardiography may be more accurate than that obtained by cardiac catheterization with pulmonary artery wedge pressure (434).

MV area is derived from either the half-time method or the continuity equation by Doppler echocardiography. These measurements correlate well in most instances with valve areas from cardiac catheterization (401,402). The Doppler half-time method may be inaccurate if there are changes in compliance of the left atrium or left ventricle

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(402,403), especially after mitral balloon valvotomy, or if there is concomitant AR. There are limitations to MV area calculations derived from catheter hemodynamic measurements, because the Gorlin equation may not be valid under varying hemodynamic conditions, and the empirical coefficient of discharge may be inaccurate with different orifice shapes (379,404). Calculation of valve area by catheterization is also dependent on measurement of transmitral gradient and cardiac output. Gradients may be inaccurate when pulmonary artery wedge pressure is used, as may cardiac output derived by the thermodilution method. When there is concomitant MR, measures of forward flow by thermodilution or the Fick method will result in underestimation of the MV area, as discussed in Section 3.7.2.2.2. Thus, there may be inaccuracies with both Doppler and catheter-derived valve areas, and a single valve area should not be the sole measure of MS severity. Estimates of the severity of MS should be based on all data, including transmitral gradient, MV area, pulmonary artery wedge pressure, and pulmonary artery pressure.

In most instances, Doppler measurements of transmitral gradient, valve area, and pulmonary pressure will correlate well with each other. Catheterization is indicated to assess hemodynamics when there is a discrepancy between Doppler-derived hemodynamics and the clinical status of a symptomatic patient. Absolute left- and right-side pressure measurements should be obtained by catheterization when there is elevation of pulmonary artery pressure out of proportion to mean gradient and valve area. Invasive hemodynamic evaluation is also necessary to assess the severity and the hemodynamic cause of increased pulmonary vascular resistance, because pulmonary vasodilator therapy may be of benefit in such patients. Catheterization including left ventriculography (to evaluate the severity of MR) is indicated when there is a discrepancy between the Doppler-derived mean gradient and valve area. Aortic root angiography may be necessary to evaluate severity of AR. If symptoms appear to be out of proportion to noninvasive assessment of resting hemodynamics, right- and left-heart catheterization with exercise may be useful. Transseptal catheterization may rarely be required for direct measurement of left atrial pressure if there is doubt about the accuracy of pulmonary artery wedge pressure. Coronary angiography may be required in selected patients who may need intervention (see Section 10.2.).

3.4.8. Indications for Percutaneous Mitral Balloon Valvotomy

CLASS I

1. Percutaneous mitral balloon valvotomy is effective for symptomatic patients (NYHA functional class II, III, or IV), with moderate or severe MS* and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: A)*
2. Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe MS* and valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: C)*

CLASS IIa

1. Percutaneous mitral balloon valvotomy is reasonable for patients with moderate or severe MS* who have a nonpliable calcified valve, are in NYHA functional class III–IV, and are either not candidates for surgery or are at high risk for surgery. *(Level of Evidence: C)*

CLASS IIb

1. Percutaneous mitral balloon valvotomy may be considered for asymptomatic patients with moderate or severe MS* and valve morphology favorable for percutaneous mitral balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR. *(Level of Evidence: C)*
2. Percutaneous mitral balloon valvotomy may be considered for symptomatic patients (NYHA functional class II, III, or IV) with MV area greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery systolic pressure greater than 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient greater than 15 mm Hg during exercise. *(Level of Evidence: C)*
3. Percutaneous mitral balloon valvotomy may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA functional class III–IV. *(Level of Evidence: C)*

CLASS III

1. Percutaneous mitral balloon valvotomy is not indicated for patients with mild MS. *(Level of Evidence: C)*
2. Percutaneous mitral balloon valvotomy should not be performed in patients with moderate to severe MR or left atrial thrombus. *(Level of Evidence: C)*

The concept of mitral commissurotomy was first proposed by Brunton in 1902, and the first successful surgical mitral commissurotomy was performed in the 1920s. By the late 1940s and 1950s, both transatrial and transventricular closed surgical commissurotomy were accepted clinical procedures. With the development of cardiopulmonary bypass, open mitral commissurotomy and replacement of the MV became the surgical procedures of choice for the treatment of MS. Percutaneous mitral balloon valvotomy emerged in the mid 1980s. This procedure, in which 1 or more large balloons is inflated across the MV by a catheter-based approach, has become the preferred procedure in selected patients compared with surgical approaches.

The mechanism of improvement from surgical commissurotomy or percutaneous valvotomy is related to the successful opening of commissures that were fused by the rheumatic process. This results in a decrease in gradient and an increase in the calculated MV area, with resulting improvement in clinical symptomatology. The extent of hemodynamic and clinical improvement is dependent on the magnitude of decrease of transmitral gradient and

*See Table 4 (27).

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increase in valve area. Patients with pliable, noncalcified valves and minimal fusion of the subvalvular apparatus achieve the best immediate and long-term results when a substantial increase in the valve area can be achieved.

Closed surgical commissurotomy with either a transatrial or transventricular approach was popularized in the 1950s and 1960s. Early and long-term postoperative follow-up studies showed that patients had a significant improvement in symptoms and survival compared with those treated medically (435–437). Closed commissurotomy remains the surgical technique of choice in many developing countries, but open commissurotomy is the accepted surgical procedure in most institutions in the United States (438–441), because it allows direct inspection of the MV apparatus and, under direct vision, division of the commissures, splitting of fused chordae tendineae and papillary muscles, and debridement of calcium deposits. Amputation of the left atrial appendage is recommended to reduce the likelihood of postoperative thromboembolic events (442). The results of the operation are dependent on the morphology of the MV apparatus and the surgeon's skill and experience. In patients with marked deformity of the MV apparatus, a decision for MV replacement can be made at the time of operation. The risk of surgery is between 1% and 3%, depending on the concomitant medical status of the patient (439–441). Although there is an inherent bias in the large reported surgical series, the 5-year reoperation rate is 4% to 7%, and the 5-year complication-free survival rate ranges from 80% to 90%.

Percutaneous mitral balloon valvotomy was first performed in the early 1980s and became a clinically approved technique in 1994. In the past decade, there have been major advances in techniques and equipment, as well as changes in patient selection. A double-balloon technique was the initial procedure used by most investigators. Today, an hourglass-shaped single balloon (Inoue balloon) is used by most centers performing the technique. Percutaneous mechanical mitral commissurotomy with a metallic valvotome has been introduced, and the results appear to be similar. The advantage of this technique is that multiple uses of the metallic device after sterilization are feasible and reduce the cost of treatment (443); however, it is not widely available, and there is limited experience with this technique. The balloon valvotomy procedure itself is technically challenging and involves a steep learning curve. There is a higher success rate and lower complication rate in experienced, high-volume centers (444). Thus, the results of the procedure are highly dependent on the experience of the operators involved, which must be considered when making recommendations for proceeding with this technique.

The immediate results of percutaneous mitral valvotomy are similar to those of mitral commissurotomy (444–453). The mean valve area usually doubles (from 1.0 to 2.0 cm^2), with a 50% to 60% reduction in transmitral gradient. Overall, 80% to 95% of patients may have a successful procedure, which is defined as a MV area greater than 1.5 cm^2 and a decrease in left atrial pressure to less than 18 mm Hg in the absence of complications. The most common acute complications reported in large series include severe MR, which occurs in 2% to 10%, and a residual atrial septal defect. A large atrial septal defect (greater than 1.5:1 left-to-right shunt) occurs in fewer than 12% of patients with the double-balloon technique and fewer than 5% with the Inoue balloon technique. Smaller atrial septal defects may be detected by transesophageal echocardiography in larger numbers of patients. Less frequent complications include perforation of the left ventricle (0.5% to 4.0%), embolic events (0.5% to 3%), and myocardial infarction (0.3% to 0.5%). The mortality rate with balloon valvotomy in larger series has ranged from 1% to 2% (444–447,453); however, with increasing experience with the procedure, percutaneous mitral valvotomy can be done in selected patients with a mortality rate of less than 1% (448). Simultaneous echocardiography may be useful in directing balloon placement and assessing hemodynamics.

Follow-up information after percutaneous balloon valvotomy is limited. Event-free survival (freedom from death, repeat valvotomy, or MV replacement) overall is 50% to 65% over 3 to 7 years, with an event-free survival of 80% to 90% in patients with favorable MV morphology (398,446, 448–455). More than 90% of patients free of events remain in NYHA functional class I or II after percutaneous mitral valvotomy. Randomized trials have compared percutaneous balloon valvotomy with both closed and open surgical commissurotomy (456–461). These trials, summarized in Table 18, consisted primarily of younger patients (aged 10 to 30 years) with pliable MV leaflets. There was no significant difference in acute hemodynamic results or complication rate between percutaneous mitral valvotomy and surgery, and early follow-up data indicate no difference in hemodynamics, clinical improvement, or exercise time. However, longer-term follow-up studies at 3 to 7 years (459,460) indicate more favorable hemodynamic and symptomatic results with percutaneous balloon valvotomy than with closed commissurotomy. Of the 2 studies that compared percutaneous balloon valvotomy with open commissurotomy, one reported equivalent results (460), and the other showed more favorable results with open commissurotomy (461). This latter study included older patients with higher MV scores.

The immediate results, acute complications, and follow-up results of percutaneous balloon valvotomy are dependent on multiple factors. It is of utmost importance that this procedure be performed in centers with skilled and experienced operators. Other factors include age, NYHA functional class, stenosis severity, LV end-diastolic pressure, cardiac output, and pulmonary artery wedge pressure (446,448,449,453). The underlying MV morphology is the factor of greatest importance in determining outcome (394–400,446,449,450,453,454,462), and immediate postvalvotomy hemodynamics are predictive of long-term clinical outcome (448,450,453). Patients with valvular calcification,

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Table 18. Randomized Trials of Percutaneous Mitral Balloon Valvotomy and Surgical Commissurotomy

Author, Year	Mean Follow-Up	Procedure	No. of Patients	Age, y	Average Score	Mitral Gradient		Mitral Valve Area		Restenosis (%)	Freedom From Reintervention (%)	NYHA FC I (%)
						Pre	Post	Pre	Post			
Patel et al., 1991 (456)	Immediate	PMBV	23	30 ± 11	6.0	12 ± 4	4 ± 3	0.8 ± 0.3	2.1 ± 0.7*	—	—	91
		CC	22	26 ± 26	6.0	12 ± 5	6 ± 3	0.7 ± 0.2	1.3 ± 0.3	—	—	—
Turi et al., 1991 (457)	7 mo	PMBV	20	27 ± 8	7.2	18 ± 4	10 ± 2	0.8 ± 2	1.6 ± 0.2	—	—	—
		CC	20	28 ± 1	8.4	20 ± 6	12 ± 2	0.9 ± 0.4	1.7 ± 0.2	—	—	—
Arora et al., 1993 (458)	22 mo	PMBV	100	19 ± 5	—	—	—	0.8 ± 0.3	2.3 ± 0.1	5	—	—
		CC	100	20 ± 6	—	—	—	0.8 ± 0.2	2.1 ± 0.4	4	—	—
Reyes et al., 1994 (459)	3 y	PMBV	30	30 ± 9	6.7	—	—	0.9 ± 0.3	2.4 ± 0.4*	10	—	72
		CC	30	31 ± 9	7.0	—	—	0.9 ± 0.3	1.8 ± 0.4	13	—	57
Ben Farhat et al., 1998 (460)	7 y	PMBV	30	29 ± 12	6.0	—	—	0.9 ± 0.2	1.8 ± 0.4	—	90	87
		OC	30	27 ± 9	6.0	—	—	0.9 ± 0.2	1.8 ± 0.3	—	93	90
		CC	30	28 ± 10	6.0	—	—	0.9 ± 0.2	1.3 ± 0.3	—	50	33
Cotrufo et al., 1999 (461)	38 mo	PMBV	111	47 ± 14	7.6	—	—	1.0 ± 0.2	1.8 ± 0.3	28	88	67
	50 mo	OC	82	49 ± 10	8.2	—	—	1.0 ± 0.2	2.3 ± 0.3	18	96	84

A dash indicates that data were not available. *Significant difference (p less than 0.05) in increased mitral valve area by percutaneous mitral balloon valvotomy (PMBV) compared with surgical commissurotomy.
CC indicates closed commissurotomy; FC, functional class; NYHA, New York Heart Association; OC, open commissurotomy; Post, postprocedure; and Pre, preprocedure.

thickened fibrotic leaflets with decreased mobility, and subvalvular fusion have a higher incidence of acute complications and a higher rate of recurrent stenosis on follow-up (Table 19). Because the success of the procedure is dependent on the ability to split fused commissures, the presence of marked fusion and severe calcification of commissures is associated with an increased complication rate and higher incidence of recurrent symptoms (396–398). Alternatively, in patients with noncalcified pliable valves, mild subvalvular fusion, and no calcium in the commissures, the procedure can be performed with a high success rate (greater than 90%), low complication rate (less than 3%), and sustained improvement in 80% to 90% over a 3- to 7-year follow-up period (397,398,400,446,448,450,453,454).

Relative contraindications to percutaneous balloon valvotomy include the presence of a left atrial thrombus and significant (3+ to 4+) MR. Transesophageal echocardiography is recommended before the procedure to determine the presence of left atrial thrombus, specifically examining the left atrial appendage. If a thrombus is found, 3 months of anticoagulation with warfarin may result in resolution of the thrombus. A prognostic model for predicting the resolution of left atrial thrombi in candidates for percutaneous mitral commissurotomy has been suggested. Combined clinical functional class and echocardiographic left atrial thrombus are predictive of the outcome of oral anticoagulation for thrombus resolution (463).

In centers with skilled, experienced operators, percutaneous balloon valvotomy should be considered the initial procedure of choice for symptomatic patients with moderate to severe MS who have a favorable valve morphology in the absence of significant MR or left atrial thrombus. Echocardiographic parameters that can predict the risks of developing severe MR after percutaneous mitral valvotomy by the Inoue technique have been reported (464), and the overall echocardiographic assessment (397,398,400) identifies patients with less favorable long-term outcome (Tables 17 and 19). In asymptomatic patients with a favorable valve morphology, percutaneous mitral valvotomy may be considered if there is evidence of a hemodynamic effect on left atrial pressure or pulmonary circulation (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise); the strength of evidence for this recommendation is low because there are no data comparing the results of percutaneous balloon valvotomy and those of medical therapy in such asymptomatic patients. It is controversial whether severely symptomatic patients with less favorable valve morphology should undergo this catheter-based procedure (465) (Fig. 7; Table 19). Although there is a higher acute complication rate and a lower event-free survival rate (approximately 50% at 5 years in these patients compared with 80% to 90% in patients with favorable valve morphology), this must be weighed against the average in-hospital mortality of surgical MV replacement of 6% (164,165), which is as high as 16% in low-volume centers (166), and the expected long-term outcome. In many cases,

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Table 19. Echocardiographic Prediction of Outcome of Percutaneous Mitral Balloon Valvotomy

Author, Year	Mean Follow-Up, mo	Echo Criteria	No. of Patients	Age, y	Survival	Survival Free of Events	Events
Cohen et al., 1992 (446)	36 ± 20	Score less than or equal to 8	84	—	—	68% at 5 y	Death, MVR, repeat PMBV
		Score greater than 8	52	—	—	28% at 5 y	
Palacios et al., 1995 (454)	20 ± 12	Score less than or equal to 8	211	48±14	98% at 4 y	98% at 4 y	Death, MVR, NYHA FC III–IV symptoms
		Score greater than 8	116	64 ± 11	39% at 4 y	39% at 4 y	
Dean et al., 1996 (449)	38 ± 16	Score less than or equal to 8	272	49 ± 13	95% at 4 y	—	Death
		Score 8 to 12	306	58 ± 15	83% at 4 y	—	
		Score greater than 12	24	58 ± 15	24% at 4 y	—	
Iung et al., 1996 (397)	32 ± 18	Group 1	87		—	89% at 3 y	Death, MVR, repeat PMBV, FC III–IV symptoms
		Group 2	311	46 ± 13	—	78% at 3 y	
		Group 3	130		—	65% at 3 y	
Cannan et al., 1997 (398)	22 ± 10	Com Ca−	120	—	—	86% at 3 y	Death, MVR, repeat PMBV
		Com Ca+	29	—	—	40% at 3 y	
Palacios et al., 2002 (453)	50 ± 44	Score greater than 8	278	63 ± 14	82% at 12 y	38% at 12 y	Death, MVR, repeat PMBV
		Score less than 8	601	51 ± 14	57% at 12 y	22% at 12 y	

Echocardiography score based on scoring system of Wilkins et al. (400); echocardiographic group based on valve flexibility, chordal fusion, and valve calcification in Iung et al. (397).
Com Ca indicates commissural calcification; echo, echocardiographic; FC, functional class; MVR, mitral valve replacement; NYHA, New York Heart Association; and PMBV, percutaneous mitral balloon valvotomy.

MV replacement is preferable for patients with severe valvular calcification and deformity.

Patients who are being considered for an intervention should undergo evaluation with a history, physical examination, and 2D and Doppler echocardiographic examination. The appearance and mobility of the MV apparatus and commissures should be evaluated by 2D echocardiography, and the transmitral gradient, MV area, and pulmonary artery pressure should be obtained from the Doppler examination. If there is a discrepancy between symptoms and hemodynamics, a formal hemodynamic exercise test may be performed. Patients thought to be candidates for percutaneous mitral valvotomy should undergo transesophageal echocardiography to rule out left atrial thrombus and to examine the severity of MR. If a left atrial thrombus is present, a repeat transesophageal echocardiogram can be performed after several months of anticoagulation. Percutaneous mitral balloon valvotomy may be safely performed if there has been resolution of the thrombus. If there is a suspicion that the severity of MR is 3+ or 4+ based on the physical examination or echocardiogram, a left ventriculogram should be performed. Mitral balloon valvotomy should not be performed in patients who have grade 3+ or 4+ MR. Percutaneous mitral balloon valvotomy should be performed only by skilled operators at institutions with extensive experience in performing the technique (444,447). Thus, the decision to proceed with percutaneous balloon valvotomy or surgical commissurotomy is dependent on the experience of the operator and institution. Because of the less invasive nature of percutaneous balloon valvotomy compared with surgical intervention, appropriate patients without symptoms or those with NYHA functional class II symptoms may be considered for catheter-based therapy (Figs. 5 and 6).

3.4.9. Indications for Surgery for Mitral Stenosis

CLASS I

1. MV surgery (repair if possible) is indicated in patients with symptomatic (NYHA functional class III–IV) moderate or severe MS* when 1) percutaneous mitral balloon valvotomy is unavailable, 2) percutaneous mitral balloon valvotomy is contraindicated because of left atrial thrombus despite anticoagulation or because concomitant moderate to severe MR is present, or 3) the valve morphology is not favorable for percutaneous mitral balloon valvotomy in a patient with acceptable operative risk. *(Level of Evidence: B)*
2. Symptomatic patients with moderate to severe MS* who also have moderate to severe MR should receive MV replacement, unless valve repair is possible at the time of surgery. *(Level of Evidence: C)*

CLASS IIa

1. MV replacement is reasonable for patients with severe MS* and severe pulmonary hypertension (pulmonary artery systolic pressure greater than 60 mm Hg) with NYHA functional class I–II symptoms who are not considered candidates for percutaneous mitral balloon valvotomy or surgical MV repair. *(Level of Evidence: C)*

*See Table 4 (27).

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CLASS IIb

1. MV repair may be considered for asymptomatic patients with moderate or severe MS* who have had recurrent embolic events while receiving adequate anticoagulation and who have valve morphology favorable for repair. *(Level of Evidence: C)*

CLASS III

1. MV repair for MS is not indicated for patients with mild MS. *(Level of Evidence: C)*
2. Closed commissurotomy should not be performed in patients undergoing MV repair; open commissurotomy is the preferred approach. *(Level of Evidence: C)*

MV replacement is an accepted surgical procedure for patients with severe MS who are not candidates for surgical commissurotomy or percutaneous mitral valvotomy. The perioperative mortality of MV replacement is dependent on multiple factors, including functional status, age, LV function, cardiac output, concomitant medical problems, and concomitant CAD. In the young, healthy person, MV replacement can be performed with a risk of less than 5%; however, in the older patient with concomitant medical problems or pulmonary hypertension at systemic levels, the perioperative mortality of MV replacement may be as high as 10% to 20% (166,167). MV replacement with preservation of subvalvular apparatus aids in maintaining LV function (466), but this can be particularly difficult in patients with rheumatic MS. Alternative approaches to ventricular preservation exist, such as artificial chordal reconstruction before MV replacement (467,468). Complications of MV replacement include valve thrombosis, valve dehiscence, valve infection, valve malfunction, and embolic events. These are discussed in Section 7.3. There is also the known risk of long-term anticoagulation in patients receiving mechanical prostheses.

If there is significant calcification, fibrosis, and subvalvular fusion of the MV apparatus, commissurotomy or percutaneous balloon valvotomy is less likely to be successful, and MV replacement will be necessary. Given the risk of MV replacement and the potential long-term complications of a prosthetic valve, there are stricter indications for MV operation in these patients with calcified fibrotic valves. In the patient with NYHA functional class III symptoms due to severe MS or combined MS/MR, MV replacement results in excellent symptomatic improvement. Postponement of surgery until the patient reaches the functional class IV symptomatic state should be avoided, because operative mortality is high and the long-term outcome is suboptimal. However, if the patient presents in NYHA functional class IV heart failure, surgery should not be denied, because the outlook without surgical intervention is grave. It is controversial whether asymptomatic or mildly symptomatic patients with severe MS (valve area less than 1 cm^2) and severe pulmonary hypertension (pulmonary artery systolic pressure greater than 60 to 80 mm Hg) should undergo MV replacement to prevent RV failure, but surgery is generally recommended in such patients. It is recognized that patients with such severe pulmonary hypertension are rarely asymptomatic.

3.4.10. Management of Patients After Valvotomy or Commissurotomy

Symptomatic improvement occurs almost immediately after successful percutaneous balloon valvotomy or surgical commissurotomy, although objective measurement of maximum oxygen consumption may continue to improve over several months postoperatively owing to slowly progressive improvement in skeletal muscle metabolism (469). Hemodynamic measurements before and after either percutaneous valvotomy or surgical commissurotomy have confirmed a decrease in left atrial pressure, pulmonary artery pressure, and pulmonary arteriolar resistance and an improvement in cardiac output (470–473). In patients with significant right heart failure after catheter-based or surgical relief of MV obstruction, inhaled nitric oxide, intravenous prostacyclin, or an endothelin antagonist may be useful in reducing pulmonary vascular resistance and pulmonary hypertension (474). Gradual regression of pulmonary hypertension over months has been demonstrated (470–472).

Recurrent symptoms after successful surgical commissurotomy have been reported to occur in as many as 60% of patients after 9 years (405,435,475); however, recurrent stenosis accounts for symptoms in fewer than 20% of patients (475). In patients with an adequate initial result, progressive MR and development of other valvular or coronary problems are more frequently responsible for recurrent symptoms (475). Thus, in patients presenting with symptoms late after commissurotomy, a comprehensive evaluation is required to look for other causes. Patients undergoing percutaneous mitral valvotomy with an unfavorable MV morphology have a higher incidence of recurrent symptoms at 1- to 2-year follow-up due to either an initial inadequate result or restenosis (476).

The management of patients after successful percutaneous balloon valvotomy or surgical commissurotomy is similar to that of the asymptomatic patient with MS. A baseline echocardiogram should be performed after the procedure to obtain a baseline measurement of postoperative hemodynamics and to exclude significant complications such as MR, LV dysfunction, or atrial septal defect (in the case of percutaneous valvotomy). This echocardiogram should be performed at least 72 h after the procedure, because acute changes in atrial and ventricular compliance immediately after the procedure affect the reliability of the half-time in calculation of valve area (402,403). Patients with severe MR or a large atrial septal defect should be considered for early surgery; however, the majority of small left-to-right shunts at the atrial level will close spontaneously over the course of 6 months. In patients with a history of atrial fibrillation, warfarin should be restarted 1 to 2 days after the procedure.

A history, physical examination, chest X-ray, and ECG should be obtained at yearly intervals in the patient who remains asymptomatic or minimally symptomatic. Prophy-

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laxis against infective endocarditis (Section 2.3.1) and recurrence of rheumatic fever (Section 2.3.2.3; Table 11) (45) should be followed. If the patient is in atrial fibrillation or has a history of atrial fibrillation, anticoagulation is recommended, as would be the case for all patients with MS. With recurrent symptoms, extensive 2D and Doppler echocardiography should be performed to evaluate the MV hemodynamics and pulmonary artery pressure and to rule out significant MR or a left-to-right shunt. As with all patients with MS, exercise hemodynamics may be indicated in the patient with a discrepancy in clinical and hemodynamic findings.

Repeat percutaneous balloon valvotomy can be performed in the patient in whom there is restenosis after either a prior surgical commissurotomy or a balloon valvotomy (378,477). The results of these procedures are adequate in many patients but may be less satisfactory than the overall results of initial valvotomy, because there is usually more valve deformity, calcification, and fibrosis than with the initial procedure (395,477,478). MV replacement should be considered in those patients with recurrent severe symptoms and severe deformity of the mitral apparatus.

3.4.11. Special Considerations

3.4.11.1. PREGNANT PATIENTS

MS often affects young women who are in their childbearing years. The increased intravascular volume, increased cardiac output, and tachycardia associated with pregnancy may raise complex issues in the patient with MS and are reviewed in Section 5.5.1. Percutaneous mitral valvuloplasty can be performed with few or no complications to the mother or the fetus and excellent clinical and hemodynamic results (479).

3.4.11.2. OLDER PATIENTS

An increasing number of older patients now present with symptomatic MS, most likely due to a change in the natural history of the disease (383,384). Older patients are more likely to have heavy calcification and fibrosis of the MV leaflets, with significant subvalvular fusion. In patients older than 65 years, the success rate of percutaneous valvotomy is lower (less than 50%) than in prior reports of younger patients. Procedural mortality is 3%, and there is an increased risk of complications, including pericardial tamponade in 5% and thromboembolism in 3%; however, in selected patients with favorable valve morphology, the procedure may be done safely with good intermediate-term results (384). The long-term clinical improvement is considerably less and mortality is higher in older than younger patients (480).

3.5. Mitral Valve Prolapse

3.5.1. Pathophysiology and Natural History

MVP refers to a systolic billowing of 1 or both mitral leaflets into the left atrium with or without MR. Utilizing current echocardiographic criteria for diagnosing MVP (valve prolapse of 2 mm or more above the mitral annulus in the long-axis parasternal view and other views [481]), the prevalence of this entity is 1% to 2.5% of the population (482). MVP occurs as a clinical entity with or without thickening (5 mm or greater, measured during diastasis) and with or without MR.

Primary MVP can be familial or nonfamilial. There is interchordal hooding due to leaflet redundancy that includes both the rough and clear zones of the involved leaflets (483). The basic microscopic feature of primary MVP is marked proliferation of the spongiosa, the delicate myxomatous connective tissue between the atrialis (a thick layer of collagen and elastic tissue that forms the atrial aspect of the leaflet) and the fibrosa or ventricularis (dense layer of collagen that forms the basic support of the leaflet). Myxomatous proliferation of the acid mucopolysaccharide–containing spongiosa tissue causes focal interruption of the fibrosa. Secondary effects of the primary MVP syndrome include fibrosis of the surface of the MV leaflets, thinning and/or elongation of the chordae tendineae, and ventricular friction lesions. Fibrin deposits often form at the MV–left atrial angle.

Familial MVP is transmitted as an autosomal trait (484,485), and several chromosomal loci have been identified (486–488). Primary MVP occurs with increased frequency in patients with Marfan syndrome and other connective tissue diseases (483,489–491). It has been speculated that the primary MVP syndrome represents a generalized disease of connective tissue. The increased incidence of MVP in Von Willebrand's disease and other coagulopathies, primary hypomastia, and various connective tissue diseases has been used to support the concept that increased incidence of MVP is a result of defective embryogenesis of cell lines of mesenchymal origin (492). Thoracic skeletal abnormalities such as straight thoracic spine and pectus excavatum are commonly associated with MVP.

The auscultatory findings in MVP, when present, may consist of a click or multiple clicks that move within systole with changes in LV dimensions and/or a late systolic or holosystolic murmur of MR. There may be left atrial dilatation and LV enlargement, depending on the presence and severity of MR. Involvement of other valves may occur. Tricuspid valve prolapse may occur in 40% of patients with MVP (485). Pulmonic and aortic valve prolapses occur in 2% to 10% of patients with MVP (483). There is an increased incidence of associated secundum atrial septal defect and/or left-sided atrioventricular bypass tracts and supraventricular arrhythmias.

The natural history of asymptomatic MVP is heterogeneous and can vary from benign and normal life expectancy to adverse with significant morbidity or mortality. The spectrum of MR ranges from absent to severe. The most frequent predictor of cardiovascular mortality is moderate to severe MR and, less frequently, an LV ejection fraction less than 0.50 (493). Echocardiographic evidence of thickened MV leaflets (5 mm or greater) is also a predictor of

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Table 20. Use of Echocardiography for Risk Stratification in Mitral Valve (MV) Prolapse

Study, Year	No. of Patients	Features Examined	Outcome	$p <$
Chandraratna et al., 1984 (494)	86	MV leaflets greater than 5.1 mm	↑ Cardiovascular abnormalities (60% vs. 6%; Marfan syndrome, TVP, MR, dilated ascending aorta)	0.001
Nishimura et al., 1985 (495)	237	MV leaflet 5 mm or greater	↑ Sum of sudden death, endocarditis, and cerebral embolus	0.02
		LVID 60 mm or greater	↑ MVR (26% vs. 3.1%)	0.001
Marks et al., 1989 (496)	456	MV leaflet 5 mm or greater	↑ Endocarditis (3.5% vs. 0%)	0.02
			↑ Moderate-severe MR (11.9% vs. 0%)	0.001
			↑ MVR (6.6% vs. 0.7%)	0.02
			↑ Stroke (7.5% vs. 5.8%)	NS
Takamoto et al., 1991 (497)	142	MV leaflet 3 mm or greater, redundant, low echo destiny	↑ Ruptured chordae (48% vs. 5%)	
Babuty et al., 1994 (498)	58	Undefined MV thickening	No relation to complex ventricular arrhythmias	NS
Zuppiroli et al., 1994 (499)	119	MV leaflet greater than 5 mm	↑ Complex ventricular arrhythmias	0.001

Reprinted from the ACC/AHA/ASE 2004 Guidelines for the Clinical Application of Echocardiography.
LVID indicates left ventricular internal diameter; MR, mitral regurgitation; MVR, mitral valve replacement; NS, not significant; and TVP, tricuspid valve prolapse. ↑ indicates increase.

complications related to MVP (Table 20) (494–499). In most patients, the MVP syndrome is associated with a benign prognosis (500,501). The age-adjusted survival rate for both men and women with MVP is similar to that of individuals without this entity (485).

The gradual progression of MR in patients with MVP may result in the progressive dilatation of the left atrium and ventricle. Left atrial dilatation may result in atrial fibrillation, and moderate to severe MR may eventually result in LV dysfunction and congestive heart failure (502). Pulmonary hypertension may occur, with associated RV dysfunction. In some patients, after an initially prolonged asymptomatic interval, the entire process may enter an accelerated phase as a result of left atrial and ventricular dysfunction and atrial fibrillation. In some instances, spontaneous rupture of MV chordae will occur (502). Infective endocarditis is a serious complication of MVP, which is the leading predisposing cardiovascular diagnosis in most series of patients reported with endocarditis (490,502,503). Because the absolute incidence of endocarditis is extremely low for the entire population with MVP, there is much controversy about the risk of endocarditis in MVP (504).

Fibrin emboli are responsible in patients with visual symptoms consistent with involvement of the ophthalmic or posterior cerebral circulation (505). Several studies have indicated an increased likelihood of cerebrovascular accidents in patients under age 45 years who have MVP beyond what would have been expected in a similar population without MVP (506).

Sudden death is a rare complication of MVP, occurring in fewer than 2% of known cases during long-term follow-up (495,500–511), with annual mortality rates less than 1% per year. The likely cause is a ventricular tachyarrhythmia, given the finding of increased incidence of complex ventricular ectopy on ambulatory ECG recordings in patients with MVP who had sudden death (512,513). Although infrequent, the highest incidence of sudden death has been reported in the familial form of MVP; some patients have also been noted to have QT prolongation (502,514).

3.5.2. Evaluation and Management of the Asymptomatic Patient (UPDATED)

CLASS I

1. Echocardiography is indicated for the diagnosis of MVP and assessment of MR, leaflet morphology, and ventricular compensation in asymptomatic patients with physical signs of MVP. *(Level of Evidence: B)*

CLASS IIa

1. Echocardiography can effectively exclude MVP in asymptomatic patients who have been diagnosed without clinical evidence to support the diagnosis. *(Level of Evidence: C)*
2. Echocardiography can be effective for risk stratification in asymptomatic patients with physical signs of MVP or known MVP. *(Level of Evidence: C)*

CLASS III

1. Echocardiography is not indicated to exclude MVP in asymptomatic patients with ill-defined symptoms in the absence of a constellation of clinical symptoms or physical findings suggestive of MVP or a positive family history. *(Level of Evidence: B)*
2. Routine repetition of echocardiography is not indicated for the asymptomatic patient who has MVP and no MR or MVP and mild MR with no changes in clinical signs or symptoms. *(Level of Evidence: C)*

The primary diagnostic evaluation of the patient with MVP is the physical examination (502,515). The principal auscultatory feature of this syndrome is the midsystolic click, a high-pitched sound of short duration. One or more clicks may vary considerably in intensity and timing in systole according to LV loading conditions and contractility. Clicks result from sudden tensing of the MV apparatus as the leaflets prolapse into the left atrium during systole. The midsystolic click may be followed by a late systolic murmur that is usually medium- to high-pitched and loudest at the cardiac apex. Occasionally the murmur has a musical or honking quality. The character and intensity of the murmur

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also vary under certain conditions, from brief and almost inaudible to holosystolic and loud. Dynamic auscultation is often useful for establishing the diagnosis of MVP syndrome (515). Changes in LV end-diastolic volume result in changes in the timing of the midsystolic click(s) and murmur. When end-diastolic volume is decreased (such as with standing), MVP occurs earlier in systole and the click–murmur complex occurs shortly after the first heart sound. In contrast, any maneuver that augments the volume of blood in the ventricle (such as squatting), reduces myocardial contractility, or increases LV afterload, lengthens the time from onset of systole to occurrence of MVP, and the click–murmur complex moves toward the second heart sound. MVP can be present in the absence of these classic auscultatory findings, and the clicks may be intermittent and variable.

Although the ECG may provide some information in patients with MVP, it is often normal. Nonspecific ST-T wave changes, T-wave inversions, prominent Q waves, and prolongation of the QT interval also occur. Continuous ambulatory ECG recordings or event monitors may be useful for documenting arrhythmias in patients with palpitations. They are not indicated as a routine test for asymptomatic patients. Most of the arrhythmias detected are not life threatening, and patients often complain of palpitations when the ambulatory ECG recording shows no abnormality.

Two-dimensional and Doppler echocardiography is the most useful noninvasive test for defining MVP. Valve prolapse of 2 mm or more above the mitral annulus in the long-axis parasternal view and other views, and especially when the leaflet coaptation occurs on the atrial side of the annular plane, indicates a high likelihood of MVP. There is disagreement concerning the reliability of echocardiographic appearance of anterior leaflet billowing when observed only in the apical 4-chamber view (496,516). Leaflet thickness of 5 mm or more indicates abnormal leaflet thickness and its added presence makes MVP even more certain. Leaflet redundancy is often associated with an enlarged mitral annulus and elongated chordae tendineae (502). The absence or presence of MR is an important consideration and MVP is more likely when MR is detected as a high velocity eccentric jet in late systole (517).

Reassurance is a major part of the management of patients with MVP. Patients with mild or no symptoms and findings of milder forms of prolapse should be reassured of the benign prognosis. A normal lifestyle and regular exercise is encouraged (502, 515).

3.5.3. Evaluation and Management of the Symptomatic Patient (UPDATED)

CLASS I

1. Aspirin therapy (75 to 325 mg per day) is recommended for symptomatic patients with MVP who experience cerebral transient ischemic attacks. *(Level of Evidence: C)*
2. In patients with MVP and atrial fibrillation, warfarin therapy is recommended for patients aged greater than 65 or those with hypertension, MR murmur, or a history of heart failure. *(Level of Evidence: C)*
3. Aspirin therapy (75 to 325 mg per day) is recommended for patients with MVP and atrial fibrillation who are less than 65 years old and have no history of MR, hypertension, or heart failure. *(Level of Evidence: C)*
4. In patients with MVP and a history of stroke, warfarin therapy is recommended for patients with MR, atrial fibrillation, or left atrial thrombus. *(Level of Evidence: C)*

CLASS IIa

1. In patients with MVP and a history of stroke who do not have MR, atrial fibrillation, or left atrial thrombus, warfarin therapy is reasonable for patients with echocardiographic evidence of thickening (5 mm or greater) and/or redundancy of the valve leaflets. *(Level of Evidence: C)*
2. In patients with MVP and a history of stroke, aspirin therapy is reasonable for patients who do not have MR, atrial fibrillation, left atrial thrombus, or echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets. *(Level of Evidence: C)*
3. Warfarin therapy is reasonable for patients with MVP with transient ischemic attacks despite aspirin therapy. *(Level of Evidence: C)*
4. Aspirin therapy (75 to 325 mg per day) can be beneficial for patients with MVP and a history of stroke who have contraindications to anticoagulants. *(Level of Evidence: B)*

CLASS IIb

1. Aspirin therapy (75 to 325 mg per day) may be considered for patients in sinus rhythm with echocardiographic evidence of high-risk MVP. *(Level of Evidence: C)*

Some patients consult their physicians about 1 or more of the common symptoms that occur with this syndrome: palpitations, often reported at a time when continuous ambulatory ECG recordings show no arrhythmias; atypical chest pain that rarely resembles classic angina pectoris; dyspnea and fatigue, when objective exercise testing often fails to show any impairment in exercise tolerance; and neuropsychiatric complaints, with many patients having panic attacks and similar syndromes (502). Bankier and Littman report that a significant number of patients with agoraphobia also have MVP; that 45% of patients with panic disorder have MVP; and that significant predictors for palpitations in these patients are depression, poor self-rated health, alcohol intoxication in women, and heavy coffee drinking and physical inactivity in men (519).

Transient cerebral ischemic episodes occur with increased incidence in patients with MVP, and some patients develop stroke syndromes. Reports of amaurosis fugax, homonymous field loss, and retinal artery occlusion have been described; occasionally, the visual loss persists (506,520–522).

The roles of cardiac auscultation and echocardiography in the assessment of symptomatic patients with mitral valve prolapse are the same as for patients without symptoms.

Patients with MVP and palpitations associated with mild tachyarrhythmias or increased adrenergic symptoms and those with chest pain, anxiety, or fatigue often respond to therapy with beta blockers (523). In many cases, however, the cessation of stimulants such as caffeine, alcohol, and

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cigarettes may be sufficient to control symptoms. In patients with recurrent palpitations, continuous or event-activated ambulatory ECG recordings may reveal the presence or absence of arrhythmias at the time of symptoms and indicate appropriate treatment of existing arrhythmias. The indications for electrophysiological testing are similar to those in the general population (e.g., aborted sudden death, recurrent syncope of unknown cause, and symptomatic or sustained ventricular tachycardia) (524).

Orthostatic symptoms due to postural hypotension and tachycardia are best treated with volume expansion, preferably by liberalizing fluid and salt intake. Mineralocorticoid therapy or clonidine may be needed in severe cases, and it may be beneficial to have the patient wear support stockings.

Daily aspirin therapy (75 to 325 mg per day) is recommended for MVP patients with documented transient focal neurological events who are in sinus rhythm with no atrial thrombi. Such patients also should avoid cigarettes and oral contraceptives. The American Stroke Association guidelines (524a) recommend aspirin for patients with MVP who have experienced an ischemic stroke (Class IIa, Level of Evidence: C), based on the evidence of efficacy of antiplatelet agents for general stroke patients. No randomized trials have addressed the efficacy of selected antithrombotic therapies for the specific subgroup of stroke patients with MVP. In the current guidelines, the committee recommends aspirin for those post-stroke patients with MVP who have no evidence of MR, atrial fibrillation, left atrial thrombus, or echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets. However, long-term anticoagulation therapy with warfarin is recommended (Class I) for post-stroke patients with MVP who have MR, atrial fibrillation, or left atrial thrombus. In the absence of these indications, warfarin is also recommended (Class IIa) in post-stroke patients with MVP who have echocardiographic evidence of thickening (5 mm or greater) or redundancy of the valve leaflets and in MVP patients who experience recurrent transient ischemic attacks while taking aspirin. In each of these situations, the international normalized ratio (INR) should be maintained between 2.0 and 3.0). In MVP patients with atrial fibrillation, warfarin therapy is indicated in patients aged greater than 65 years and in those with MR, hypertension, or a history of heart failure (INR 2.0 to 3.0). Aspirin therapy is satisfactory in patients with atrial fibrillation who are younger than 65 years old, have no MR, and have no history of hypertension or heart failure (525,526). Daily aspirin therapy is often recommended for patients with high-risk echocardiographic characteristics.

A normal lifestyle and regular exercise are encouraged for most patients with MVP, especially those who are asymptomatic (511,526). Whether exercise-induced ischemia develops in some patients with MVP remains controversial (527,528). Restriction from competitive sports is recommended when moderate LV enlargement, LV dysfunction, uncontrolled tachyarrhythmias, long-QT interval, unexplained syncope, prior resuscitation from cardiac arrest, or aortic root enlargement is present individually or in combination (502). A familial occurrence of MVP should be explained to the patient and is particularly important in those with associated disease who are at greater risk for complications. There is no contraindication to pregnancy based on the diagnosis of MVP alone.

Asymptomatic patients with MVP and no significant MR can be evaluated clinically every 3 to 5 years. Serial echocardiography is not necessary in most patients and is recommended only in patients who have high-risk characteristics on the initial echocardiogram and in those who develop symptoms consistent with cardiovascular disease or who have a change in physical findings that suggests development of significant MR. Patients who have high-risk characteristics, including those with moderate to severe MR, should be followed up once a year.

Patients with severe MR with symptoms or impaired LV systolic function require cardiac catheterization and evaluation for MV surgery (see Section 3.6.4.2). The thickened, redundant MV can often be repaired rather than replaced with a low operative mortality and excellent short- and long-term results (529,530). Follow-up studies also suggest lower thrombotic and endocarditis risk with valve repair than with prosthetic valves.

3.5.4. Surgical Considerations

Management of MVP may require valve surgery, particularly in those patients who develop a flail mitral leaflet due to rupture of chordae tendineae or their marked elongation. Most such valves can be repaired successfully by surgeons experienced in MV repair, especially when the posterior leaflet of the MV is predominantly affected. MV repair for MR due to MVP is associated with excellent long-term survival and remains superior to MV replacement beyond 10 years and up to 20 years after surgery (529,530). Anterior leaflet MV repair is associated with a higher risk for reoperation than posterior leaflet repair. As noted in Section 3.6.4.2, cardiologists are strongly encouraged to refer patients who are candidates for complex MV repair to surgical centers experienced in performing MV repair. Residual MR is associated with a higher risk for reoperation (530). Symptoms of heart failure, severity of MR, presence or absence of atrial fibrillation, LV systolic function, LV end-diastolic and end-systolic volumes, and pulmonary artery pressure (rest and exercise) all influence the decision to recommend MV surgery. Recommendations for surgery in patients with MVP and MR are the same as for those with other forms of nonischemic severe MR. For further detail, please review Section 7.3. on MV surgery.

3.6. Mitral Regurgitation

3.6.1. Etiology

The common causes of organic MR include MVP syndrome, rheumatic heart disease, CAD, infective endocardi-

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tis, certain drugs, and collagen vascular disease. MR may also occur secondary to a dilated annulus from dilatation of the left ventricle. In some cases, such as ruptured chordae tendineae, ruptured papillary muscle, or infective endocarditis, MR may be acute and severe. Alternatively, MR may worsen gradually over a prolonged period of time. These 2 ends of the spectrum have quite different clinical presentations.

3.6.2. Acute Severe Mitral Regurgitation

3.6.2.1. PATHOPHYSIOLOGY

In acute severe MR, a sudden volume overload is imposed on the left atrium and left ventricle. Acute volume overload increases LV preload, allowing for a modest increase in total LV stroke volume (531). However, in the absence of compensatory eccentric hypertrophy (which has had no time to develop), forward stroke volume and cardiac output are reduced. At the same time, the unprepared left atrium and left ventricle cannot accommodate the regurgitant volume, which causes large v waves in the left atrium and results in pulmonary congestion. In this phase of the disease, the patient has both reduced forward output (even shock) and simultaneous pulmonary congestion. In severe MR, the hemodynamic overload often cannot be tolerated, and MV repair or replacement must often be performed urgently.

3.6.2.2. DIAGNOSIS

The patient with acute severe MR is almost always severely symptomatic. Physical examination of the precordium may be misleading, because a normal-sized left ventricle does not produce a hyperdynamic apical impulse. The systolic murmur of MR may not be holosystolic and may even be absent. A third heart sound or early diastolic flow rumble may be the only abnormal physical finding present. Transthoracic echocardiography may demonstrate the disruption of the MV and help provide semiquantitative information on lesion severity; however, transthoracic echocardiography may underestimate lesion severity by inadequate imaging of the color flow jet. Thus, if there is hyperdynamic systolic function of the left ventricle on a transthoracic echocardiogram in a patient with acute heart failure, the suspicion of severe MR should be raised. Because transesophageal echocardiography can more accurately assess the color flow jet (532), transesophageal imaging should be performed if MV morphology and regurgitant severity are still in question after transthoracic echocardiography. Transesophageal echocardiography is also helpful in demonstrating the anatomic cause of acute severe MR and directing successful surgical repair.

In the hemodynamically stable patient, if CAD is suspected or there are risk factors for CAD (see Section 10.2), coronary arteriography is necessary before surgery because myocardial revascularization should be performed during MV surgery in those patients with concomitant CAD (533,534).

3.6.2.3. MEDICAL THERAPY

In acute severe MR, medical therapy has a limited role and is aimed primarily to stabilize hemodynamics in preparation for surgery. The goal of nonsurgical therapy is to diminish the amount of MR, in turn increasing forward output and reducing pulmonary congestion. In the normotensive patient, administration of nitroprusside may effectively accomplish all 3 goals. Nitroprusside increases forward output not only by preferentially increasing aortic flow but also by partially restoring MV competence as LV size diminishes (535,536). In the patient rendered hypotensive because of a severe reduction in forward output, nitroprusside should not be administered alone, but combination therapy with an inotropic agent (such as dobutamine) and nitroprusside is of benefit in some patients. In such patients, aortic balloon counterpulsation increases forward output and mean arterial pressure while diminishing regurgitant volume and LV filling pressure and can be used to stabilize the patient while they are prepared for surgery. If infective endocarditis is the cause of acute MR, identification and treatment of the infectious organism are essential.

3.6.3. Chronic Asymptomatic Mitral Regurgitation

3.6.3.1. PATHOPHYSIOLOGY AND NATURAL HISTORY

Patients with mild to moderate MR may remain asymptomatic with little or no hemodynamic compromise for many years; however, MR from a primary MV abnormality tends to progress over time with an increase in volume overload due to an increase in the effective orifice area. Progression of the MR is variable and determined by progression of lesions or mitral annulus size (537).

Once the MR has become severe, there has been time for development of eccentric cardiac hypertrophy in which new sarcomeres are laid down in series, which increases the length of individual myocardial fibers (228,531). The resulting increase in LV end-diastolic volume is compensatory because it permits an increase in total stroke volume, which allows for restoration of forward cardiac output (538). At the same time, the increase in LV and left atrial size allows accommodation of the regurgitant volume at a lower filling pressure, and the symptoms of pulmonary congestion abate. In this phase of compensated MR, the patient may be entirely asymptomatic, even during vigorous exercise. It should be noted that in the compensatory phase, augmented preload and reduced or normal afterload (provided by the unloading of the left ventricle into the left atrium) facilitate LV ejection, which results in a large total stroke volume and a normal forward stroke volume.

The compensated phase of MR is variable but may last for many years. However, the prolonged burden of volume overload may eventually result in LV dysfunction. In this phase, contractile dysfunction impairs ejection, and end-systolic volume increases. There may be further LV dilatation and increased LV filling pressure. These hemodynamic events result in reduced forward output and pulmonary congestion. However, the still favorable

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loading conditions often maintain ejection fraction in the low normal range (0.50 to 0.60) despite the presence of significant muscle dysfunction (531,539,540). Correction of MR should be performed before the advanced phases of LV decompensation.

Numerous studies indicate that patients with chronic severe MR have a high likelihood of developing symptoms or LV dysfunction over the course of 6 to 10 years (518,526,541,542). However, the incidence of sudden death in asymptomatic patients with normal LV function varies widely among these studies.

The natural history of severe MR due to a flail posterior leaflet has been documented (518). At 10 years, 90% of patients are dead or require MV operation. The mortality rate in patients with severe MR caused by flail leaflets is 6% to 7% per year. However, patients at risk of death are predominantly those with LV ejection fractions less than 0.60 or with NYHA functional class III–IV symptoms, and less so those who are asymptomatic and have normal LV function (518,543). Severe symptoms also predict a poor outcome after MV repair or replacement (543).

3.6.3.2. DIAGNOSIS

In evaluating the patient with chronic MR, the history is invaluable. A well-established estimation of baseline exercise tolerance is important in gauging the subtle onset of symptoms at subsequent evaluations. Physical examination should demonstrate displacement of the LV apical impulse, which indicates that MR is severe and chronic, producing cardiac enlargement. A third heart sound or early diastolic flow rumble is usually present and does not necessarily indicate LV dysfunction. Findings consistent with pulmonary hypertension are worrisome because they indicate advanced disease with worsened prognosis (544). An ECG and chest X-ray are useful in establishing rhythm and for assessment of the pulmonary vascularity and pulmonary congestion.

3.6.3.3. INDICATIONS FOR TRANSTHORACIC ECHOCARDIOGRAPHY

CLASS I

1. Transthoracic echocardiography is indicated for baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure, and severity of MR (Table 4) in any patient suspected of having MR. *(Level of Evidence: C)*
2. Transthoracic echocardiography is indicated for delineation of the mechanism of MR. *(Level of Evidence: B)*
3. Transthoracic echocardiography is indicated for annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate to severe MR. *(Level of Evidence: C)*
4. Transthoracic echocardiography is indicated in patients with MR to evaluate the MV apparatus and LV function after a change in signs or symptoms. *(Level of Evidence: C)*
5. Transthoracic echocardiography is indicated to evaluate LV size and function and MV hemodynamics in the initial evaluation after MV replacement or MV repair. *(Level of Evidence: C)*

CLASS IIa

1. Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity. *(Level of Evidence: C)*

CLASS III

1. Transthoracic echocardiography is not indicated for routine follow-up evaluation of asymptomatic patients with mild MR and normal LV size and systolic function. *(Level of Evidence: C)*

An initial comprehensive 2D, Doppler echocardiogram is indispensable in the management of the patient with MR. The echocardiogram provides a baseline estimation of LV and left atrial size, an estimation of LV ejection fraction, and approximation of the severity of regurgitation (2). Quantification of the severity of MR (Table 4) (27) is strongly recommended (27,541,545,546). In the majority of patients, an estimate of pulmonary artery pressure can be obtained from the TR peak velocity (547). Changes from these baseline values are subsequently used to guide the timing of MV surgery. The blood pressure at the time of each study should be documented, because the afterload on the ventricle will affect the measured severity of the MR.

The initial transthoracic echocardiogram should disclose the anatomic cause of the MR. A central color flow jet of MR with a structurally normal MV apparatus suggests the presence of functional MR, which may be due to annular dilatation from LV dilatation or tethering of the posterior leaflet because of regional LV dysfunction in patients with ischemic heart disease. An eccentric color flow jet of MR with abnormalities of the MV apparatus indicates organic MR. In patients with organic MR, the echocardiogram should assess the presence of calcium in the annulus or leaflets, the redundancy of the valve leaflets, and the MV leaflet involved (anterior leaflet, posterior leaflet, or bileaflet). These factors will help determine the feasibility of valve repair if surgery is contemplated. The system proposed by Carpentier (548) allows the echocardiographer to focus on the anatomic and physiologic characteristics of the valve that aid the surgeon in planning the repair. The valve dysfunction is described on the basis of the motion of the free edge of the leaflet relative to the plane of the annulus: type I, normal; type II, increased, as in MVP; type IIIA, restricted during systole and diastole, and type IIIB, restricted during systole.

The diagnosis of severe MR should be made by correlating the findings on physical examination with the findings from a comprehensive 2D, Doppler echocardiogram. Multiple parameters from the Doppler examination should be used to diagnose severe MR (Table 4) (27), including the color flow jet width and area, the intensity of the continuous-wave Doppler signal, the pulmonary venous flow contour, the peak early mitral inflow velocity, and quantitative measures of effective orifice area and regurgitation volume (2). In addition, there should be enlargement of the left ventricle and left atrium in chronic severe MR.

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Abnormalities of the MV apparatus are often present if there is severe MR, but ischemic LV dysfunction may also result in severe MR. If a discrepancy is present, or if the patient has poor windows on transthoracic echocardiography, then further evaluation of the severity of MR is required, including cardiac catheterization, magnetic resonance imaging, or transesophageal echocardiography.

3.6.3.4. INDICATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY (SEE ALSO SECTION 8.1.4.)

CLASS I

1. Preoperative or intraoperative transesophageal echocardiography is indicated to establish the anatomic basis for severe MR in patients in whom surgery is recommended to assess feasibility of repair and to guide repair. *(Level of Evidence: B)*
2. Transesophageal echocardiography is indicated for evaluation of MR patients in whom transthoracic echocardiography provides nondiagnostic information regarding severity of MR, mechanism of MR, and/or status of LV function. *(Level of Evidence: B)*

CLASS IIa

1. Preoperative transesophageal echocardiography is reasonable in asymptomatic patients with severe MR who are considered for surgery to assess feasibility of repair. *(Level of Evidence: C)*

CLASS III

1. Transesophageal echocardiography is not indicated for routine follow-up or surveillance of asymptomatic patients with native valve MR. *(Level of Evidence: C)*

3.6.3.5. SERIAL TESTING

The aim of serial follow-up of the patient with MR is to subjectively assess changes in symptomatic status and objectively assess changes in LV function and exercise tolerance that can occur in the absence of symptoms. Asymptomatic patients with mild MR and no evidence of LV enlargement, LV dysfunction, or pulmonary hypertension can be followed on a yearly basis with instructions to alert the physician if symptoms develop in the interim. Yearly echocardiography is not necessary unless there is clinical evidence that MR has worsened. In patients with moderate MR, clinical evaluation including echocardiography should be performed annually and sooner if symptoms occur.

Asymptomatic patients with severe MR should be followed up with history, physical examination, and echocardiography every 6 to 12 months to assess symptoms or transition to asymptomatic LV dysfunction. Exercise stress testing may be used to add objective evidence regarding symptoms and changes in exercise tolerance. Exercise testing is especially important if a good history of the patient's exercise capacity cannot be obtained. Measurement of pulmonary artery pressure and assessment of severity of MR during exercise may be helpful.

Interpretation of LV ejection fraction in the patient with MR is made difficult because the loading conditions present in MR facilitate ejection and increase ejection fraction, the standard guide to LV function. Nonetheless, several studies have indicated that the preoperative ejection fraction is an important predictor of postoperative survival in patients with chronic MR (539,544,549–551). Ejection fraction in a patient with MR with normal LV function is usually greater than or equal to 0.60. Consistent with this concept, postoperative ventricular function is lower and survival is reduced in patients with a preoperative ejection fraction less than 0.60 compared with patients with higher ejection fractions (550,551).

Alternatively or in concert, echocardiographic LV end-systolic dimension (or volume) can be used in the timing of MV surgery. End-systolic dimension, which may be less load dependent than ejection fraction (552), should be less than 40 mm preoperatively to ensure normal postoperative LV function (538,551–553). If patients become symptomatic, they should undergo MV surgery even if LV function is normal.

3.6.3.6. GUIDELINES FOR PHYSICAL ACTIVITY AND EXERCISE

Recommendations regarding participation in competitive athletics were published by the Task Force on Acquired Valvular Heart Disease of the 36th Bethesda Conference (138). Asymptomatic patients with MR of any severity who are in sinus rhythm and who have normal LV and left atrial dimensions and normal pulmonary artery pressure may exercise without restriction (138). However, those with definite LV enlargement (greater than or equal to 60 mm), pulmonary hypertension, or any degree of LV systolic dysfunction at rest should not participate in any competitive sports.

3.6.3.7. MEDICAL THERAPY

In the asymptomatic patient with chronic MR, there is no generally accepted medical therapy. Although intuitively, the use of vasodilators may appear to be logical for the same reasons that they are effective in acute MR, there are no large, long-term studies to indicate that they are beneficial. Furthermore, because MR with normal ejection fraction is a disease in which afterload is not increased (230,538,554,555), drugs that reduce afterload might produce a physiological state of chronic low afterload with which there is very little experience. There has not been a consistent improvement in LV volumes and severity of MR in the small studies that have examined the effect of ACE inhibitors (312,556–558). The beneficial effect seen in some studies may be more related to blockade of tissue angiotensin rather than the vasodilatory effect of the drug (559). Thus, in the absence of systemic hypertension, there is no known indication for the use of vasodilating drugs or ACE inhibitors in asymptomatic patients with MR and preserved LV function.

However, in patients with functional or ischemic MR (resulting from dilated or ischemic cardiomyopathy), there is reason to believe that preload reduction may be beneficial (535). If LV systolic dysfunction is present, primary treatment of the LV systolic dysfunction with drugs such as ACE inhibitors or beta blockers (particularly carvedilol) and biventricular pacing have all been shown to reduce the severity of functional MR (560–563).

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In patients with MR who develop symptoms but have preserved LV function, surgery is the most appropriate therapy. If atrial fibrillation develops, heart rate should be controlled with rate-lowering calcium channel blockers, beta blockers, digoxin, or, rarely, amiodarone. In patients with severe MR and chronic atrial fibrillation, a Maze procedure may be added to an MV repair (see Section 3.6.4.2.4), because this will reduce the risk of postoperative stroke. Although the risk of embolism with the combination of MR and atrial fibrillation was formerly considered similar to that of MS and atrial fibrillation, subsequent studies suggest that embolic risk may be less in MR (564,565). Nonetheless, it is recommended that the INR be maintained at 2 to 3 in this population.

3.6.3.8. INDICATIONS FOR CARDIAC CATHETERIZATION

CLASS I

1. Left ventriculography and hemodynamic measurements are indicated when noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery. *(Level of Evidence: C)*
2. Hemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR as assessed by noninvasive testing. *(Level of Evidence: C)*
3. Left ventriculography and hemodynamic measurements are indicated when there is a discrepancy between clinical and noninvasive findings regarding severity of MR. *(Level of Evidence: C)*
4. Coronary angiography is indicated before MV repair or MV replacement in patients at risk for CAD. *(Level of Evidence: C)*

CLASS III

1. Left ventriculography and hemodynamic measurements are not indicated in patients with MR in whom valve surgery is not contemplated. *(Level of Evidence: C)*

Cardiac catheterization, with or without exercise, is necessary when there is a discrepancy between clinical and noninvasive findings. Catheterization is also performed when surgery is contemplated in cases in which there is still some doubt about the severity of MR after noninvasive testing or when there is a need to assess extent and severity of CAD preoperatively. In patients with MR who have risk factors for CAD (e.g., advanced age, hypercholesterolemia, or hypertension) or when there is a suspicion that MR is ischemic in origin (either because of known myocardial infarction or suspected ischemia), coronary angiography should be performed before surgery.

Patients should usually not undergo valve surgery unless the degree of MR is severe. If there is a discrepancy regarding the severity of MR between the physical examination or elements of the comprehensive 2D, Doppler examination, then transesophageal echocardiography, magnetic resonance imaging, or left ventriculography should be performed. Although the standard semiquantitative approach to determining the severity of MR from ventriculography has its own limitations (566), ventriculography does provide an additional method to assess LV dilatation and function and gauge the severity of MR. Exercise hemodynamics may provide additional information that is helpful in decision making.

During the catheterization procedure, a right-heart catheterization should be performed if the severity of MR is uncertain to obtain right-sided pressures to quantify the increase in left atrial pressure (pulmonary artery wedge pressure) and pulmonary artery pressure. The presence or absence of a large v wave has little diagnostic impact when combined with data from the rest of the catheterization (567).

3.6.4. Indications for Surgery

3.6.4.1. TYPES OF SURGERY

Three different MV operations are currently used for correction of MR: 1) MV repair; 2) MV replacement with preservation of part or all of the mitral apparatus; and 3) MV replacement with removal of the mitral apparatus. Each procedure has its advantages and disadvantages, and therefore, the indications for each procedure are somewhat different.

In most cases, MV repair is the operation of choice when the valve is suitable for repair and appropriate surgical skill and expertise are available. This procedure preserves the patient's native valve without a prosthesis and therefore avoids the risk of chronic anticoagulation (except in patients in atrial fibrillation) or prosthetic valve failure late after surgery. Additionally, preservation of the mitral apparatus leads to better postoperative LV function and survival than in cases in which the apparatus is disrupted (545,568–573). Improved postoperative function occurs with repair because the mitral apparatus is an integral part of the left ventricle that is essential for maintenance of normal shape, volume, and function of the left ventricle (574). However, MV repair is technically more demanding than MV replacement, may require longer extracorporeal circulation time, and may occasionally fail. Valve morphology and surgical expertise are of critical importance for the success of valve repair (see below).

The reoperation rate after MV repair is similar to the reoperation rate after MV replacement (530). There is a 7% to 10% reoperation rate at 10 years in patients undergoing MV repair, usually for severe recurrent MR (530,575–578). Approximately 70% of the recurrent MR is thought to be due to the initial procedure and 30% to progressive valve disease (575). The reoperation rate is lower in those patients who had the initial operation for posterior leaflet abnormalities than in those who had bileaflet or anterior leaflet abnormalities (518,577).

The advantage of MV replacement with preservation of the chordal apparatus is that this operation ensures postoperative MV competence, preserves LV function, and enhances postoperative survival compared with MV replacement, in which the apparatus is disrupted (570,579–582). The disadvantage is the use of a prosthetic valve, with the risks of deterioration inherent in tissue valves or the need for anticoagulation inherent in mechanical valves.

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MV replacement in which the MV apparatus is resected should almost never be performed. It should only be performed in those circumstances in which the native valve and apparatus are so distorted by the preoperative pathology (rheumatic disease, for example) that the mitral apparatus cannot be spared. As noted previously (Section 3.4.9), artificial chordal reconstruction does extend the opportunities for repair in some such patients with rheumatic MR (467,468).

The advantages of MV repair make it applicable across the full spectrum of MR, including the 2 extremes of the spectrum. Valve repair might be possible in patients with far-advanced symptomatic MR and depressed LV function because it preserves LV function at the preoperative level (572); MV replacement with disruption of the apparatus in such patients could lead to worsened or even fatal LV dysfunction after surgery. At the other extreme, in the relatively asymptomatic patient with well-preserved LV function, repair of a severely regurgitant valve might be contemplated to avoid the onset of ventricular dysfunction from longstanding volume overload (583). However, failed MV repair would result in the need for a prosthetic valve; this would represent a clear complication, because it would impose the risks of a prosthesis on a patient who did not previously require it. Hence, "prophylactic" surgery in an asymptomatic patient with MR and normal LV function requires a high likelihood of successful repair.

3.6.4.2. INDICATIONS FOR MITRAL VALVE OPERATION

CLASS I

1. MV surgery is recommended for the symptomatic patient with acute severe MR.* *(Level of Evidence: B)*
2. MV surgery is beneficial for patients with chronic severe MR* and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction less than 0.30) and/or end-systolic dimension greater than 55 mm. *(Level of Evidence: B)*
3. MV surgery is beneficial for asymptomatic patients with chronic severe MR* and mild to moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end-systolic dimension greater than or equal to 40 mm. *(Level of Evidence: B)*
4. MV repair is recommended over MV replacement in the majority of patients with severe chronic MR* who require surgery, and patients should be referred to surgical centers experienced in MV repair. *(Level of Evidence: C)*

CLASS IIa

1. MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR* with preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom the likelihood of successful repair without residual MR is greater than 90%. *(Level of Evidence: B)*
2. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and new onset of atrial fibrillation. *(Level of Evidence: C)*
3. MV surgery is reasonable for asymptomatic patients with chronic severe MR,* preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest or greater than 60 mm Hg with exercise). *(Level of Evidence: C)*
4. MV surgery is reasonable for patients with chronic severe MR* due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction less than 0.30 and/or end-systolic dimension greater than 55 mm) in whom MV repair is highly likely. *(Level of Evidence: C)*

CLASS IIb

1. MV repair may be considered for patients with chronic severe secondary MR* due to severe LV dysfunction (ejection fraction less than 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing. *(Level of Evidence: C)*

CLASS III

1. MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) in whom significant doubt about the feasibility of repair exists. *(Level of Evidence: C)*
2. Isolated MV surgery is not indicated for patients with mild or moderate MR. *(Level of Evidence: C)*

In many cases, the type of operation, MV repair versus replacement, is important in timing surgery. In fact, although the type of surgery to be performed is never actually established until the operation, many situations lend themselves to preoperative prediction of the operation that can be performed. This prediction is based on the skill and experience of the surgeon in performing repair and on the location and type of MV disease that caused the MR. Nonrheumatic posterior leaflet prolapse due to degenerative MV disease or a ruptured chordae tendineae can usually be repaired using a resection of the portion of the valve and an annuloplasty (584,585). Involvement of the anterior leaflet or both anterior and posterior leaflets diminishes the likelihood of repair because the operation requires other interventions, such as chordal shortening, chordal transfer, and innovative anatomic repairs (586–591). Consequently, the skill and experience of the surgeon are probably the most important determinants of the eventual operation that will be performed. In general, rheumatic involvement of the MV and calcification of the MV leaflets or annulus diminish the likelihood of repair, even in experienced hands (592).

The number of patients undergoing MV repair for MR has increased steadily over the past decade in the United States and Canada in relation to the number undergoing MV replacement. However, among isolated MV procedures reported in the STS National Cardiac Database from 1999 to 2000 (593), the frequency of repair was only 35.7% (3027 of a total of 8486 procedures), which suggests that MV repair is underutilized. The STS National Database also indicates an operative mortality rate of under 2% in patients undergoing isolated MV repair in 2004, which compares favorably to the greater than 6% operative mortality rate for patients undergoing isolated MV replacement (165). Considering the beneficial effect of MV repair on survival and

*See Table 4 (27).

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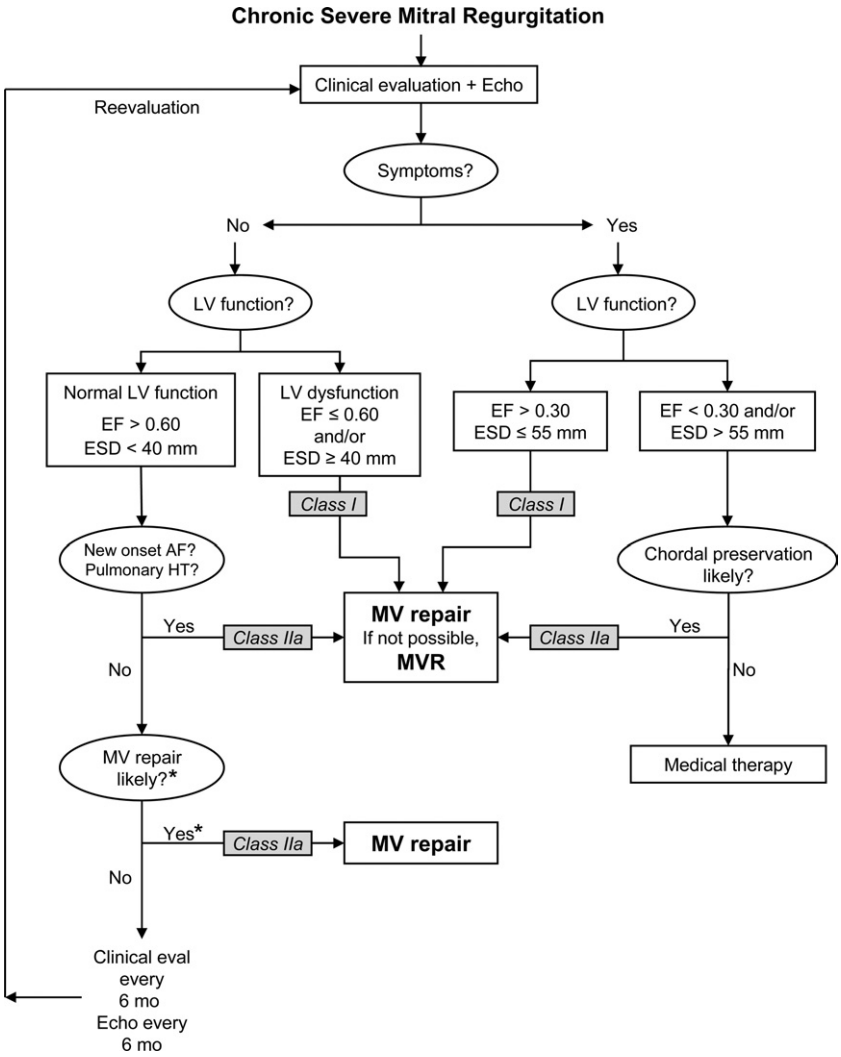

Figure 8. Management Strategy for Patients With Chronic Severe Mitral Regurgitation

*Mitral valve (MV) repair may be performed in asymptomatic patients with normal left ventricular (LV) function if performed by an experienced surgical team and if the likelihood of successful MV repair is greater than 90%. AF indicates atrial fibrillation; Echo, echocardiography; EF, ejection fraction; ESD, end-systolic dimension; eval, evaluation; HT, hypertension; and MVR, mitral valve replacement.

LV function, cardiologists are strongly encouraged to refer patients who are candidates for MV repair to surgical centers experienced in performing MV repair.

3.6.4.2.1. SYMPTOMATIC PATIENTS WITH NORMAL LEFT VENTRICULAR FUNCTION. Patients with symptoms of congestive heart failure despite normal LV function on echocardiography (ejection fraction greater than 0.60 and end-systolic dimension less than 40 mm) require surgery. Surgery should be performed in patients with mild symptoms and severe MR (Fig. 8), especially if it appears that MV repair rather than replacement can be performed. The feasibility of repair is dependent on several factors, including valve anatomy and surgical expertise. Successful surgical repair improves symptoms, preserves LV function, and avoids the problems of a prosthetic valve. When repair is not feasible, MV replacement with chordal preservation should relieve symptoms and maintain LV function.

3.6.4.2.2. ASYMPTOMATIC OR SYMPTOMATIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION. Preoperative variables that are predictive of postoperative survival, symptomatic improvement, and postoperative LV function are summarized in Table 21 (538,539,544,549–552). The timing of surgery for asymptomatic patients is controversial, but most would now agree that MV surgery is indicated with the appearance of echocardiographic indicators of LV dysfunction. These include LV ejection fraction less than or equal to 0.60 and/or LV end-systolic dimension greater than or equal to 40 mm (Fig. 8). Surgery performed at this time will likely prevent further deterioration in LV function and improve longevity. This is true whether repair or replacement is performed (551), although repair is clearly preferred. It must be emphasized that, unlike with the timing of AVR for AR, LV ejection fraction should not be allowed to fall into the lower limit of the normal range in patients

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Table 21. Preoperative Predictors of Surgical Outcome in Mitral Regurgitation

Study, Year	Study Design	Type of Surgery	No. of Patients	Outcome Assessed	Findings
Schuler et al., 1979 (539)	Retrospective	MVR	20	LV function	12 Patients with average LV EF 0.70 had normal postoperative EF; 4 patients with average EF 0.58 had postoperative EF 0.25
Phillips et al., 1981 (549)	Retrospective	MVR	105	Survival	EF less than 0.50 predicted poor survival
Zile et al., 1984 (538)	Prospective	MVR	16	Heart failure, LV function	LV ESD index greater than 2.6 cm per m^2 (45 mm) and LV FS less than 0.32 predicted poor outcome
Crawford et al., 1990 (544)	Prospective	MVR	48	Survival, LV function	LV EF less than 0.50 predicted reduced survival; ESV less than 50 ml per m^2 predicted persistent LV dilatation
Wisenbaugh et al., 1994 (552)	Registry	MVR	26	Survival, LV function	ESD, EDD, and FS predicted poor survival and LV function; only ESD significant in multivariate analysis
		MVR-CP	35		
Enriquez-Sarano et al., 1994 (550)	Retrospective	MVR	214	Survival	LV EF 0.60 or less predicted poor survival whether MVR or CP was performed; EF estimated by echo FS or visual analysis
		MV repair	195		
Enriquez-Sarano et al., 1994 (551)	Retrospective	MVR	104	LV function	EF, ESD, LV diameter/thickness ratio, and end-systolic wall stress predicted outcome; EF estimated by echo FS or visual analysis
		MV repair	162		

CP indicates chordal sparing procedure; echo, echocardiographic; EDD, end-diastolic dimension; EF, ejection fraction; ESD, end-systolic dimension; ESV, end-systolic volume; FS, fractional shortening; LA, left atrial; LV, left ventricular; MV, mitral valve; MVR, mitral valve replacement; PAWP, pulmonary artery wedge pressure.

with chronic MR (551,594–596). The data regarding postoperative survival are much stronger with LV ejection fraction than with end-systolic dimension (544,549–551), whereas both ejection fraction and end-systolic dimension strongly influence postoperative LV function and heart failure (538,539,544,551,552). MV surgery should also be recommended for symptomatic patients with evidence of LV systolic dysfunction (ejection fraction less than or equal to 0.60, and/or end-systolic dimension greater than or equal to 40 mm).

Determining the surgical candidacy of the symptomatic patient with MR and far-advanced LV dysfunction is a common clinical dilemma. The question that often arises is whether the patient with MR has such advanced LV dysfunction that he or she is no longer a candidate for surgery. Often such cases present difficulty in distinguishing primary cardiomyopathy with secondary MR from primary MR with secondary myocardial dysfunction. In the latter case, if MV repair appears likely, surgery should still be contemplated (Fig. 8). Even though such a patient is likely to have persistent LV dysfunction, surgery is likely to improve symptoms and prevent further deterioration of LV function (328). If MV replacement is necessary in such patients, it should be performed only if the chordal apparatus can be preserved. The modification of MV geometry by an "undersized" annular ring in patients with severe LV dysfunction and significant functional MR may be beneficial in a subset of patients with primary myocardial disease (597–602), although the impact on outcomes compared with aggressive medical therapy, including beta blockers and cardiac resynchronization therapy (560–563), has not been studied in a prospective randomized trial.

3.6.4.2.3. ASYMPTOMATIC PATIENTS WITH NORMAL LEFT VENTRICULAR FUNCTION. As noted previously, repair of a severely regurgitant valve may be contemplated in an asymptomatic patient with severe MR and normal LV function to preserve LV size and function and prevent the sequelae of chronic severe MR (541). Although there are no randomized data with which to recommend this approach to all patients, the committee recognizes that some experienced centers are moving in this direction for patients for whom the likelihood of successful repair is high. Natural history studies indicate uniformly that asymptomatic patients with severe MR and normal LV function have a high likelihood of developing symptoms and/or LV dysfunction warranting operation over the course of 6 to 10 years (518,526,541,542). Two recent studies have also addressed the risk of sudden death (541,542) in asymptomatic patients with severe MR and normal LV function. In a long-term retrospective study in which severity of MR was quantified by Doppler echocardiography (541), 198 patients with an effective orifice area greater than 40 mm^2 had a 4% per year risk of cardiac death during a mean follow-up period of 2.7 years. However, in the second study of 132 patients followed up prospectively for 5 years, during which the indications for surgery were symptoms, development of LV dysfunction (ejection fraction less than 0.60), LV dilatation (LV end-systolic dimension greater than 45 mm), atrial fibrillation, or pulmonary hypertension, there was only 1 cardiac death in an asymptomatic patient, but this patient

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had refused surgery which was indicated by development of LV dilation (542).

MV repair is often recommended in hemodynamically stable patients with newly acquired severe MR, such as might occur with ruptured chordae. Surgery is also recommended in an asymptomatic patient with chronic MR with recent onset of atrial fibrillation in whom there is a high likelihood of successful valve repair (see below).

Surgery for asymptomatic patients with severe MR and normal LV function should only be considered if there is a greater than 90% likelihood of successful valve repair in a center experienced in this procedure. As noted above, cardiologists are strongly encouraged to refer patients who are candidates for MV repair to surgical centers experienced in performing MV repair.

3.6.4.2.4. ATRIAL FIBRILLATION. Atrial fibrillation is a common, potentially morbid arrhythmia associated with MR. In patients with MR due to MVP, there is a high risk of development of atrial fibrillation. The development of atrial fibrillation is independently associated with a high risk of cardiac death or heart failure (603). Preoperative atrial fibrillation is an independent predictor of reduced long-term survival after MV surgery for chronic MR (551,603–605). The persistence of atrial fibrillation after MV surgery can lead to thromboembolism and partially nullifies an advantage of mitral repair by requiring anticoagulation (605). Predictors of the persistence of atrial fibrillation after successful valve surgery are the presence of atrial fibrillation for greater than 1 year and left atrial size greater than 50 mm (606). In 1 study, an even shorter duration of preoperative atrial fibrillation (3 months) was a predictor of persistent atrial fibrillation after MV repair (607); persistent atrial fibrillation after surgery occurred in 80% of patients with preoperative atrial fibrillation greater than or equal to 3 months but in no patient with preoperative atrial fibrillation less than 3 months. Although patients who develop atrial fibrillation also usually manifest other symptomatic or functional changes that would warrant MV operation, many clinicians would consider the recent onset of atrial fibrillation to be an indication in and of itself for surgery, if there is a high likelihood of valve repair (Fig. 8) (582,607). In patients presenting for MV operation with chronic atrial fibrillation, a concomitant Maze procedure may prevent future thromboembolic events by restoring normal sinus rhythm (608–614). The decision to proceed with a Maze procedure should be based on the age and health of the patient, as well as the surgical expertise, because this procedure may add to the morbidity of the operation.

3.6.5. Ischemic Mitral Regurgitation

The outlook for the patient with ischemic MR is substantially worse than that for regurgitation from other causes (533,615). A worse prognosis accrues from the fact that ischemic MR is usually caused by LV dysfunction resulting from myocardial infarction. Furthermore, the MV itself is usually anatomically normal, and MR is secondary to papillary muscle displacement and tethering of the mitral leaflet(s). The mechanism of MR in chronic ischemic disease is local LV remodeling (apical and posterior displacement of papillary muscles), which leads to excess valvular tenting and loss of systolic annular contraction (616–623). The indication for MV operation in the patient who undergoes CABG with mild to moderate MR is still unclear, but there are data to indicate benefit of MV repair in such patients (624–627). Patients with ischemic heart disease who have MR have a worse prognosis than those who do not have MR (628–631). CABG alone may improve LV function and reduce ischemic MR in selected patients (629,632), especially those with transient severe MR due to ischemia, in whom myocardial revascularization can eliminate episodes of severe MR. However, CABG alone is usually insufficient and leaves many patients with significant residual MR, and these patients would benefit from concomitant MV repair at the time of the CABG (623–627,633–642). Mitral annuloplasty alone with a downsized annuloplasty ring is often effective at relieving MR (637,638,641).

In severe MR secondary to acute myocardial infarction, hypotension and pulmonary edema often occur. Severe MR occurs in 6% to 7% of patients with cardiogenic shock (643). The cause of the MR should be established, because the MR may be due to a ruptured papillary muscle, papillary muscle displacement with leaflet tethering, or annular dilatation from severe LV dilatation. Those patients with an acute rupture of the papillary muscle should undergo surgery on an emergency basis, with either valve repair or MV replacement (644). In those patients with papillary muscle dysfunction, treatment should initially consist of hemodynamic stabilization, usually with insertion of an intra-aortic balloon pump. Surgery should be considered for those patients who do not improve with aggressive medical therapy. Correction of acute severe ischemic MR usually requires valve surgery in addition to revascularization. The best operation for ischemic MR is controversial (645,646), but MV repair with an annuloplasty ring is the best approach in most instances (624,627,633–642).

3.6.6. Evaluation of Patients After Mitral Valve Replacement or Repair

After MV surgery, follow-up is necessary to detect late surgical failure and assess LV function, as discussed in Section 9.3. For patients in whom a bioprosthesis has been inserted, the specter of eventual deterioration is always present and must be anticipated. If a mechanical valve has been inserted, anticoagulation is required, and chronic surveillance of prothrombin time and INR is necessary. After valve repair, follow-up to assess the effectiveness of the repair is indicated early, especially because most repair failures are detected soon after surgery.

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3.6.7. Special Considerations in the Elderly

Elderly patients with MR fare more poorly with valve surgery than do their counterparts with AS. In general, operative mortality increases and survival is reduced in patients older than 75 years of age, especially if MV replacement must be performed or if the patient has concomitant CAD or other valve lesions (164,167,545,647–650). Operative mortality in the elderly is low in experienced centers (651), but the overall operative mortality for MV replacement in this age group in the United States exceeds 14% (167,649,650) and is particularly high (greater than 20%) in low-volume centers (167). Although the risks are reduced if MV repair is performed rather than MV replacement, the majority of patients in this age group require concomitant CABG (650). The average operative risk for combined MV repair plus CABG in the United States is 8% (165), which will undoubtedly be higher in the older population. These risks are worth taking in patients with significant symptoms. However, under most circumstances, asymptomatic patients or patients with mild symptoms should be treated medically.

3.7. Multiple Valve Disease

3.7.1. Introduction

Remarkably few data exist to objectively guide the management of mixed valve disease. The large number of combined hemodynamic disturbances (and their varied severity) yields a large number of potential combinations to consider, and few data exist for any specific category. Hence, each case must be considered individually, and management must be based on understanding the potential derangements in hemodynamics and LV function and the probable benefit of medical versus surgical therapy. Other than recommending evaluation with physical examination, echocardiography, and cardiac catheterization as clinically indicated for patient evaluation and management, the committee has developed no specific recommendations in this section.

3.7.2. Mixed Single Valve Disease

3.7.2.1. PATHOPHYSIOLOGY

In mixed mitral or aortic valve disease, 1 lesion usually predominates over the other, and the pathophysiology resembles that of the pure dominant lesion. Thus, for the patient with mixed AS and AR in whom stenosis predominates, the pathophysiology and management resemble that of pure AS. The left ventricle develops concentric hypertrophy rather than dilatation. The timing of AVR is based on symptomatic status. However, if the attendant regurgitation is more than mild, it complicates the pathophysiology by placing the concentrically hypertrophied and noncompliant left ventricle on a steeper portion of its diastolic pressure-volume curve, in turn causing pulmonary congestion. The effect is that neither lesion by itself might be considered severe enough to warrant surgery, but both together produce substantial hemodynamic compromise that necessitates intervention.

In patients with severe AR and mild AS, the high total stroke volume due to extensive regurgitation may produce a substantial transvalvular gradient. Because the transvalvular gradient varies with the square of the transvalvular flow (139), a high gradient in predominant AR may be predicated primarily on excess transvalvular flow rather than on a severely compromised orifice area.

In mixed mitral disease, predominant MS produces a left ventricle of normal volume, whereas in predominant MR, chamber dilatation occurs. A substantial transvalvular gradient may exist in regurgitation-predominant disease because of high transvalvular flow, but, as in mixed aortic valve disease with predominant regurgitation, the gradient does not represent severe orifice stenosis.

3.7.2.2. DIAGNOSIS

3.7.2.2.1. TWO-DIMENSIONAL AND DOPPLER ECHOCARDIOGRAPHIC STUDIES. As noted above, chamber geometry is important in assessing the dominant lesion (stenotic versus regurgitant), which in turn is important in management. For instance, a small left ventricle is inconsistent with chronic severe regurgitation. Doppler interrogation of the aortic valve and MVs with mixed disease should provide a reliable estimate of the transvalvular mean gradient; however, there may be a significant discrepancy between the Doppler-derived maximum instantaneous gradient and catheter peak gradient with mixed aortic valve disease. Exercise hemodynamics derived by Doppler echocardiography have been helpful in managing mixed valve disease. MV area can be measured accurately by the half-time method in mixed MS/MR. Aortic valve area would be measured inaccurately at the time of cardiac catheterization in mixed AS/AR if cardiac output were measured by either thermodilution or the Fick method. The valve area can be measured more accurately by the continuity equation from Doppler echocardiography in mixed AS/AR; however, the continuity equation calculation of valve area may not be completely independent of flow (652). Although these valve area measurements by Doppler echocardiography are more accurate than those obtained at cardiac catheterization, in general, the confusing nature of mixed valve disease makes cardiac catheterization necessary to obtain additional hemodynamic information in most patients.

3.7.2.2.2. CARDIAC CATHETERIZATION. Catheterization is often necessary to fully assess hemodynamics. The diagnosis of "moderate" mixed disease is frequently made on the basis of noninvasive tests alone. This term suggests that the valve disease is not severe enough to mandate surgery. However, as noted previously, the nondominant lesion may exacerbate the pathophysiology of the dominant lesion and produce symptoms. In this context, a complete hemodynamic evaluation that includes exercise hemodynamics may be important. For example, resting hemodynamics in mixed mitral disease might show a transmitral gradient of 5 mm Hg, a

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valve area of 1.5 cm^2, and 2+ MR, with a resting pulmonary artery wedge pressure of 15 mm Hg. However, with exercise, the wedge pressure can increase dramatically, identifying a hemodynamic cause for the patient's symptoms and suggesting that mechanical correction will be of benefit. Many cases of mixed valve disease require hemodynamic exercise testing to delineate proper assessment (653).

Hemodynamic estimation of valve area requires determination of total valve flow and transvalvular gradient. The presence of valvular regurgitation in a primarily stenotic valve causes forward cardiac output to underestimate total valve flow, which is the sum of forward plus regurgitant flow. Thus, if standard measures of forward cardiac output (e.g., thermodilution or Fick method) are used to calculate valve area, the area will be underestimated. One approach to this problem is to use total stroke volume (angiographic end-diastolic volume minus end-systolic volume) in place of forward stroke volume (Fick or thermodilution cardiac output/heart rate) in the Gorlin formula. Although this approach is logically valid, it has not been clinically tested or vetted against a "gold standard." Furthermore, angiographic stroke volume is dependent on accurate calculation of cardiac volumes, which can be difficult in the very large and/or spherical left ventricles encountered in valvular regurgitation (654). In general, the utility of this approach is limited. Doppler pressure half-time may be very useful in this situation.

3.7.2.3. MANAGEMENT

Unlike the management of a severe pure valve lesion, solid guidelines for mixed disease are difficult to establish. The most logical approach is to surgically correct disease that produces more than mild symptoms or, in the case of -dominant aortic valve disease, to operate in the presence of even mild symptoms. In regurgitant dominant lesions, surgery can be delayed until symptoms develop or asymptomatic LV dysfunction (as gauged by markers used in pure regurgitant disease) becomes apparent. The use of vasodilators to forestall surgery in patients with asymptomatic mixed disease is untested. Anticoagulants should be used in mixed mitral disease if atrial fibrillation is present. In mixed mitral disease with moderate or severe (3+ to 4+) regurgitation, percutaneous mitral balloon valvotomy is contraindicated because regurgitation may worsen.

3.7.3. Combined Mitral Stenosis and Aortic Regurgitation

3.7.3.1. PATHOPHYSIOLOGY

When both AR and MS coexist, severe MS usually coexists with mild AR with pathophysiology similar to that of isolated MS. However, the coexistent AR is occasionally severe. The combination of coexistent severe MS and severe AR may present confusing pathophysiology and often leads to misdiagnosis. MS restricts LV filling, blunting the impact of AR on LV volume (341). Thus, even severe AR may fail to cause a hyperdynamic circulation, so that typical signs of AR are absent during physical examination. Likewise, echocardiographic LV cavitary dimensions may be only mildly enlarged. Doppler half-time measurements of MV area may be inaccurate in the presence of significant AR. The picture presented by this complex combination of lesions usually requires all diagnostic modalities, including cardiac catheterization, for resolution.

3.7.3.2. MANAGEMENT

Mechanical correction of both lesions is eventually necessary in most patients. Development of symptoms or pulmonary hypertension is the usual indication for intervention. Combined aortic valve and MV replacement is a reasonable approach, but when correction is anticipated in patients with predominant MS, balloon mitral valvotomy followed by AVR may be performed. This obviates the need for double-valve replacement, which has a higher risk of perioperative mortality and postoperative complications than single-valve replacement (165). In most cases, it is advisable to perform mitral valvotomy first and then monitor the patient for symptomatic improvement. If symptoms disappear, correction of AR can be delayed.

3.7.4. Combined Mitral Stenosis and Tricuspid Regurgitation

3.7.4.1. PATHOPHYSIOLOGY

When TR coexists with MS, some elements of pulmonary hypertension are also usually present. Thus, the issue arises whether TR will or will not improve when MS is corrected and pulmonary artery pressure decreases (655). Unfortunately, the status of the tricuspid valve after correction of MS is difficult to predict. In general, if pulmonary hypertension is severe and the tricuspid valve anatomy is not grossly distorted, improvement in TR can be expected after correction of MS (656). On the other hand, if there is severe rheumatic deformity of the tricuspid valve, dilatation of the tricuspid annulus, or severe TR, competence is likely to be restored only by surgery.

3.7.4.2. DIAGNOSIS

Once TR is suspected by physical examination to coexist with MS, both can be further evaluated by Doppler echocardiographic studies. The presence of TR almost guarantees that an estimation of pulmonary artery pressure can be made by Doppler interrogation of the tricuspid valve. An evaluation of the anatomy of both the mitral and tricuspid valves can be made.

3.7.4.3. MANAGEMENT

If the MV anatomy is favorable for percutaneous balloon valvotomy and there is concomitant pulmonary hypertension, valvotomy should be performed regardless of symptom status. After successful mitral valvotomy, pulmonary hypertension and TR almost always diminish (656).

If MV surgery is performed, concomitant tricuspid annuloplasty should be considered, especially if there are preoperative signs or symptoms of right-sided heart failure,

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rather than risking severe persistent TR, which may necessitate a second operation (657). If intraoperative assessment suggests that TR is functional without significant dilatation of the tricuspid annulus, it may not be necessary to perform an annuloplasty. However, there is growing evidence that TR associated with dilatation of the tricuspid annulus should be repaired (658,659). Tricuspid dilatation is an ongoing process that may progress to severe TR if untreated. Annuloplasty of the tricuspid valve based on tricuspid dilatation improves functional status independent of the degree of TR (658). Residual TR after tricuspid annuloplasty is determined principally by the degree of preoperative tricuspid leaflet tethering (660).

3.7.5. Combined Mitral Regurgitation and Aortic Regurgitation

3.7.5.1. PATHOPHYSIOLOGY

As noted in the previous discussions of isolated MR and AR, these are 2 very different diseases with different pathophysiological effects and different guidelines for the timing of surgery. Thus, in the patient with double-valve regurgitation, proper management becomes problematic. The most straightforward approach is the same as for mixed single-valve disease, that is, to determine which lesion is dominant and to treat primarily according to that lesion. Although both lesions produce LV dilatation, AR will produce modest systemic systolic hypertension and a mild increase in LV wall thickness.

3.7.5.2. DIAGNOSIS AND THERAPY

Doppler echocardiographic interrogation shows bivalve regurgitation and an enlarged left ventricle. 2D echocardiography is usually performed to assess the severity of AR and MR, LV size and function, left atrial size, pulmonary artery pressure, and feasibility of MV repair. When surgery is required, AVR plus MV repair is the preferred strategy when MV repair is possible (661).

3.7.6. Combined Mitral Stenosis and Aortic Stenosis

3.7.6.1. PATHOPHYSIOLOGY

Combined stenotic disease is almost always secondary to rheumatic heart disease. Obstruction of flow at the MV diminishes aortic valve flow as well. Thus, the problem of evaluating aortic valve severity in a low-flow/low-gradient situation often exists.

3.7.6.2. DIAGNOSIS AND THERAPY

In patients with significant AS and MS, the physical findings of AS generally dominate, and those of MS may be overlooked, whereas the symptoms are usually those of MS. Noninvasive evaluation should be performed with 2D and Doppler echocardiographic studies to evaluate the severity of AS and MS, paying special attention to suitability for mitral balloon valvotomy in symptomatic patients, and to assess ventricular size and function. If the degree of AS appears to be mild and the MV is acceptable for balloon valvotomy, this should be attempted first. If mitral balloon valvotomy is successful, the aortic valve should then be re-evaluated.

3.7.7. Combined Aortic Stenosis and Mitral Regurgitation

3.7.7.1. PATHOPHYSIOLOGY

Combined AS and MR often develop secondary to rheumatic heart disease. However, congenital AS and MVP may occur in combination in younger patients, as may degenerative AS and MR in the elderly. If severe, AS will worsen the degree of MR. In addition, MR may cause difficulty in assessing the severity of AS because of reduced forward flow. MR will also enhance LV ejection performance, thereby masking the early development of LV systolic dysfunction caused by AS. Development of atrial fibrillation and loss of atrial systole may further reduce forward output because of impaired filling of the hypertrophied left ventricle.

3.7.7.2. DIAGNOSIS AND THERAPY

Noninvasive evaluation should be performed with 2D and Doppler echocardiography to evaluate the severity of both AS and MR. Attention should be paid to LV size, wall thickness, and function; left atrial size; right-heart function; and pulmonary artery pressure. Particular attention should be paid to MV morphology in patients with these combined lesions. Patients with severe AS and severe MR (with abnormal MV morphology) with symptoms, LV dysfunction, or pulmonary hypertension should undergo combined AVR and MV replacement or MV repair. AVR plus MV repair is the preferred strategy when MV repair is possible (661). However, in patients with severe AS and lesser degrees of MR, the severity of MR may improve greatly after isolated AVR, particularly when there is normal MV morphology. Intraoperative transesophageal echocardiography and, if necessary, visual inspection of the MV should be performed at the time of AVR to determine whether additional MV surgery is warranted in these patients.

In patients with mild to moderate AS and severe MR in whom surgery on the MV is indicated because of symptoms, LV dysfunction, or pulmonary hypertension, preoperative assessment of the severity of AS may be difficult because of reduced forward stroke volume. If the mean aortic valve gradient is greater than 30 mm Hg, AVR should be performed. In patients with less severe aortic valve gradients, inspection of the aortic valve and its degree of opening on 2D or transesophageal echocardiography and visual inspection by the surgeon may be important in determining the need for concomitant AVR.

3.8. Tricuspid Valve Disease

3.8.1. Pathophysiology

Tricuspid valve dysfunction can occur with normal or abnormal valves. When normal tricuspid valves develop dysfunction, the resulting hemodynamic abnormality is almost always pure regurgitation. This occurs with elevation

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of RV systolic and/or diastolic pressure, RV cavity enlargement, and tricuspid annular dilatation (662,663); RV systolic hypertension occurs in MS, pulmonic valve stenosis, and the various causes of pulmonary hypertension. RV diastolic hypertension occurs in dilated cardiomyopathy, RV infarction, and RV failure of any cause (662,663). Pacemaker-induced severe TR is rare but may require intervention.

Abnormalities of the tricuspid valve leading to TR can occur with rheumatic valvulitis, infective endocarditis, carcinoid, rheumatoid arthritis, radiation therapy, trauma (such as repeated endomyocardial biopsies), Marfan syndrome, tricuspid valve prolapse, tricuspid annular dilatation, or congenital disorders such as Ebstein's anomaly (663) or a cleft tricuspid valve as part of atrioventricular canal malformations. Anorectic drugs may also cause TR (see Section 3.9).

Tricuspid stenosis is most commonly rheumatic in origin. On very rare occasions, infective endocarditis (with large bulky vegetations), congenital abnormalities, carcinoid, Fabry's disease, Whipple's disease, or previous methysergide therapy may be implicated (664). Right atrial mass lesions represent a nonvalvular cause of obstruction to the tricuspid orifice and may also over time destroy the leaflets and cause regurgitation. Rheumatic tricuspid involvement usually results in both stenosis and regurgitation.

3.8.2. Diagnosis

The clinical features of tricuspid stenosis include a giant a wave and diminished rate of y descent in the jugular venous pulse, a tricuspid opening snap, and a murmur that is presystolic as well as middiastolic and that increases on inspiration (665). Because chronic rheumatic valve disease is the most common cause of tricuspid stenosis, there is usually associated mitral and/or aortic disease, and the clinical findings include those associated with the other 2 valves, especially the MV.

The clinical features of TR include abnormal systolic c and v waves in the jugular venous pulse, a lower left parasternal systolic murmur (holosystolic or less than holosystolic, depending on the severity of hemodynamic derangement) that may increase on inspiration (Carvallo's sign), a middiastolic murmur in severe regurgitation, and systolic hepatic pulsation. In rare instances, severe TR may produce systolic propulsion of the eyeballs (666), pulsatile varicose veins (667), or a venous systolic thrill and murmur in the neck (668). Other associated clinical features are related to the cause of TR. Moderate or severe TR may be present without the classic clinical features.

Echocardiography is valuable in assessing tricuspid valve structure and motion, measuring annular size, and identifying other cardiac abnormalities that might influence tricuspid valve function. Doppler echocardiography permits estimation of the severity of TR (669), RV systolic pressure, and the tricuspid valve diastolic gradient. Although echocardiography is a valuable diagnostic tool, it should be pointed out that clinically insignificant TR is detected by color Doppler imaging in many normal persons (16,19–22). This is not an indication for either routine follow-up or prophylaxis against bacterial endocarditis. Clinical correlation and judgment must accompany the echocardiographic results. Systolic pulmonary artery pressures greater than 55 mm Hg are likely to cause TR with anatomically normal tricuspid valves, whereas TR occurring with systolic pulmonary artery pressures less than 40 mm Hg is likely to reflect a structural abnormality of the valve apparatus. Systolic pulmonary artery pressure estimation combined with information about annular circumference will further improve the accuracy of clinical assessment (662).

3.8.3. Management

CLASS I

1. Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery. *(Level of Evidence: B)*

CLASS IIa

1. Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic. *(Level of Evidence: C)*
2. Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair. *(Level of Evidence: C)*

CLASS IIb

Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation. *(Level of Evidence: C)*

CLASS III

1. Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mm Hg in the presence of a normal MV. *(Level of Evidence: C)*
2. Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR. *(Level of Evidence: C)*

The patient's clinical status and the cause of the tricuspid valve abnormality usually determine the appropriate therapeutic strategy. Medical and/or surgical management may be required. For example, in the patient with severe MS and pulmonary hypertension with resulting RV dilatation and TR, relief of MS and the resulting decrease in pulmonary artery pressure may result in substantial diminution of the degree of TR. The timing of surgical intervention for TR remains controversial, as do the surgical techniques. To some extent, this controversy has diminished since the advent of 2D and Doppler echocardiography for preoperative diagnosis and assessment. Intraoperative transesophageal Doppler echocardiography allows refinement of annuloplasty techniques to optimize outcome (670–672). At present, surgery on the tricuspid valve for TR occurs commonly at the time of MV surgery. As noted in Section 3.7.4.3, TR associated with dilatation of the tricuspid annulus should be repaired (658,659), because tricuspid dilatation is an ongoing process that may progress to severe TR if left untreated.

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Tricuspid valve balloon valvotomy has been advocated for tricuspid stenosis of various causes (673–675). However, severe TR is a common consequence of this procedure, and results are poor when severe TR develops.

Patients with severe TR of any cause have a poor long-term outcome because of RV dysfunction and/or systemic venous congestion (676). Tricuspid valve and chordal reconstruction can be attempted in some cases of TR resulting from endocarditis and trauma (677–679). In recent years, annuloplasty has become an established surgical approach to significant TR (657–660,680–684).

When the valve leaflets themselves are diseased, abnormal, or destroyed, valve replacement with a low-profile mechanical valve or bioprosthesis is often necessary (685). A biological prosthesis is preferred because of the high rate of thromboembolic complications with mechanical prostheses in the tricuspid position. In patients with associated conduction defects, insertion of a permanent epicardial pacing electrode at the time of valve replacement can avoid the later need to pass a transvenous lead across the prosthetic valve.

3.9. Drug-Related Valvular Heart Disease

In addition to the common causes of the valvular lesions described in the preceding sections, there are a number of uncommon causes related to systemic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, and ankylosing spondylitis), drugs (e.g., ergotamine, methysergide, anorexiant medications, and pergolide), and toxins. It is beyond the scope of these guidelines to discuss the specific pathology and natural history of valve disease stemming from each of these many causes. In general, the evaluation and management strategies for patients with valve disease related to these disorders are directed both toward the underlying systemic process when appropriate and to the diagnosis and treatment of the associated valvular disease according to the guidelines developed for each of the valve lesions as described in Section 3.

The sympathomimetic appetite-suppressant drug fenfluramine and its pure d-enantiomer, dexfenfluramine, were removed from the market in September 1997 after several reports of unusual left-sided valvular heart disease (AR and MR) linked to these agents (686–690). These medications, when used alone or in combination with the noradrenergic agent phentermine, had been previously implicated as a cause of pulmonary hypertension, even when used for less than 1 month (691–693). The echocardiographic and histopathological findings reported were similar to those described in patients with carcinoid or ergotamine-induced valvular heart disease (694–699). The fibroproliferative response appears to be mediated via the 5-HT_{2B} receptor (700). Subsequent reports have estimated a lower prevalence of anorexiant drug–related valvulopathy meeting Food and Drug Administration (FDA) criteria and have identified age, dose, and duration of exposure as risk factors for its development (701–706). In the meta-analysis by Sachdev and colleagues, the pooled prevalence of qualifying valvular regurgitation among patients treated for more than 90 days was 12.0% compared with 5.9% for the unexposed group (odds ratio 2.2, 95% confidence interval 1.7–2.7) (707). This increase was primarily the result of mild or greater AR (exposed 9.6% and unexposed 4.5%, odds ratio 2.5, 95% confidence interval 1.9–3.3). The prevalence among patients exposed for less than 90 days was 6.8% compared with 5.8% for unexposed patients (odds ratio 1.4, 95% confidence interval 0.8–2.4) (707). Isolated reports have implied that the valvular disease associated with combination- or single-drug therapy does not progress and may improve after cessation of treatment (708,709). Concomitant therapy with a selective serotonin reuptake inhibitor for depression or panic disorder does not appear to confer incremental risk (703). Fewer patients are now presenting for initial evaluation since the drugs were removed from the market in 1997. To date, an excess prevalence of valvular heart disease has not been reported for sibutramine, a serotonin and norepinephrine reuptake inhibitor, or for phentermine when used as monotherapy for obesity (710,711). The lipase inhibitor orlistat is not known to produce valvular disease. There are now several reports of a carcinoid-like valvulopathy in Parkinson's disease patients treated with pergolide, a dopamine-receptor agonist (712–714). A history of exposure to any of the ergotamine-like agents briefly reviewed here should prompt a careful cardiovascular examination, echocardiography when indicated, and treatment as would be dictated by the nature and severity of the heart valve lesion(s).

3.10. Radiation Heart Disease

Mediastinal radiation may produce cardiac valve abnormalities that usually become evident at least 5 years after the radiation injury. The assessment and treatment of these patients can be difficult in part because these valve lesions occur within a context of multiple cardiac and noncardiac abnormalities produced by radiation. Radiation-induced valvular lesions are based on calcification of valve leaflets and the fibrous skeleton of the heart. Mixed aortic valve disease that combines stenosis and insufficiency is the most common lesion, but MR and TR may also occur. Nonvalvular aspects of radiation-induced heart disease include a restrictive cardiomyopathy, aortic and great vessel calcification, coronary artery stenoses including ostial lesions and diffuse lesions, pericardial constriction, and conduction abnormalities. Noncardiac abnormalities such as skin and sternal necrosis, recurrent pleural effusions, and radiation-induced pulmonary dysfunction can also play a role in the overall picture.

Valve dysfunction is often part of a presenting picture of congestive heart failure and dyspnea, but the relative contributions of valve dysfunction and restrictive cardiomyopathy may be difficult to separate. In addition, recurrent pleural effusions are often prominent, and radiation-induced

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pulmonary dysfunction can occur. Thus, for these patients, dyspnea is a multifactorial problem.

For patients with radiation heart disease, surgery for any cardiac lesion should be approached with caution (715). First, symptom relief secondary to valve surgery may be incomplete because the restrictive cardiomyopathy may limit improvement of congestive heart failure symptoms, and pulmonary dysfunction may contribute to ongoing symptoms of dyspnea. Second, surgical risks are increased for patients with radiation heart disease both from cardiac disease and noncardiac conditions, such as aortic calcification and skin necrosis. Thus, logic dictates that patients be significantly symptomatic before undergoing surgery or have substantial jeopardy from severe coronary artery lesions. Third, reoperation for a patient with mediastinal radiation is an extremely difficult issue, because the radiation injury appears to be ongoing after a primary operation, creating severe mediastinal adhesions and an increased risk of reoperation (715). The most common indication for surgery for patients with radiation heart disease is CAD, a common cause of late mortality after mediastinal radiation. During coronary artery surgery, even moderately dysfunctional aortic valves should be replaced to avoid the dangers of early reoperation in the future (716). Aortic and aortic root calcification can make even primary surgery for AVR difficult, and the lack of aortic root enlargement may limit the size of a prosthesis that can be implanted. Overall, radiation heart disease constitutes one of the most difficult management problems in acquired heart disease, and patients with this condition should be evaluated in centers with experience in its management (717).

4. EVALUATION AND MANAGEMENT OF INFECTIVE ENDOCARDITIS

CLASS I

1. Patients at risk for infective endocarditis who have unexplained fever for more than 48 h should have at least 2 sets of blood cultures obtained from different sites. *(Level of Evidence: B)*

CLASS III

1. Patients with known valve disease or a valve prosthesis should not receive antibiotics before blood cultures are obtained for unexplained fever. *(Level of Evidence: C)*

Infective endocarditis may be suspected in a patient with a cardiac murmur suggestive of organic valvular or congenital heart disease or in a patient with a prosthetic heart valve by the presence of fever, anemia, hematuria, and physical findings such as petechiae, Osler's nodes, Janeway lesions, Roth spots, splenomegaly, and splinter hemorrhages. A definitive diagnosis may be made with positive blood cultures and/or characteristic echocardiographic findings. The diagnosis of infective endocarditis is often imprecise, because bacteremia can occur without endocardial infection, and endocarditis can occur with negative blood cultures, especially if a patient has received antibiotics for minor undiagnosed febrile illness (30). The role of echocardiography has emerged with visualization of vegetation by transthoracic echocardiography in approximately 60% to 75% of patients and by transesophageal echocardiography in more than 95% of patients (718).

Criteria for the diagnosis of infective endocarditis were proposed by Van Reyn et al. (719) based on the combination of blood cultures, clinical signs, and symptoms. Durack et al proposed a new set of diagnostic criteria that placed echocardiographic findings of endocardial lesions on an equal footing as positive blood cultures (720). The Duke criteria designated a patient as "definite," "rejected," or "possible" with regard to the likelihood of infective endocarditis. Because the designation of "possible" infective endocarditis seemed overly broad based on 1 minor criterion if the patient did not meet requirements for "rejected" (721), a more recent modification of the Duke criteria has been developed with the intent to improve diagnostic specificity without sacrificing sensitivity (722). These modified Duke criteria are shown in Table 22, which defines major and minor criteria, and in Table 23, which uses the diagnostic classifications of definite, possible, or rejected.

The diagnosis of infective endocarditis in a patient with a pathological murmur or a valvular prosthesis and unexplained fever lasting more than 72 h should include an assessment for vascular and immunologic phenomena, 3 to 5 sets of blood cultures, and a transthoracic echocardiogram. When the echocardiogram is technically inadequate, is nondiagnostic, or is negative for infective endocarditis, transesophageal echocardiography should be obtained.

4.1. Antimicrobial Therapy

Antimicrobial therapy in endocarditis is guided by identification of the causative organism. The majority (80%) of cases of endocarditis are due to streptococcal and staphylococcal organisms. The latter species is also the most frequent organism in endocarditis resulting from intravenous drug abuse. Eighty percent of tricuspid valve infection is by Staphylococcus aureus. This organism is also a frequent cause of infective endocarditis in patients with insulin-dependent diabetes mellitus. With prosthetic valve endocarditis, a wide spectrum of organisms can be responsible within the first year of operation. However, in "early" prosthetic valve endocarditis, usually defined as endocarditis during the first 2 months after surgery, Staphylococcus epidermidis is the predominant offending organism. Late-onset prosthetic valve endocarditis follows the profile of native valve endocarditis, that is, streptococci (viridans) and staphylococci. Enterococcus faecalis and E. faecium account for 90% of enterococcal endocarditis, which is usually associated with malignancy or manipulation of the genitourinary or gastrointestinal tract. Gram-positive and Gram-negative bacilli are relatively uncommon causes of endocarditis. In recent years, the HACEK group of organisms (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,

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Table 22. Definition of Terms Used in the Proposed Modified Duke Criteria for the Diagnosis of Infective Endocarditis*

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus;* or
Community-acquired enterococci in the absence of a primary focus; or
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures of blood samples drawn more than 12 h apart; or
All of 3 or a majority of greater than 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetti* or anti-phase 1 IgG antibody titer greater than 1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition or injection drug use
Fever, temperature greater than 38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena; glomerulonephritis, Osler's nodes. Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion,† or serological evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

*Modifications are shown in bold type. †Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis. Reprinted with permission from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8 (722).
IE indicates infective endocarditis; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

and Kingella species) has become an important cause of endocarditis. These organisms cause large vegetations (greater than 1 cm), large-vessel embolism, and congestive heart failure. They should be considered along with fungal endocarditis when large vegetations are noted. Fungi, especially Candida, are important causes of endocarditis in patients with prosthetic valves, compromised immune systems, and intravenous drug abuse. Several of the AHA recommendations for antimicrobial regimens, updated in 2005, are given in Tables 24 through 29 (723). Complete treatment regimens for resistant organisms are provided in that statement from the AHA which can be found at http://www.americanheart.org/presenter.jhtml?identifier=2158 (723).

Table 23. Definition of Infective Endocarditis According to the Proposed Modified Duke Criteria*

Definite infective endocarditis
Pathological criteria
(1) Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
(2) Pathological lesions; vegetation, or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria
(1) 2 major criteria, or
(2) 1 major criterion and 3 minor criteria; or
(3) 5 minor criteria
Possible infective endocarditis
(1) **1 major criterion and 1 minor criterion;** or
(2) **3 minor criteria**
Rejected
(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
(2) Resolution of infective endocarditis syndrome with antibiotic therapy for less than 4 days; or
(3) No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for less than 4 days; or
(4) Does not meet criteria for possible infective endocarditis, as noted above

*Modifications are shown in bold type. Reprinted with permission from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8 (722).

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Table 24. Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

Regimen	Dosage and Route*	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	12–18 million U per 24 h IV either continuously or in 4 or 6 equally divided doses	4	Preferred in most patients greater than 65 y of age or patients with impairment of 8th cranial nerve function or renal function
or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	4	
	Pediatric dose†: penicillin 200 000 U per kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg per kg per 24 h IV/IM in 1 dose		
Aqueous crystalline penicillin G sodium	12–18 million U per 24 h IV either continuously or in 6 equally divided doses	2	Two-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of less than 20 ml per min, impaired 8th cranial nerve function, or Abiotrophia, Granulicatella, or Gemella spp infection. Gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 mcg per ml and trough serum concentration of less than 1 μg per ml when 3 divided doses are used; nomogram used for single daily dosing.
or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	2	
plus			
Gentamicin sulfate‡	3 mg per kg per 24 h IV/IM in 1 dose	2	
	Pediatric dose: penicillin 200 000 U per kg per 24 h IV in 4–6 equally divided doses; ceftriaxone 100 mg per kg per 24 h IV/IM in 1 dose; gentamicin 3 mg per kg per 24 h	2	
	IV/IM in 1 dose or 3 equally divided doses§		
Vancomycin hydrochloride‖	30 mg per kg per 24 h IV in 2 equally divided doses not to exceed 2 g per 24 h unless concentrations in serum are inappropriately low	4	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 h after infusion completed) serum concentration of 30–45 μg per ml and a trough concentration range of 10–15 μg per ml
	Pediatric dose: 40 mg per kg per 24 h IV in 2–3 equally divided doses		

Minimum inhibitory concentration less than or equal to 0.12 μg per ml. *Dosages recommended are for patients with normal renal function. †Pediatric dose should not exceed that of a normal adult. ‡Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. §Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist. ‖Vancomycin dosages should be infused during course of at least 1 h to reduce risk of histamine-release "red man" syndrome. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).

IM indicates intramuscular; and IV, intravenous.

4.2. Culture-Negative Endocarditis

Culture-negative endocarditis most frequently (62%) results from prior antibiotic treatment before blood cultures are drawn (724,725). Other reasons for negative blood cultures include infections due to Candida; Aspergillus; other fastidious, slow-growing organisms (726) such as Q-fever and Bartonella organisms; and noninfective endocarditis such as Libman-Sacks endocarditis in patients with systemic lupus erythematosus. A proposed regimen for culture-negative, presumed bacterial endocarditis (723) is shown in Table 30.

4.3. Endocarditis in HIV-Seropositive Patients

Endocarditis in patients who are HIV (human immunodeficiency virus) seropositive usually occurs as a complication of injection drug use or long-term indwelling central catheters. S. aureus is the most frequent pathogen. When endocarditis is not related to intravenous drug use, right- and left-sided valves are equally involved. Intravenous drug use is the most common cause of tricuspid valve endocarditis. Endocarditis-related mortality in patients with acquired immune deficiency syndrome (AIDS) exceeds that of HIV-positive patients without AIDS. Thus, it is recommended that endocarditis in patients with AIDS be treated with maximum-duration antibiotic regimens (723).

4.4. Indications for Echocardiography in Suspected or Known Endocarditis

Echocardiography is useful for the detection and characterization of the hemodynamic and pathological consequences of infection. These consequences include valvular vegetations; valvular regurgitation; ventricular dysfunction; and associated lesions such as abscesses, shunts, and ruptured chordae (727). The indications for transthoracic and transesophageal echocardiography are discussed in the "ACC/AHA/ASE 2004 Guidelines for the Clinical Application of Echocardiography" (2) and the 2005 AHA endocarditis

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Table 25. Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin

Regimen	Dosage* and Route	Duration, wk	Comments
Aqueous crystalline penicillin G sodium	24 million U per 24 h IV either continuously or in 4 to 6 equally divided doses	4	Patients with endocarditis caused by penicillin-resistant (MIC greater than 0.5 μg per ml) strains should be treated with regimen recommended for enterococcal endocarditis
or			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	4	Recommended for enterococcal endocarditis (see Table 26) (723)
plus			
Gentamicin sulfate†	3 mg per kg per 24 h IV/IM in 1 dose Pediatric dose‡: penicillin 300 000 U per 24 h IV in 4 to 6 equally divided doses; ceftriaxone 100 mg per kg per 24 h IV/IM in 1 dose; gentamicin 3 mg per kg per 24 h IV/IM in 1 dose or 3 equally divided doses	2	
Vancomycin hydrochloride‡	30 mg per kg per 24 h IV in 2 equally divided doses not to exceed 2 g per 24 h, unless serum concentrations are inappropriately low Pediatric dose: 40 mg per kg per 24 h in 2 or 3 equally divided doses	4	Vancomycin§ therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

Minimum inhibitory concentration (MIC) greater than 0.12 μg per ml to less than or equal to 0.5 μg per ml. *Dosages recommended are for patients with normal renal function. †See Table 24 for appropriate dosage of gentamicin. ‡Pediatric dose should not exceed that of a normal adult. §See Table 24 for appropriate dosage of vancomycin. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).

IM indicates intramuscular; IV, intravenous; and MIC, minimum inhibitory concentration.

guidelines (723). Transesophageal imaging is more sensitive in detecting vegetations than transthoracic imaging (718,723,728), particularly in patients with prosthetic valves, and in determining the presence and severity of important complications such as abscesses and perforations. In patients with prosthetic valves, it is reasonable to proceed directly to transesophageal imaging as the first-line diagnostic test when endocarditis is suspected. Echocardiography can be

Table 26. Therapy for Native Valve or Prosthetic Valve Enterococcal Endocarditis Caused by Strains Susceptible to Penicillin, Gentamicin, and Vancomycin

Regimen	Dosage* and Route	Duration, wk	Comments
Ampicillin sodium	12 g per 24 h IV in 6 equally divided doses	4 to 6	Native valve: 4-wk therapy recommended for patients with symptoms of illness less than or equal to 3 mo; 6-wk therapy recommended for patients with symptoms greater than 3 mo
or			
Aqueous crystalline penicillin G sodium	18–30 million U per 24 h IV either continuously or in 6 equally divided doses	4 to 6	Prosthetic valve or other prosthetic cardiac material: minimum of 6-wk therapy recommended
plus			
Gentamicin sulfate†	3 mg per kg per 24 h IV/IM in 3 equally divided doses Pediatric dose‡: ampicillin 300 mg per kg per 24 h IV in 4 to 6 equally divided doses; penicillin 300 000 U per kg per 24 h IV in 4 to 6 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses	4 to 6	
Vancomycin hydrochloride§	30 mg per kg per 24 IV in 2 equally divided doses	6	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ampicillin
plus			
Gentamicin sulfate	3 mg per kg per 24 h IV/IM in 3 equally divided doses Pediatric dose: vancomycin 40 mg per kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses	6	6 wk of vancomycin therapy recommended because of decreased activity against enterococci

*Dosages recommended are for patients with normal renal function. †Dosage of gentamicin should be adjusted to achieve peak serum concentration of 3 to 4 μg per ml and a trough concentration of less than 1 μg per ml. Patients with a creatinine clearance of less than 50 ml per min should be treated in consultation with an infectious diseases specialist. ‡Pediatric dose should not exceed that of a normal adult. §See Table 24 for appropriate dosing of vancomycin. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723). See full document for treatment regimens of resistant organisms.

IM indicates intramuscular; IV, intravenous.

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Table 27. Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage* and Route	Duration	Comments
Oxacillin-susceptible strains			
Nafcillin or oxacillin†	12 g per 24 h IV in 4–6 equally divided doses	6 wk	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see full text)
with			
Optional addition of gentamicin sulfate‡	3 mg per kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d	Clinical benefit of aminoglycosides has not been established
	Pediatric dose§: Nafcillin or oxacillin 200 mg per kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses		
For penicillin-allergic (nonanaphylactoid type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6g per 24 h IV in 3 equally divided doses	6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to beta lactams; vancomycin should be used in these cases§
with			
Optional addition of gentamicin sulfate	3 mg per kg per 24 h IV/IM in 2 or 3 equally divided doses	3–5 d	Clinical benefit of aminoglycosides has not been established
	Pediatric dose: cefazolin 100 mg per kg per 24 h IV in 3 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses		
Oxacillin-resilient strains			
Vancomycin‖	30 mg per kg per 24 h IV in 2 equally divided doses	6 wk	Adjust vancomycin dosage to achieve 1-h serum concentration of 30–45 μg per ml and trough concentration of 10–15 μg per ml

*Dosages recommended are for patients with normal renal function. †Penicillin G 24 million U per 24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration less than or equal to 0.1 μg per ml) and dose does not produce beta lactamase. ‡Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing. §Pediatric dose should not exceed that of a normal adult. ‖For specific dosing adjustment and issues concerning vancomycin, see Table 24 footnotes. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).

IE indicates infective endocarditis; IM, intramuscular; and IV, intravenous.

useful in the case of culture-negative endocarditis (729) or the diagnosis of a persistent bacteremia the source of which remains unidentified after appropriate evaluation (2).

4.4.1. Transthoracic Echocardiography in Endocarditis

CLASS I

1. Transthoracic echocardiography to detect valvular vegetations with or without positive blood cultures is recommended for the diagnosis of infective endocarditis. *(Level of Evidence: B)*
2. Transthoracic echocardiography is recommended to characterize the hemodynamic severity of valvular lesions in known infective endocarditis. *(Level of Evidence: B)*
3. Transthoracic echocardiography is recommended for assessment of complications of infective endocarditis (e.g., abscesses, perforation, and shunts). *(Level of Evidence: B)*
4. Transthoracic echocardiography is recommended for reassessment of high-risk patients (e.g., those with a virulent organism, clinical deterioration, persistent or recurrent fever, new murmur, or persistent bacteremia). *(Level of Evidence: C)*

CLASS IIa

1. Transthoracic echocardiography is reasonable to diagnose infective endocarditis of a prosthetic valve in the presence of persistent fever without bacteremia or a new murmur. *(Level of Evidence: C)*

CLASS IIb

1. Transthoracic echocardiography may be considered for the re-evaluation of prosthetic valve endocarditis during antibiotic therapy in the absence of clinical deterioration. *(Level of Evidence: C)*

CLASS III

1. Transthoracic echocardiography is not indicated to re-evaluate uncomplicated (including no regurgitation on baseline echocardiogram) native valve endocarditis during antibiotic treatment in the absence of clinical deterioration, new physical findings or persistent fever. *(Level of Evidence: C)*

4.4.2. Transesophageal Echocardiography in Endocarditis

CLASS I

1. Transesophageal echocardiography is recommended to assess the severity of valvular lesions in symptomatic patients with infective endocarditis, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*
2. Transesophageal echocardiography is recommended to diagnose infective endocarditis in patients with valvular heart disease and positive blood cultures, if transthoracic echocardiography is nondiagnostic. *(Level of Evidence: C)*
3. Transesophageal echocardiography is recommended to diagnose complications of infective endocarditis with potential impact on prognosis and management (e.g., abscesses, perforation, and shunts). *(Level of Evidence: C)*

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Table 28. Therapy for Prosthetic Valve Endocarditis Caused by Staphylococci

Regimen	Dosage* and Route	Duration, wk	Comments
Oxacillin-susceptible strains			
Nafcillin or oxacillin	12 g per 24 h IV in 6 equally divided doses	At least 6	Penicillin G 24 million U per 24 h IV in 4 to 6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration less than or equal to 0.1 mcg per ml) and does not produce β-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 24 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins
plus			
Rifampin	900 mg per 24 h IV/PO in 3 equally divided doses	At least 6	
plus			
Gentamicin†	3 mg per kg per 24 h IV/IM in 2 or 3 equally divided doses		
	Pediatric dose‡: nafcillin or oxacillin 200 mg per kg per 24 h IV in 4 to 6 equally divided doses; rifampin 20 mg per kg per 24 h IV/PO in 3 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 2 equally divided doses		
Oxacillin-resistant strains			
Vancomycin	30 mg per kg per 24 h in 2 equally divided doses	At least 6	Adjust vancomycin to achieve 1-h serum concentration of 30 to 45 μg per ml and trough concentration of 10 to 15 μg per ml
plus			
Rifampin	900 mg per 24 h IV/PO in 3 equally divided doses	At least 6	
plus			
Gentamicin	3 mg per kg per 24 h IV/IM in 2 or 3 equally divided doses		
	Pediatric dose: vancomycin 40 mg per kg per 24 h IV in 2 or 3 equally divided doses; rifampin 20 mg per kg per 24 h IV/PO in 3 equally divided doses (up to adult dose); gentamicin 3 mg per kg per 24 h IV or IM in 3 equally divided doses		

*Dosages recommended are for patients with normal renal function. †Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. ‡Pediatric dose should not exceed that of a normal adult. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).
IM indicates intramuscular; IV, intravenous; and PO, by mouth.

4. Transesophageal echocardiography is recommended as first-line diagnostic study to diagnose prosthetic valve endocarditis and assess for complications. *(Level of Evidence: C)*
5. Transesophageal echocardiography is recommended for preoperative evaluation in patients with known infective endocarditis, unless the need for surgery is evident on transthoracic imaging and unless preoperative imaging will delay surgery in urgent cases. *(Level of Evidence: C)*
6. Intraoperative transesophageal echocardiography is recommended for patients undergoing valve surgery for infective endocarditis. *(Level of Evidence: C)*

CLASS IIa

1. Transesophageal echocardiography is reasonable to diagnose possible infective endocarditis in patients with persistent staphylococcal bacteremia without a known source. *(Level of Evidence: C)*

CLASS IIb

1. Transesophageal echocardiography might be considered to detect infective endocarditis in patients with nosocomial staphylococcal bacteremia. *(Level of Evidence: C)*

4.5. Outpatient Treatment

Patients with penicillin-susceptible S. viridans endocarditis who are hemodynamically stable, compliant, and capable of managing the technical aspects of outpatient therapy may be candidates for a single daily-dose regimen of ceftriaxone (723). Clinical reports suggest that right-sided endocarditis caused by S. aureus in intravenous drug users may be amenable to a short 2-week course of therapy (730,731). Monotherapy with ceftriaxone or combination therapy with an aminoglycoside has been tried as an outpatient therapeutic option (732); however, more data are needed to deter-

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Table 29. Therapy for Both Native and Prosthetic Valve Endocarditis Caused by HACEK* Microorganisms

Regimen	Dosage and Route	Duration, wk	Comments
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose†	4	Cefotaxime or another third- or fourth-generation cephalosporin may be substituted
or			
Ampicillin-sulbactam‡	12 g per 24 IV in 4 equally divided doses	4	
or			
Ciprofloxacin‡§	1000 mg per 24 h PO or 800 mg per 24 h IV in 2 equally divided doses Pediatric dose‖: Ceftriaxone 100 mg per kg per 24 h IV/IM once daily; ampicillin-sulbactam 300 mg per kg per 24 h IV divided into 4 or 6 equally divided doses; ciprofloxacin 20 to 30 mg per kg per 24 h IV/PO in 2 equally divided doses	4	Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin, gatifloxacin, or moxifloxacin may be substituted; fluoroquinolones generally not recommended for patients less than 18 y old Prosthetic valve: patients with endocarditis involving prosthetic cardiac valve or other prosthetic cardiac material should be treated for 6 wk

**Haemophilus parainfluenzae, Haphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.* †Patients should be informed that intramuscular injection of ceftriaxone is painful. ‡Dosage recommended for patients with normal renal function. §Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on use of fluoroquinolone therapy for endocarditis caused by HACEK are minimal. ‖Pediatric dose should not exceed that of a normal adult. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).

IM indicates intramuscular; IV, intravenous; and PO, by mouth.

mine with more certainty whether such outpatient regimens have therapeutic effectiveness equivalent to the established 4- to 6-week regimens.

4.6. Indications for Surgery in Patients With Acute Infective Endocarditis

Surgery is indicated in patients with life-threatening congestive heart failure or cardiogenic shock due to surgically treatable valvular heart disease with or without proven infective endocarditis if the patient has reasonable prospects of recovery with satisfactory quality of life after the operation (615,723,733–757). Surgery should not be delayed in the setting of acute infective endocarditis when congestive heart failure intervenes. Surgery is not indicated if complications (severe embolic cerebral damage) or comorbid conditions make the prospect of recovery remote.

The indications for surgery for infective endocarditis in patients with stable hemodynamics are less clear. Consultation with a cardiovascular surgeon is recommended in a patient with complicated endocarditis so that the surgical team is aware of the patient who may suddenly need surgery. Surgery is recommended in patients with annular or aortic abscesses, heart block, recurrent emboli on appropriate antibiotic therapy, infections resistant to antibiotic therapy, and fungal endocarditis. It is recognized that the presence of valvular vegetations poses a threat of embolic events. Prosthetic valve endocarditis and native valve endocarditis caused by S. aureus are almost always surgical diseases. Early surgery in MV endocarditis caused by virulent organisms (such as S. aureus or fungi) may make repair possible. Echocardiography, especially with transesophageal imaging, identifies vegetations and provides size estimation in many instances. Patients with a vegetation diameter greater than 10 mm have a significantly higher incidence of embolization than those with a vegetation diameter less than or equal to 10 mm (718), and this risk appears to be higher in patients with MV endocarditis than in those with aortic valve endocarditis. However, surgery on the basis of vegetation size alone is controversial.

Patients with prosthetic valves who receive warfarin anticoagulation and develop endocarditis should have their warfarin discontinued and replaced with heparin. This recommendation is less related to the possibility of hemorrhagic complications of endocarditis (758) than the possibility of urgent surgery. If surgery is required, the effects of warfarin will have dissipated, and heparin can easily be reversed. Likewise, aspirin, if part of the medical regimen, should also be discontinued. If neurological symptoms develop, anticoagulation should be discontinued until an intracranial hemorrhagic event is excluded by magnetic resonance imaging or computed tomographic scanning.

4.6.1. Surgery for Native Valve Endocarditis

CLASS I

1. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with valve stenosis or regurgitation resulting in heart failure. *(Level of Evidence: B)*
2. Surgery of the native valve is indicated in patients with acute infective endocarditis who present with AR or MR with hemodynamic evidence of elevated LV end-diastolic or left atrial pressures (e.g., premature closure of MV with AR, rapid decelerating MR signal by continuous-wave Doppler (v-wave cutoff sign), or moderate or severe pulmonary hypertension). *(Level of Evidence: B)*
3. Surgery of the native valve is indicated in patients with infective endocarditis caused by fungal or other highly resistant organisms. *(Level of Evidence: B)*
4. Surgery of the native valve is indicated in patients with infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (e.g., sinus of Valsalva to right atrium, right ventricle, or left atrium fistula; mitral leaflet perforation

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Table 30. Therapy for Culture-Negative Endocarditis Including *Bartonella* Endocarditis

Regimen	Dosage* and Route	Duration, wk	Comments
Native valve			
Ampicillin-sulbactam	12 g per 24 h IV in 4 equally divided doses	4–6	Patients with culture-negative endocarditis should be treated with consultation with an infectious diseases specialist
plus			
Gentamicin sulfate†	3 mg per kg per 24 h IV/IM in 3 equally divided doses	4–6	
Vancomycin‡	30 mg per kg per 24 h IV in 2 equally divided doses	4–6	Vancomycin recommended only for patients unable to tolerate penicillins
plus			
Gentamicin sulfate	3 mg per kg per 24 h IV/IM in 3 equally divided doses	4–6	
plus			
Ciprofloxacin	1000 mg per 24 h PO or 800 mg per 24 h IV in 2 equally divided doses	4–6	
	Pediatric dose§: ampicillin-sulbactam 300 mg per kg per 24 h IV in 4–6 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses; vancomycin 40 mg per kg per 24 h in 2 or 3 equally divided doses; ciprofloxacin 20–30 mg per kg per 24 h IV/PO in 2 equally divided doses		
Prosthetic valve (early—less than or equal to 1 y)			
Vancomycin	30 mg per kg per 24 h IV in 2 equally divided doses	6	
plus			
Gentamicin sulfate	3 mg per kg per 24 h IV/IM in 3 equally divided doses	2	
plus			
Cefepime	6 g per 24 h IV in 3 equally divided doses	6	
plus			
Rifampin	900 mg per 24 h PO/IV in 3 equally divided doses	6	
	Pediatric dose: vancomycin 40 mg per kg per 24 h IV in 2 or 3 equally divided doses; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses; cefepime 150 mg per kg per 24 h IV in 3 equally divided doses; rifampin 20 mg per kg per 24 h PO/IV in 3 equally divided doses		
Prosthetic valve (late—greater than 1 y)		6	Same regimens as listed above for native valve endocarditis
Suspected *Bartonella,* culture negative			
Ceftriaxone sodium	2 g per 24 h IV/IM in 1 dose	6	Patients with *Bartonella* endocarditis should be treated in consultation with an infectious diseases specialist
plus			
Gentamicin sulfate	3 mg per kg per 24 h IV/IM in 3 equally divided doses	2	
with/without			
Doxycycline	200 mg per kg per 24 h IV/PO in 2 equally divided doses	6	
Documented *Bartonella,* culture positive			
Doxycycline	200 mg per 24 h IV or PO in 2 equally divided doses	6	If gentamicin cannot be given, then replace with rifampin, 600 mg per 24 h PO/IV in 2 equally divided doses
plus			
Gentamicin sulfate	3 mg per kg per 24 h IV/IM in 3 equally divided doses	2	
	Pediatric dose: ceftriaxone 100 mg per kg per 24 h IV/IM once daily; gentamicin 3 mg per kg per 24 h IV/IM in 3 equally divided doses; doxycycline 2–4 mg per kg per 24 h IV/PO in 2 equally divided doses; rifampin 20 mg per kg per 24 h PO/IV in 2 equally divided doses		

*Dosages recommended are for patients with normal renal function. †See Table 24 for appropriate dosing of gentamicin. ‡See Table 24 for appropriate dosing of vancomycin. §Pediatric dose should not exceed that of a normal adult. Modified from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434 (723).

IM indicates intramuscular; IV, intravenous; and PO, by mouth.

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with aortic valve endocarditis; or infection in annulus fibrosa). *(Level of Evidence: B)*

CLASS IIa

1. Surgery of the native valve is reasonable in patients with infective endocarditis who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy. *(Level of Evidence: C)*

CLASS IIb

1. Surgery of the native valve may be considered in patients with infective endocarditis who present with mobile vegetations in excess of 10 mm with or without emboli. *(Level of Evidence: C)*

Patients with left-sided native valve endocarditis complicated by congestive heart failure, systemic embolization to vital organs, or presence of a large vegetation on echocardiography have poor outcomes on medical treatment alone. A large cohort study using a multivariate model reported that valve surgery was associated with improved 6-month survival (759). An additional benefit of early surgery is likely to include successful valve repair as an outcome, especially for the MV. When at all possible, MV repair should be performed instead of MV replacement in the setting of active infection because of the risk of infection of prosthetic materials (760–762). Aortic valves may often be repaired as well if there are leaflet perforations, and this is preferable to AVR for the same reasons.

4.6.2. Surgery for Prosthetic Valve Endocarditis

CLASS I

1. Consultation with a cardiac surgeon is indicated for patients with infective endocarditis of a prosthetic valve. *(Level of Evidence: C)*
2. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with heart failure. *(Level of Evidence: B)*
3. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with dehiscence evidenced by cine fluoroscopy or echocardiography. *(Level of Evidence: B)*
4. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with evidence of increasing obstruction or worsening regurgitation. *(Level of Evidence: C)*
5. Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with complications (e.g., abscess formation). *(Level of Evidence: C)*

CLASS IIa

1. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with evidence of persistent bacteremia or recurrent emboli despite appropriate antibiotic treatment. *(Level of Evidence: C)*
2. Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with relapsing infection. *(Level of Evidence: C)*

CLASS III

1. Routine surgery is not indicated for patients with uncomplicated infective endocarditis of a prosthetic valve caused by first infection with a sensitive organism. *(Level of Evidence: C)*

5. MANAGEMENT OF VALVULAR DISEASE IN PREGNANCY

5.1. Physiological Changes of Pregnancy

The evaluation and management of valvular heart disease in the pregnant patient requires an understanding of the normal physiological changes associated with gestation, labor, delivery, and the early postpartum period. On average, there is a 50% increase in circulating blood volume during pregnancy that is accompanied by a commensurate increase in cardiac output that usually peaks between the midportion of the second and third trimesters. The augmented cardiac output derives from an increase in the stroke volume, although there is also a smaller increase in heart rate, averaging 10 to 20 beats per minute. Because of the effects of uterine circulation and endogenous hormones, systemic vascular resistance falls with a disproportionately greater lowering of diastolic blood pressure and a wide pulse pressure. Inferior vena caval obstruction from a gravid uterus in the supine position can result in an abrupt decrease in cardiac preload, which leads to hypotension with weakness and lightheadedness. These symptoms resolve quickly with a change in position (763).

There is a further abrupt increase in cardiac output during labor and delivery related in part to the associated anxiety and pain. Uterine contractions can lead to marked increases in both systolic and diastolic blood pressure. After delivery, there is an initial surge in preload related to the autotransfusion of uterine blood into the systemic circulation and to caval decompression (763).

Pregnancy is also associated with a hypercoagulable state due to relative decreases in protein S activity, stasis, and venous hypertension (764). Estrogens can interfere with collagen deposition within the media of the medium and large muscular arteries. Circulating elastase can break up the elastic lamellae and weaken the aortic media during pregnancy. Weakening of the vascular wall may in turn predispose to dissection with or without an underlying connective tissue disorder (765). Relaxin, an insulin-like growth factor hormone, is detectable in serum during pregnancy and causes a decrease in collagen synthesis and may predispose to aortic dissection during pregnancy (766).

5.2. Physical Examination

The physical examination of the normal parturient is notable for a slightly fast resting heart rate, bounding pulses, a widened pulse pressure with a low normal peak systolic pressure, and warm extremities. Venous pressure is usually at or near the upper limits for nonpregnant women but rarely in a clearly abnormal range. The thyroid gland may be enlarged in the absence of clinical hyperthyroidism. Depending on the stage of pregnancy, the lung volumes may be low because of the raised diaphragms. The precordial impulse is hyperkinetic, and the first heart sound may be louder than normal, with prominent splitting. The second

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Table 31. Valvular Heart Lesions Associated With High Maternal and/or Fetal Risk During Pregnancy

1. Severe AS with or without symptoms
2. AR with NYHA functional class III–IV symptoms
3. MS with NYHA functional class II–IV symptoms
4. MR with NYHA functional class III–IV symptoms
5. Aortic and/or mitral valve disease resulting in severe pulmonary hypertension (pulmonary pressure greater than 75% of systemic pressures)
6. Aortic and/or mitral valve disease with severe LV dysfunction (EF less than 0.40)
7. Mechanical prosthetic valve requiring anticoagulation
8. Marfan syndrome with or without AR

AR indicates aortic regurgitation; AS, aortic stenosis; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; and NYHA, New York Heart Association.

heart sound is usually physiologically split but may also widen and appear fixed during the later stages of pregnancy. Third heart sounds are present in most patients. A soft grade 1 to 2 midsystolic murmur that is best heard along the mid to upper left sternal edge is a frequent finding (26). A continuous murmur, which reflects either a venous hum or a mammary souffle, may sometimes be heard during auscultation. The cervical venous hum is best appreciated in the right supraclavicular fossa and can be obliterated by movement of the chin toward the stethoscope or digital pressure over the ipsilateral jugular vein. The mammary souffle is a systolic or continuous sound over the engorged breast that can usually be obliterated with firm pressure applied to the diaphragm of the stethoscope. It is heard in the supine position and attenuates or disappears when standing. It is appreciated in the late stages of pregnancy or early in the puerperium. Diastolic heart murmurs are unusual. The increased blood volume and enhanced cardiac output associated with normal pregnancy can accentuate the murmurs associated with stenotic heart valve lesions (e.g., MS and AS). On the other hand, murmurs of AR, MR, and ventricular septal defect can actually attenuate or become inaudible as systemic vascular resistance is lowered (767).

5.3. Echocardiography

Normal pregnancy is accompanied by echocardiographic evidence of mild ventricular chamber enlargement. Pulmonic and tricuspid valvular regurgitation, as assessed by Doppler interrogation, is the rule rather than the exception (768). Most women will demonstrate Doppler evidence of "physiological" MR in the absence of structural valve disease. Atrioventricular valve regurgitation may result from the annular dilatation that accompanies ventricular enlargement. Appreciation of these echocardiographic and Doppler findings in normal individuals is an important foundation for the noninvasive evaluation of subjects with suspected valvular disease. The use of ultrasound during pregnancy poses no risk to the mother or fetus.

5.4. General Management Guidelines

Clinical experience has shown that there are several cardiac conditions in which the physiological changes of pregnancy are poorly tolerated. For some conditions, such as cyanotic heart disease, Eisenmenger syndrome, or severe pulmonary hypertension, pregnancy should be discouraged. Valvular heart lesions associated with high maternal and fetal risk during pregnancy are listed in Table 31. Lesions associated with low risk during pregnancy are listed in Table 32.

Reimold and Rutherford (769) and Elkayam and Bitar (770,771) have published excellent reviews for the clinical practitioner involved in managing pregnant patients who have either valvular or prosthetic heart disease. They delineate the increased risk of adverse maternal, fetal, and neonatal outcomes on the basis of valvular abnormality and the NYHA functional class. Additionally, Siu et al. have identified predictors of adverse maternal and fetal outcomes in a heterogeneous group of Canadian women with congenital or acquired heart disease (772,773). Abnormal functional capacity (NYHA functional class II or higher) and left-sided heart obstruction were predictors of neonatal complications that included premature birth, intrauterine growth retardation, respiratory distress syndrome, intraventricular hemorrhage, and death. However, outcomes data are limited for pregnant patients with valvular heart disease, except for those with MS (769,770).

Individual counseling usually requires a multidisciplinary approach and should include information regarding contraception, maternal and fetal risks of pregnancy, and expected long-term outcomes. However, many patients with valvular heart disease can be successfully managed throughout pregnancy and during labor and delivery with conservative medical measures designed to optimize intravascular volume and systemic loading conditions.

Simple interventions such as bed rest and avoidance of the supine position should not be overlooked. Whenever possible, symptomatic or severe valvular lesions should be addressed and rectified before conception and pregnancy. Contemporaneous management with a dedicated obstetric team accustomed to working with high-risk patients is encouraged. Drugs should generally be avoided whenever possible (Table 33) (763).

Table 32. Valvular Heart Lesions Associated With Low Maternal and Fetal Risk During Pregnancy

1. Asymptomatic AS with low mean gradient (less than 25 mm Hg and aortic valve area greater than 1.5 cm^2) in presence of normal LV systolic function (EF greater than 0.50)
2. NYHA functional class I or II AR with normal LV systolic function
3. NYHA functional class I or II MR with normal LV systolic function
4. MVP with no MR or with mild to moderate MR with normal LV systolic function
5. Mild MS (MVA greater than 1.5 cm^2, gradient less than 5 mm Hg) without severe pulmonary hypertension
6. Mild to moderate pulmonary valve stenosis

AR indicates aortic regurgitation; AS, aortic stenosis; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVP, mitral valve prolapse; and NYHA, New York Heart Association.

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Table 33. Cardiovascular Drugs in Pregnancy

Drug	Use in Pregnancy	Potential Side Effects	Breast Feeding	Risk Factors
Adenosine	Maternal and fetal arrhythmias	No side effects reported; data on use during first trimester are limited	Data NA	C
Amiodarone	Maternal arrhythmias	IUGR, prematurity, congenital goiter, hypothyroidism and hyperthyroidism, transient bradycardia, and prolonged QT in the newborn	Not recommended	C
Angiotensin-converting enzyme inhibitors	Hypertension	Oligohydramnios, IUGR, prematurity, neonatal hypotension, renal failure, anemia, death, skull ossification defect, limb contractures, patent ductus arteriosus	Compatible	C
Beta blockers	Hypertension, maternal arrhythmias, myocardial ischemia, mitral stenosis, hypertrophic cardiomyopathy, hyperthyroidism, Marfan syndrome	Fetal bradycardia, low placental weight, possible IUGR, hypoglycemia, no information on carvedilol	Compatible, monitoring of infant's heart rate recommended	Acebutolol: B Labetalol: C Metoprolol: C Propranolol: C Atenolol: D
Digoxin	Maternal and fetal arrhythmias, heart failure	No evidence for unfavorable effects on the fetus	Compatible	C
Diltiazem	Myocardial ischemia, tocolysis	Limited data; increased incidence of major birth defects	Compatible	C
Disopyramide	Maternal arrhythmias	Limited data; may induce uterine contraction and premature delivery	Compatible	C
Diuretics	Hypertension, congestive heart failure	Hypovolemia leads to reduced uteroplacental perfusion, fetal hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia; thiazide diuretics can inhibit labor and suppress lactation	Compatible	C
Flecainide	Maternal and fetal arrhythmias	Limited data; 2 cases of fetal death after successful treatment of fetal SVT reported, but relation to flecainide uncertain	Compatible	C
Heparin	Anticoagulation	None reported	Compatible	C
Hydralazine	Hypertension	None reported	Compatible	C
Lidocaine	Local anesthesia, maternal arrhythmias	No evidence for unfavorable fetal effects; high serum levels may cause central nervous depression at birth	Compatible	C
Nifedipine	Hypertension, tocolysis	Fetal distress related to maternal hypotension reported	Compatible	C
Nitrates	Myocardial infarction and ischemia, hypertension, pulmonary edema, tocolysis	Limited data; use is generally safe, few cases of fetal heart rate deceleration and bradycardia have been reported	Data NA	C
Procainamide	Maternal and fetal arrhythmias	Limited data; no fetal side effects reported	Compatible	C
Propafenone	Fetal arrhythmias	Limited data; fetal death reported after direct intrauterine administration in fetuses with fetal hydrops	Data NA	C
Quinidine	Maternal and fetal arrhythmias	Minimal oxytoxic effect, high doses may cause premature labor or abortion; transient neonatal thrombocytopenia and damage to eighth nerve reported	Compatible	C
Sodium nitroprusside	Hypertension, aortic dissection	Limited data; potential thiocyanate fetal toxicity, fetal mortality reported in animals	Data NA	C
Sotalol	Maternal arrhythmias, hypertension, fetal tachycardia	Limited data; 2 cases of fetal death and 2 cases of significant neurological morbidity in newborns reported, as well as bradycardia in newborns	Compatible, monitoring of infant's heart rate recommended	B
Verapamil	Maternal and fetal arrhythmias, hypertension, tocolysis	Limited data; other than a single case of fetal death of uncertain cause, no adverse fetal or newborn effects have been reported	Compatible	C
Warfarin	Anticoagulation	Crosses placental barrier; fetal hemorrhage in utero, embryopathy, central nervous system abnormalities	Compatible	X

FDA classification: Category B: Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women. Category C: Either studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if potential benefits justify the potential risk to the fetus. Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant woman may be acceptable despite the risk. Category X: Studies in animals or human beings have demonstrated fetal abnormalities. The risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. Source: Drug Information for the Health Care Professional (USDPI Vol 1); Micromedex; 23rd ed (January 1, 2003). Adapted and modified with permission from Elkayam U. Pregnancy and cardiovascular disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier, 2005:1965 (763). The guidelines committee added warfarin, heparin, and hydralazine to this list.
IUGR indicates intrauterine growth retardation; NA, not available; and SVT, supraventricular tachycardia.

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5.5. Specific Lesions

5.5.1. Mitral Stenosis

Young pregnant women with a previous history of acute rheumatic fever and carditis should continue to receive penicillin prophylaxis as indicated in the nonpregnant state. Patients with mild to moderate MS can almost always be managed with judicious use of diuretics and beta blockade. Diuretics are given to relieve pulmonary and excess systemic venous congestion, but care must be taken to avoid vigorous volume depletion to protect against uteroplacental hypoperfusion. Beta blockers are chiefly indicated to treat or prevent tachycardia to optimize diastolic filling. Although the nonselective beta blocker propranolol has been in use for decades, some authorities recommend a cardioselective beta blocker such as metoprolol or atenolol to prevent the potential deleterious effects of epinephrine blockade on myometrial activity.

Patients with severe MS who are symptomatic before conception will not predictably tolerate the hemodynamic burden of pregnancy and should be considered for percutaneous balloon mitral valvotomy before conception, provided the valve is anatomically suitable. Patients with severe MS who develop NYHA functional class III–IV symptoms during pregnancy should undergo percutaneous balloon valvotomy (774).

For the rare patients with MS who fail medical management during pregnancy with repetitive or persistent heart failure, there is now a nearly 10-year experience with balloon mitral valvotomy, either with very limited fluoroscopy (less than 1 to 2 minutes' exposure with both pelvic and abdominal shielding) or echocardiographic guidance. The reported results with mitral balloon valvotomy have been excellent, with few maternal or fetal complications, although caution is advised in interpreting outcomes from individual centers reporting relatively few patients (775–784). Percutaneous mitral balloon valvotomy should only be performed in experienced centers and only after aggressive medical measures have been exhausted. In developing countries, there is a long history of successful surgical closed commissurotomy for pregnant women (785).

5.5.2. Mitral Regurgitation

MVP is the most common cause of MR in pregnant women. The physical findings pertinent to MVP may be obscured or varied by the physiological changes of pregnancy, especially the increased blood volume and reduced systemic vascular resistance. Associated MR can usually be managed medically, although on rare occasions, MV surgery is required because of ruptured chordae and acute, severe worsening of the regurgitant lesion. Medical management includes diuretics for the rare patient with pulmonary congestion. Vasodilator therapy is indicated only in the presence of concomitant systemic hypertension and should not be advised in the setting of normal or low systemic blood pressure. Angiotensin-converting enzyme inhibitors are considered unsafe and are contraindicated because of their multiple adverse effects on fetal development. There is wide experience with hydralazine, an agent generally considered safe. When MV surgery is required, repair is always preferred, as would be the case for any young patient but especially in relation to the desirability of avoiding the potential need for anticoagulation.

5.5.3. Aortic Stenosis

The most common cause of AS in pregnant women is congenital aortic valve disease. Patients with mild obstruction and normal LV systolic function can be managed conservatively throughout the pregnancy. Patients with moderate to severe obstruction (Table 4) (27) or symptoms should be advised to delay conception until relief of AS can be obtained. Women with severe AS who become pregnant but who remain asymptomatic or have mild symptoms may often be managed conservatively during pregnancy with bed rest, oxygen, and beta blockers. In women with severe AS who develop symptoms, consideration may have to be given to either percutaneous aortic balloon valvotomy (786,787) or surgery (depending on the anatomic findings) before labor and delivery. These procedures are fraught with danger to both the mother and fetus, although successful outcomes have been reported. Neither is to be undertaken without caution and forewarning. There is an association between the presence of a bicuspid aortic valve and aortic root dilatation, which may predispose to spontaneous aortic dissection, usually in the third trimester, especially if there is an associated aortic coarctation.

5.5.4. Aortic Regurgitation

Isolated AR, like MR, can usually be managed medically with a combination of diuretics and, if necessary, vasodilator therapy (788). Angiotensin-converting enzyme inhibitors are considered unsafe and are contraindicated because of their multiple adverse effects on fetal development. Women with symptoms or signs of LV failure should be monitored throughout labor and delivery with strict attention to volume status and blood pressure. As is true for MR, surgery during pregnancy should be contemplated only for control of refractory NYHA functional class III or IV symptoms. Consideration regarding LV size or systolic function in less symptomatic patients should not apply. The recommendations for AVR based on LV size that apply to nonpregnant patients should not be used for pregnant patients.

5.5.5. Pulmonic Stenosis

Pulmonic valve stenosis can exist in isolation but frequently accompanies other congenital heart lesions. In general, patients with cyanotic congenital heart disease tolerate the stresses of pregnancy far less well than those with acyanotic lesions. Isolated pulmonic stenosis is rarely a significant impediment to a successful pregnancy. This lesion can be approached with percutaneous valvotomy under echocardiographic guidance when necessary.

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5.5.6. Tricuspid Valve Disease

Tricuspid valve disease may be congenital (Ebstein's anomaly, tricuspid atresia) or acquired (endocarditis, myxomatous replacement/proliferation, carcinoid). The approach to the patient with tricuspid valve involvement as part of a more complex congenital heart disease syndrome is predicated on the features of the associated lesions. Isolated TR should not pose a significant problem during pregnancy, although greater care may be necessary to protect against diuretic-induced hypoperfusion.

5.5.7. Marfan Syndrome

The Marfan syndrome is an inheritable disorder of connective tissue that often stems from abnormalities in the fibrillin gene on chromosome 15. It is transmitted in an autosomal dominant fashion and is recognized clinically by its ocular, skeletal, and cardiovascular expressions. Spontaneous aortic dissection or rupture is the most feared cardiovascular complications associated with pregnancy (765,789, 790). Dissection can occur at any point along the aorta but most commonly originates in the ascending portion. Enlargement of the aortic root to greater than 4.0 cm identifies a particularly high-risk group, although a normal dimension is by no means a guarantee against this catastrophic complication. Aortic root enlargement may or may not be accompanied by regurgitation and an audible heart murmur. MVP with regurgitation is also frequently detected.

Any woman with Marfan syndrome should be counseled against pregnancy, because aortic rupture or dissection can occur in any root size. All patients with Marfan syndrome should have a screening transthoracic echocardiogram with careful assessment of aortic root dimensions. Enlargement greater than 4.5 cm is generally considered an indication for elective repair before conception, usually with a composite valve-graft conduit and reimplantation of the coronary arteries. If any degree of aortic root enlargement (greater than 4.0 cm) is first detected during pregnancy, some authorities recommend termination of the pregnancy with prompt aortic repair, although this is controversial. Less controversial is prompt repair if serial imaging studies demonstrate progressive dilatation over time. Dissection and rupture are most likely to occur during the third trimester or near the time of delivery. Special care must be taken to provide adequate analgesia to prevent wide surges in blood pressure and its rate of rise (dP/dt) during labor and delivery. Obstetric techniques to shorten the second stage of labor are appropriate. General anesthesia and caesarean section may allow more optimal hemodynamic control. The use of prophylactic beta blockade throughout the pregnancy is strongly recommended. Such treatment has been shown to slow the rate of aortic dilatation and reduce the cumulative incidence of cardiovascular complications in nonpregnant adolescents and adults (359). Successful surgical correction does not confer a normal risk during subsequent pregnancy, because such patients remain at increased for aortic dissection, albeit reduced compared with patients with Marfan syndrome who have not undergone surgical intervention.

5.6. Endocarditis Prophylaxis (UPDATED)

The Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the AHA does not recommend routine antibiotic prophylaxis in patients with valvular heart disease undergoing uncomplicated vaginal delivery or caesarean section unless infection is suspected. Antibiotics are optional for high-risk patients with prosthetic heart valves, a previous history of endocarditis, complex congenital heart disease, or a surgically constructed systemic-pulmonary conduit (1070,1072).

5.7. Cardiac Valve Surgery

The performance of cardiac valve surgery is a difficult and complex undertaking in the pregnant patient. Even under ideal conditions, including the use of cardiopulmonary bypass techniques that promote high flow rates and warm perfusion temperatures, there is a high incidence of fetal distress, growth retardation, or wastage (791–795). If possible, it is always preferable to delay surgery until the time the fetus is viable and a caesarean section can be performed as part of a concomitant procedure (796,797). Surgery should be pursued only in the setting of medically refractory cardiac symptoms (pulmonary congestion), especially if a low-output syndrome intervenes.

For suitable valve lesions, repair is always preferred over replacement. If valve replacement is necessary, the choice of a heart valve substitute can be problematic. Bioprosthetic valves degenerate more quickly in younger patients, a process that can be further accelerated during pregnancy (798). Although such valves may not require longer-term anticoagulation, they do expose the young patient to an earlier risk of failure and need for reoperation. Mechanical valve substitutes are more durable, but the obligate need for anticoagulation may complicate current and future pregnancies. For aortic valve disease, homograft valves or pulmonary autografts should be considered (799).

5.8. Anticoagulation During Pregnancy

Given the paucity of data regarding the efficacy of anticoagulants during pregnancy, recommendations concerning their use during pregnancy are based largely on extrapolations from data from nonpregnant patients, from case reports, and from case series of pregnant patients (771,799–802).

5.8.1. Warfarin

Warfarin (vitamin K antagonist therapy) crosses the placenta and has been associated with an increased incidence of spontaneous abortion, prematurity, and stillbirth. Warfarin can also cause bleeding in the fetus, and fetal cerebral hemorrhage can complicate labor and delivery, especially if forceps evacuation is necessary. The manufacturer considers the use of warfarin during pregnancy to be strictly contra-

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indicated because of its association with embryopathy, consisting of nasal hypoplasia and/or stippled epiphyses after in utero exposure during the first trimester of pregnancy, and central nervous system abnormalities after exposure during any trimester. The true incidence of warfarin embryopathy has been difficult to ascertain. This has ranged from less than 5% to as high as 67% (801–804), and an estimate of 4% to 10% seems reasonable (805,806). However, the risk of clinically important embryopathy may be lower if the dose of warfarin is less than or equal to 5 mg per day.

Warfarin is probably safe during the first 6 weeks of gestation, but there is a risk of embryopathy if warfarin is taken between 6 and 12 weeks of gestation. For women requiring long-term warfarin therapy who are attempting pregnancy, it seems wise to perform frequent pregnancy tests with the substitution of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for warfarin when pregnancy is achieved. Warfarin is also relatively safe during the second and third trimesters of pregnancy but must be discontinued and switched to a heparin compound several weeks before delivery.

5.8.2. Unfractionated Heparin

Several studies suggest that UFH or LMWH therapy is safe for the fetus (800–804). Heparin does not cross the placenta and does not have the potential to cause fetal bleeding or teratogenicity. Thus, heparin is generally considered safer than warfarin during pregnancy in terms of the development of embryopathy (805,807). However, bleeding at the uteroplacental junction is possible, and numerous case series and patient registries attest to a high incidence of thromboembolic complications (12% to 24%), including fatal valve thrombosis, in high-risk pregnant women managed with subcutaneous UFH or LMWH (805,808–810). When heparin is used during the first trimester, the risks of maternal thromboembolism and maternal death are more than doubled. These studies have been criticized because of the inclusion of a predominant population of women with older-generation and more thrombogenic prostheses, inadequate heparin dosing, and/or the lack of meticulous monitoring strategies. Unfortunately, the efficacy of adjusted-dose subcutaneous heparin has not been definitively established.

During pregnancy, the activated partial thromboplastin time (aPTT) response to heparin is often attenuated because of increased levels of factor VIII and fibrinogen. Adjusted-dose subcutaneous UFH can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use before labor. Bleeding complications appear to be very uncommon with LMWH (811).

5.8.3. Low-Molecular-Weight Heparins

LMWHs have potential advantages over UFH during pregnancy because they 1) cause less heparin-induced thrombocytopenia; 2) have a longer plasma half-life and a more predictable dose response than UFH; 3) have greater ease of administration, with lack of need for laboratory monitoring and the potential for once-daily dosing administration; 4) are likely associated with a lower risk of heparin-induced osteoporosis; and 5) appear to have a low risk of bleeding complications. They do not cross the placenta and are likely safe for the fetus (811). Allergic skin reactions to both LMWH and UFH can occur.

As the pregnancy progresses (and most women gain weight), the potential volume of distribution for LMWH changes. It is thus necessary to measure plasma anti-Xa levels 4 to 6 h after the morning dose and adjust the dose of LMWH to achieve an anti-Xa level of approximately 0.7 to 1.2 units per ml.

Although LMWHs have been used successfully to treat deep venous thrombosis in pregnant patients, there are no data to guide their use in the management of patients with mechanical heart valves (810). Reports of LMWH use in pregnant women with prosthetic heart valves are becoming more frequent, and many physicians now prescribe these agents during pregnancy in women with mechanical valves, but treatment failures have been reported. The use of LMWH during pregnancy remains controversial because of an early warning by the manufacturer and FDA in July 2001 regarding safety concerns in this situation. In 2004, labeling approved by the FDA indicated specifically that use of LMWH for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been studied adequately.

In a clinical study of pregnant women with prosthetic heart valves given subcutaneous enoxaparin (1 mg per kg twice daily), 2 of 8 women developed prosthetic valve thromboses that led to maternal and fetal death. Although a causal relationship has not been established, these deaths may have been due to therapeutic failure or inadequate anticoagulation (811).

5.8.4. Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves

CLASS I

1. All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring (see Section 9.2.). *(Level of Evidence: B)*
2. For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored with discussions about subsequent anticoagulation therapy, so that anticoagulation can be continued uninterrupted when pregnancy is achieved. *(Level of Evidence: C)*
3. Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH. *(Level of Evidence: C)*
4. For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic

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valve thrombosis, systemic embolization, infection, osteoporosis, and heparin-induced thrombocytopenia are relatively higher. *(Level of Evidence: C)*

5. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U per ml 4 h after administration. *(Level of Evidence: C)*
6. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should be at least twice control. *(Level of Evidence: C)*
7. In pregnant patients with mechanical prosthetic valves who receive warfarin, the INR goal should be 3.0 (range 2.5 to 3.5). *(Level of Evidence: C)*
8. In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2 to 3 weeks before planned delivery. *(Level of Evidence: C)*

CLASS IIa

1. In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation owing to the high risk of fetal defects. *(Level of Evidence: C)*
2. In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4 to 6 h after delivery and begin oral warfarin in the absence of significant bleeding. *(Level of Evidence: C)*
3. In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75 to 100 mg per day) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin. *(Level of Evidence: C)*

CLASS III

1. LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4 to 6 h after administration. *(Level of Evidence: C)*
2. Dipyridamole should not be used instead of aspirin as an alternative antiplatelet agent in pregnant patients with mechanical prosthetic valves because of its harmful effects on the fetus. *(Level of Evidence: B)*

In April 2004, labeling approved by the FDA stated that pregnancy alone conferred an increased risk for thromboembolism and an even higher risk with thrombotic disease and certain high-risk pregnancy conditions. Although not adequately studied, women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy regardless of the anticoagulant used, and when pregnant, they have a higher rate of fetal loss from stillbirth, spontaneous abortion, and premature delivery.

With both warfarin and UFH, monitoring is required to assess whether the antithrombotic effects of these drugs change during pregnancy because of alterations in intravascular volume. Both European and North American guidelines emphasize that the use of oral coumarin derivatives throughout pregnancy targeted to an INR of 2.0 to 3.0 confers the greatest maternal protection (5.7% risk of death or thromboembolism) and that heparin used during the first trimester confers a lesser degree of protection. Unfortunately, these drugs are also associated with a great risk of fetal loss (up to 30%) (812).

To examine the validity of these conclusions and explore optimum antithrombotic regimens, Chan and colleagues (813) performed a systematic review of the literature examining fetal and maternal outcomes of pregnant women with prosthetic heart valves. Because no randomized trials were identified, the overview consisted of prospective and retrospective cohort studies. This analysis suggests that warfarin is more efficacious than UFH for thromboembolic prophylaxis of women with mechanical heart valves in pregnancy, but with an increased risk of embryopathy (813). The use of low-dose UFH is inadequate; the use of adjusted-dose UFH warrants aggressive monitoring and appropriate dose adjustment. Contemporary aPTT reagents are more sensitive to the anticoagulant effect of heparin. Therefore, a minimum target aPTT ratio of 1.5 times the control is likely to be inadequate. A target aPTT ratio of at least twice the control should be attained.

Thus, there are still insufficient grounds to make definitive recommendations about optimal antithrombotic therapy in pregnant patients with mechanical heart valves, because properly designed studies have not been performed. Substantial concern remains about the fetal safety of warfarin, the efficacy of subcutaneous UFH and of LMWH in preventing thromboembolic complications, and the risks of maternal bleeding with various regimens. European experts have recommended warfarin therapy throughout pregnancy in view of the reports of poor maternal outcomes with heparin and their impression that the risk of embryopathy with coumarin derivatives has been overstated, especially if the dosage of warfarin is less than or equal to 5 mg per day.

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy (814,815) concluded that it is reasonable to use 1 of the following 3 regimens: 1) either LMWH or UFH between 6 and 12 weeks and close to term only, with warfarin used at other times; 2) aggressive dose-adjusted UFH throughout pregnancy; or 3) aggressive adjusted-dose LMWH throughout pregnancy. Before any of these approaches is used, it is crucial to explain the risks in detail to the patient. If warfarin is used, the dose should be adjusted to attain a target INR of 3.0 (range 2.5 to 3.5). If subcutaneous UFH is used, it should be initiated in high doses (17 500 to 20 000 U every 12 h) and adjusted to prolong a 6-h postinjection aPTT of at least twice the control. Adjusted-dose LMWH appears to be a reasonable substitute for UFH, but further information is required about dosing during pregnancy. If LMWH is used during pregnancy, it has been recommended that it be administered twice daily and dosed to achieve anti-Xa levels of 0.7 to 1.2 U per ml 4 to 6 h after injection (771,814). The addition of aspirin 75 to 100 mg can be considered in an attempt to reduce the risk of thrombosis, with the recognition that it can increase the risk of bleeding (808).

Dipyridamole should not be considered as an alternative antiplatelet agent because of its harmful effects on the fetus. Neither warfarin nor heparin is contraindicated in postpartum mothers who breast-feed (807).

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5.9. Selection of Valve Prostheses in Young Women

A major area of ongoing controversy concerns the use of prosthetic heart valves in women likely to become pregnant (769,771). Bioprostheses are not as durable as mechanical prostheses, although they may eliminate the need for anticoagulation therapy associated with mechanical prostheses. Also, MV repair is preferable to MV replacement whenever possible in women contemplating pregnancy, because it does not require anticoagulation. Furthermore, MV balloon commissurotomy is an alternative to surgery in many patients with MS. The Ross procedure in patients requiring AVR is an attractive option for women who wish to become pregnant, but this should be performed only in institutions with established expertise in this procedure (799).

6. MANAGEMENT OF CONGENITAL VALVULAR HEART DISEASE IN ADOLESCENTS AND YOUNG ADULTS (UPDATED)

Although the majority of valvular heart disease in older adults is acquired, the predominant cause is congenital in adolescents and young adults. It has been estimated that the prevalence of moderate or complex congenital heart disease in adults is approximately 419 000 in the United States (816). Many patients with congenital heart disease have some valvular involvement; frequently, it is part of a more complex congenital cardiac anomaly, that is, tricuspid stenosis in children with pulmonary atresia and an intact ventricular septum or AS as part of a series of left-sided heart obstruction lesions (Shone's syndrome). The management of these complex diseases with multiple valve involvement is beyond the scope of these guidelines. Rather, this section concerns isolated valve involvement when it is the primary anatomic abnormality.

In evaluating valvular stenosis in children, the severity of valvular obstruction is usually reported as the peak ventricular–to–peak great artery systolic gradient at cardiac catheterization or maximum instantaneous or mean gradient by Doppler echocardiography rather than valve area. In the catheterization laboratory, the variation in body size from the neonate to the adult, difficulties in measuring cardiac output (especially in young children), and the relatively rare patient with low cardiac output have made peak ventricular–to–peak great artery pressure gradients for semilunar valves and atrial a-wave–to–RV or LV end-diastolic or mean pressure gradients for atrioventricular valves the reference standards rather than valve area. With the development of Doppler echocardiographic assessment of valvular obstruction, many pediatric cardiologists have continued to rely on gradients calculated from peak velocity for the semilunar valves rather than on mean gradient or valve area. The peak gradient measured by Doppler velocity (based on maximum instantaneous velocity) is almost always higher than the peak ventricular–to–peak great vessel gradient measured at catheterization. The difference between Doppler peak instantaneous and catheterization peak-to-peak gradients is greater with AS than with pulmonic stenosis and has resulted in most cardiologists using mean gradients, especially in patients with AS. Significant valvular regurgitation may exacerbate the differences. In contrast to children and adolescents, valve area is used by many centers in evaluation of the young adult.

Ventricular end-systolic or end-diastolic diameter or volumes used in evaluating patients with valvular regurgitation are frequently corrected for the large variations in body size among adolescents and young adults. Chamber size is corrected for body surface area (m^2) or commonly by the number of standard deviations (z score) above or below the mean with standard nomograms that correct for body size (817).

The management of the neonate, infant, and young child differs significantly from that of the adolescent and young adult. This section will deal exclusively with adolescents and young adults.

6.1. Aortic Stenosis

6.1.1. Pathophysiology

Although most adults with valvular AS have a degenerative-calcific process that produces immobilization of the valve cusps, adolescents and young adults with isolated AS almost always have congenital fusion of 1 or more commissures that results in a bicuspid or unicuspid valve. Although the prevalence of bicuspid and unicuspid valves may be as high as 1% to 2%, only 1 of 50 children born with these abnormalities will actually have significant obstruction or regurgitation by adolescence.

For purposes of these guidelines, adolescents and young adults are defined as patients with minimally calcified valves who are less than 30 years old. Some adults with minimally calcified valves who are more than 30 years old may also benefit under these guidelines.

Much of what has been written in these guidelines for adults with acquired AS may be transferred to the adolescent or young adult (see Section 3.1.); however, certain important differences must be emphasized. Throughout childhood, the aortic annulus and aortic valve must grow in parallel with somatic growth. If growth of either the annulus or valve leaflets lags, increased obstruction may occur. Therefore, the rate of progression during childhood and adolescent growth can be different from that in the adult with acquired heart disease. The report from the joint study on the Natural History of Congenital Heart Defects (818) followed 473 patients (before the advent of echocardiography), 60% of whom were initially evaluated between 2 and 11 years of age and 34% between 11 and 21 years of age. One third of the children had an increase in the transaortic gradient measured by cardiac catheterization during the 4- to 8-year follow-up period. However, the 54 patients greater than 12 years of age showed very small increases. Those

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with higher initial gradients had a greater likelihood of demonstrating an increase in the gradient.

Long-term results of the original cohort have been reported (819), with a mean follow-up period of 20 years. Only 20% of those with initial peak LV–to–peak aortic pressure gradients less than 25 mm Hg at initial catheterization had any intervention. However, in those with an initial catheter-derived LV–to–peak aortic gradient greater than 50 mm Hg, arrhythmias, sudden death, or other morbid events (including endocarditis, congestive heart failure, syncope, angina, myocardial infarction, stroke, and pacemaker insertion) occurred at a rate on average of 1.2% per year. Sudden cardiac death occurred in 25 of the 370 patients followed up over an average of 8000 patient years, for an average incidence of 0.3% per year. The severity of obstruction in those who died could not be determined, and a higher-risk subgroup could not be excluded.

6.1.2. Evaluation of Asymptomatic Adolescents or Young Adults With Aortic Stenosis

CLASS I

1. An ECG is recommended yearly in the asymptomatic adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m per second (peak gradient greater than 50 mm Hg) and every 2 years if the echocardiographic Doppler mean gradient is less than or equal to 30 mm Hg or the peak velocity is less than or equal to 3.5 m per second (peak gradient less than or equal to 50 mm Hg). *(Level of Evidence C)*
2. Doppler echocardiography is recommended yearly in the asymptomatic adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m per second (peak gradient greater than 50 mm Hg) and every 2 years if the Doppler gradient is less than or equal to 30 mm Hg or the peak jet velocity is less than or equal to 3.5 m per second (peak gradient less than or equal to 50 mm Hg). *(Level of Evidence C)*
3. Cardiac catheterization for the evaluation of AS is an effective diagnostic tool in the asymptomatic adolescent or young adult when results of Doppler echocardiography are equivocal regarding severity of AS or when there is a discrepancy between clinical and noninvasive findings regarding severity of AS. *(Level of Evidence: C)*
4. Cardiac catheterization is indicated in the adolescent or young adult with AS who has symptoms of angina, syncope, or dyspnea on exertion if the Doppler mean gradient is greater than 30 mm Hg or the peak velocity is greater than 3.5 m per second (peak gradient greater than 50 mm Hg). *(Level of Evidence: C)*
5. Cardiac catheterization is indicated in the asymptomatic adolescent or young adult with AS who develops T-wave inversion at rest over the left precordium if the Doppler mean gradient is greater than 30 mm Hg or the peak velocity is greater than 3.5 m per second (peak gradient greater than 50 mm Hg). *(Level of Evidence: C)*

CLASS IIa

1. Graded exercise testing is a reasonable diagnostic evaluation in the adolescent or young adult with AS who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m per second (peak gradient greater than 50 mm Hg) if the patient is interested in athletic participation, or if the clinical findings and Doppler findings are disparate. *(Level of Evidence: C)*
2. Cardiac catheterization for the evaluation of AS is a reasonable diagnostic tool in the asymptomatic adolescent or young adult who has a Doppler mean gradient greater than 40 mm Hg or a peak velocity greater than 4 m per second (peak gradient greater than 64 mm Hg). *(Level of Evidence C)*
3. Cardiac catheterization for the evaluation of AS is reasonable in the adolescent or young adult who has a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m per second (peak gradient greater than 50 mm Hg) if the patient is interested in athletic participation or becoming pregnant, or if the clinical findings and the Doppler echocardiographic findings are disparate. *(Level of Evidence C)*

The diagnosis of AS can usually be made clinically, with severity estimated by ECG and Doppler echocardiographic studies. Diagnostic cardiac catheterization is occasionally required if there is a discrepancy among clinical evaluation, ECG, and/or Doppler echocardiographic findings. Exercise testing may be useful, especially in those interested in athletic participation. Diagnostic cardiac catheterization may be helpful if the clinical findings and the Doppler echocardiographic assessment are disparate.

6.1.3. Indications for Aortic Balloon Valvotomy in Adolescents and Young Adults

CLASS I

1. Aortic balloon valvotomy is indicated in the adolescent or young adult patient with AS who has symptoms of angina, syncope, or dyspnea on exertion and a catheterization peak LV–to–peak aortic gradient greater than or equal to 50 mm Hg without a heavily calcified valve. *(Level of Evidence: C)**
2. Aortic balloon valvotomy is indicated for the asymptomatic adolescent or young adult patient with AS who has a catheterization peak LV–to–peak aortic gradient greater than 60 mm Hg. *(Level of Evidence: C)**
3. Aortic balloon valvotomy is indicated in the asymptomatic adolescent or young adult patient with AS who develops ST or T-wave changes over the left precordium on ECG at rest or with exercise and who has a catheterization peak LV–to–aortic gradient greater than 50 mm Hg. *(Level of Evidence: C)**

CLASS IIa

1. Aortic balloon valvotomy is reasonable in the asymptomatic adolescent or young adult patient with AS when catheterization peak LV–to–peak aortic gradient is greater than 50 mm Hg and the patient wants to play competitive sports or desires to become pregnant. *(Level of Evidence: C)**
2. In the adolescent or young adult patient with AS, aortic balloon valvotomy is probably recommended over valve surgery when balloon valvotomy is possible. Patients should be referred to a center with expertise in balloon valvotomy. *(Level of Evidence: C)**

CLASS III

1. Aortic balloon valvotomy should not be performed when the asymptomatic adolescent or young adult patient with AS has a catheterization peak LV–to–peak aortic gradient less than 40 mm Hg without symptoms or ECG changes. *(Level of Evidence: C)**

*Gradients are usually obtained with patients sedated. If general anesthesia is used, the gradients may be somewhat lower.

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Balloon valvotomy for calcific AS in older adults constitutes at best very short-term palliation. In contrast, balloon valvotomy in children and adolescents with obstruction due to fusion of commissures is considerably more efficacious. There are insufficient published data to establish an age cutoff. Until more information becomes available, recommendations for balloon valvotomy should be limited to adolescents and young adults. In a large collaborative registry involving 606 patients from 23 institutions, the peak LV–to–peak aortic pressure gradients at catheterization were reduced by a mean of 60% (820). In a single-institution study of 148 patients dilated at age 1 month to 20 years (821), midterm results showed an 8-year actuarial survival of 95%, with 3 of the 4 deaths occurring in infants who were dilated at less than 1 year of age. Seventy percent of patients were free from operation and 50% were free from intervention 8 years after dilation, which was similar to results reported with surgical valvuloplasty. Long-term follow-up information is incomplete because balloon valvotomy was not introduced until the 1980s.

Although balloon dilation has become standard in children and adolescents with AS, it is rarely recommended in older adults with calcific valves, because even short-term palliation is uncommon. Because balloon valvotomy has resulted in good midterm palliation with little morbidity and little or no short- or intermediate-term mortality in children, adolescents, and young adults, the indications for intervention are considerably more liberal than those in older adults, in whom intervention usually involves valve replacement.

Surgical valvotomy is of historic interest but is now rarely used except in situations in which interventional cardiologists are not available. Children and young adults with peak Doppler gradients of 64 mm Hg or more or mean gradients greater than 40 mm Hg and those with symptoms may be considered for cardiac catheterization and possible balloon dilation. Patients with lower gradients (50 mm Hg peak or 30 mm Hg mean) are sometimes referred for catheterization if they are interested in participating in athletics, are contemplating pregnancy, or have developed ST–T-wave changes over the left precordium at rest or with exercise. The gradient should be confirmed hemodynamically before proceeding with dilation. Gradients are usually obtained with the patient sedated. If general anesthesia is used, the gradients may be lower. It is reasonable to perform valvotomy in asymptomatic patients with catheterization gradients greater than 60 mm Hg and in some patients with a catheterization peak LV–to–peak aortic pressure gradient of 50 to 60 mm Hg who have symptoms, have associated ischemic changes on rest or exercise ECG, are interested in participating in vigorous athletics, or are contemplating pregnancy. In those children who have had a balloon valvuloplasty when younger, a repeat attempt is usually tried before surgical valve replacement using the above criteria if significant AR is not present.

When balloon aortic valvotomy is ineffective or significant AR is present, valve repair or replacement may be necessary. Long-term follow-up into adulthood is mandatory, because the long-term cumulative risks of endocarditis, thromboembolism, and bleeding from anticoagulation over 20- to 40-year follow-up have been problematic, and progressive stenosis has been observed (153,822). Because degeneration of homograft or bioprosthetic valves is usually accelerated in the young (see Sections 7.2 and 7.3), AVR is usually performed with a mechanical valve. Recently, there has been a renewed interest in valve repair or the Ross operation (153,822), that is, moving the native pulmonary valve to the aortic position using a homograft to replace the pulmonary valve. Three studies from the Netherlands (343 patients; mean age 26 years) (823), Canada (155 patients; mean age 35 years) (824), and the United States (328 patients) (825) have shown relatively low operative mortality (2.6%, 0.6%, and 4.6%, respectively) with actuarial survival of 94% and 98% at 7 years in 2 of the studies and 89.9% at 8 years in the other. The most common complications were AR, usually secondary to neoaortic root dilation, and RV outflow tract obstruction, with intervention necessary in approximately 10% of patients within 7 to 10 years.

Although the Ross operation, homograft, heterograft, and valve repair each appear to offer an attractive alternative to a mechanical valve for those with a relative contraindication to warfarin for anticoagulation (e.g., athletes or woman desiring pregnancy), in the absence of long-term results, it is not believed that the indications for surgery with the Ross operation, heterograft, or homograft differ from those for mechanical valve replacement at this time.

6.2. Aortic Regurgitation

CLASS I

1. An adolescent or young adult with chronic severe AR* with onset of symptoms of angina, syncope, or dyspnea on exertion should receive aortic valve repair or replacement. *(Level of Evidence: C)*
2. Asymptomatic adolescent or young adult patients with chronic severe AR* with LV systolic dysfunction (ejection fraction less than 0.50) on serial studies 1 to 3 months apart should receive aortic valve repair or replacement. *(Level of Evidence: C)*
3. Asymptomatic adolescent or young adult patients with chronic severe AR* with progressive LV enlargement (end-diastolic dimension greater than 4 standard deviations above normal) should receive aortic valve repair or replacement. *(Level of Evidence: C)*
4. Coronary angiography is recommended before AVR in adolescent or young adult patients with AR in whom a pulmonary autograft (Ross operation) is contemplated when the origin of the coronary arteries has not been identified by noninvasive techniques. *(Level of Evidence: C)*

CLASS IIb

1. An asymptomatic adolescent with chronic severe AR* with moderate AS (peak LV–to–peak aortic gradient greater than 40 mm Hg at cardiac catheterization) may be considered for aortic valve repair or replacement. *(Level of Evidence: C)*

*See Table 4 (27).

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2. An asymptomatic adolescent with chronic severe AR* with onset of ST depression or T-wave inversion over the left precordium on ECG at rest may be considered for aortic valve repair or replacement. *(Level of Evidence: C)*

AR is an uncommon isolated congenital lesion, although it may occasionally develop in adolescents and young adults with a bicuspid aortic valve, discrete subaortic obstruction, or prolapse of 1 aortic cusp into a ventricular septal defect. It is commonly the consequence of attempts to relieve stenosis of the valve by either balloon dilation or surgical valvulotomy, as part of a connective tissue disorder, or when the pulmonary artery is relocated in the aortic position (Ross procedure or arterial switch repair of transposition). The indications for surgery with severe isolated AR or mixed aortic valve disease are at present similar to those for adults, that is, symptoms, LV dysfunction (ejection fraction less than 0.50), or very increased LV end-diastolic or end-systolic diameter, taking into account variations in body size. If the durability of pulmonary autograft and homograft valves in the RV outflow tract is substantiated in long-term studies, the indications for autograft valve replacement are likely to become more liberal. Surgery has usually involved mechanical or biological valve replacement (see Sections 3.2.3.8 and 7.2), but some have performed the Ross operation or aortic valve repair. Although not all valves are amenable to repair, some success has been reported for AR after balloon dilation (100% freedom from reoperation at 1 year and 80% from reintervention at 3 years) (826) and with a prolapsing leaflet (freedom from reoperation of 95%, 87%, and 84% at 1, 5, and 7 years, respectively) (827). Aortic valve repair is a viable alternative in some centers and may be preferred in the future, but in view of the relative youth of the patients and lack of long-term durability of valve repair or replacement with biological valves, these alternatives to mechanical valve replacement may be appropriate only for those with a contraindication to anticoagulation in the majority of centers. Indications for surgery in patients with AR and dilated aortic roots or ascending aortas are the same as in older adult patients (see Sections 3.2.4 and 3.3).

6.3. Mitral Regurgitation

CLASS I

1. MV surgery is indicated in the symptomatic adolescent or young adult with severe congenital MR* with NYHA functional class III or IV symptoms. *(Level of Evidence: C)*
2. MV surgery is indicated in the asymptomatic adolescent or young adult with severe congenital MR* and LV systolic dysfunction (ejection fraction less than or equal to 0.60). *(Level of Evidence: C)*

CLASS IIa

1. MV repair is reasonable in experienced surgical centers in the asymptomatic adolescent or young adult with severe congenital MR* with preserved LV systolic function if the likelihood of successful repair without residual MR is greater than 90%. *(Level of Evidence: B)*

*See Table 4 (27).

CLASS IIb

1. The effectiveness of MV surgery is not well established in asymptomatic adolescent or young adult patients with severe congenital MR* and preserved LV systolic function in whom valve replacement is highly likely. *(Level of Evidence: C)*

MR caused by myxomatous MV disease and MVP is a common congenital lesion, but other forms of isolated congenital MR are extremely uncommon. MR can be associated with MVP in adolescents or young adults with connective tissue, metabolic, or storage diseases. It can be seen with acquired inflammatory diseases such as rheumatic fever, endocarditis, or Kawasaki disease or with certain collagen vascular disorders.

MR also develops commonly in children with primum atrioventricular septal defects. These defects are caused by a deficiency of the atrioventricular septum in the embryonic heart. There may be an isolated ostium primum atrial septal defect; ventricular septal defect in the inlet (posterior) septum; abnormalities of the mitral or tricuspid valve, including clefts; or some combination of the above. In a complete atrioventricular septal defect, there is a combination of a large primum atrial septal defect, a large inlet (posterior) ventricular septal defect, and a common atrioventricular valve that failed to develop into separate mitral and tricuspid valves. Repair of the defects in early childhood, with low mortality and morbidity, is now commonplace. The most common long-term sequela of surgery is MR, which can be mild, moderate, or severe.

The pathophysiology, diagnosis, and medical therapy of residual MR in atrioventricular septal defects, rheumatic fever, or MVP are similar to those discussed for the adult with MR (Section 3.5). When MR is associated with symptoms or deteriorating LV systolic function on echocardiography or angiography, surgery should be performed. In children with MR associated with atrioventricular septal defects, the MR can usually be reduced or eliminated with surgery. In patients with MR after atrioventricular septal defect repair or MR secondary to MVP, rheumatic fever, or inflammatory disease, it is usually possible to decrease the MR with MV repair and annular reduction. Rarely, MV replacement with a mechanical or biological valve is necessary. When valve repair rather than replacement is likely, surgery for severe MR is frequently performed in asymptomatic patients before the development of heart failure or LV dysfunction. On the other extreme, for symptomatic patients with MR and severe LV dysfunction, cardiac transplantation may be the preferred option to MV replacement or repair.

6.4. Mitral Stenosis

CLASS I

1. MV surgery is indicated in adolescent or young adult patients with congenital MS who have symptoms (NYHA functional class III or IV)

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and mean MV gradient greater than 10 mm Hg on Doppler echocardiography.* *(Level of Evidence: C)*

CLASS IIa

1. MV surgery is reasonable in adolescent or young adult patients with congenital MS who have mild symptoms (NYHA functional class II) and mean MV gradient greater than 10 mm Hg on Doppler echocardiography.* *(Level of Evidence: C)*
2. MV surgery is reasonable in the asymptomatic adolescent or young adult with congenital MS with pulmonary artery systolic pressure 50 mm Hg or greater and a mean MV gradient greater than or equal to 10 mm Hg.* *(Level of Evidence: C)*

CLASS IIb

1. The effectiveness of MV surgery is not well established in the asymptomatic adolescent or young adult with congenital MS and new-onset atrial fibrillation or multiple systemic emboli while receiving adequate anticoagulation.* *(Level of Evidence: C)*

In developed countries, MS in adolescents and young adults is often congenital in origin. In developing areas of the world, MS is more likely to result from rheumatic fever. Congenital MS is usually classified by the component of the mitral apparatus that is abnormal, that is, the leaflets, annulus, chordae, or papillary muscles. Frequently, multiple valve components are involved, which results in rolled, thickened leaflet margins; shortened and thickened chordae tendineae; obliteration of the interchordal spaces with abnormal chordal insertions; papillary muscle hypoplasia; and fusion of the anterolateral and posteromedial papillary muscles (828). This latter condition causes the mitral apparatus to appear like a funnel or a parachute. MS results from the inability of blood to pass unobstructed from the left atrium to the LV through a very abnormal mitral apparatus.

Congenital MS may be associated with a wide variety of other congenital cardiac malformations of the left side of the heart, including bicuspid aortic valve and AS, supravalvar mitral ring, and/or coarctation of the aorta.

The clinical, electrocardiographic, and radiologic features of congenital MS are similar to those of acquired MS in adults. The echocardiogram is essential in evaluating the MV apparatus and papillary muscles and may provide considerable insight into the feasibility of successful valve repair. The information obtained from transthoracic imaging is usually sufficient, but in adolescents and young adults, a transesophageal echocardiogram is sometimes necessary.

Medical management including beta blockers and diuretics may be of some utility with mild MS. It is important to prevent and treat common complications such as pulmonary infections, endocarditis, and atrial fibrillation. Surgical intervention may be necessary in severe cases. The surgical management of congenital MS has improved considerably with the improved appreciation of the mechanism of MV function and the improved ability to visualize the valve afforded by transesophageal echocardiography. In those patients with a parachute MV, creation of fenestrations among the fused chordae may increase effective orifice area and improve symptoms dramatically. MV replacement may occasionally be necessary but is especially problematic in those with a hypoplastic mitral annulus, in whom an annulus-enlarging operation may be necessary. Recently, balloon dilation of congenital MS has been attempted (829), but its utility is limited in patients with significant stenosis of the subvalvular apparatus. This is one of the most difficult and dangerous therapeutic catheterization procedures and should be undertaken only in centers with operators who have established experience and skill in this interventional procedure. In adolescent and young adult patients with rheumatic MS, the results of balloon dilation are similar to those in older adults (see Section 3.4.8). Pulmonary artery hypertension usually resolves with relief of the MS.

*See Table 4 (27).

6.5. Tricuspid Valve Disease

6.5.1. Pathophysiology

Acquired disease of the tricuspid valve is very uncommon in adolescents and young adults. Other than occasional cases of TR secondary to trauma, bacterial endocarditis in intravenous drug abusers, and small ventricular septal defects in adolescents in whom the jet through the ventricular septum creates endothelial damage to the tricuspid valve, virtually all cases of acquired TR are limited to case reports.

Most cases of tricuspid valve disease are congenital, with Ebstein's anomaly of the tricuspid valve being the most common. In Ebstein's anomaly, there is inferior displacement of the septal and posterior leaflets of the valve into the right ventricle. If there is significant adherence of the leaflets to the RV wall, the normal or relatively normal anterior leaflet fails to coapt with the abnormal posterior leaflet, creating severe TR. If the valve leaflets are not adherent, there is redundancy of valve tissue with severe prolapse associated with varying degrees of TR.

There is wide variation in the severity of valve leaflet abnormalities in Ebstein's disease. Some children may have severe TR, especially in the perinatal period, when pulmonary vascular resistance and resulting RV pressures are high. Others have very mild abnormalities that may not be recognized until a chest X-ray obtained for other reasons shows cardiomegaly. An interatrial communication, usually in the form of a patent foramen ovale, is present in most cases. If TR elevates right atrial pressure above left atrial pressure, right-to-left shunting can occur, with resulting hypoxemia. One or more accessory conduction pathways are quite common, with a risk of paroxysmal atrial tachycardia of approximately 25%.

Patients with Ebstein's anomaly may be asymptomatic with no cyanosis and no atrial arrhythmias. They often are cyanotic owing to right-to-left shunting (830), which is associated with exercise intolerance. RV dysfunction may eventually lead to right-sided congestive heart failure frequently exacerbated by an atrial arrhythmia such as atrial

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tachycardia, atrial flutter, or atrial fibrillation. Exercise testing may be useful in determining symptom status and degree of exercise-induced arterial desaturation.

The natural history of Ebstein's anomaly varies. In patients who present in the perinatal period, the 10-year actuarial survival is 61% (831). In a study that included more children who presented after the perinatal period, the probability of survival was 50% at 47 years of age (832). Predictors of poor outcome include NYHA functional class III or IV symptoms, cardiothoracic ratio greater than 65%, atrial fibrillation, severity of cyanosis, and magnitude of TR. However, patients with Ebstein's anomaly who reach late adolescence and adulthood often have an excellent outcome (832).

6.5.2. Evaluation of Tricuspid Valve Disease in Adolescents and Young Adults

CLASS I

1. An ECG is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1 to 3 years, depending on severity. *(Level of Evidence: C)*
2. Chest X-ray is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1 to 3 years, depending on severity. *(Level of Evidence: C)*
3. Doppler echocardiography is indicated for the initial evaluation of adolescent and young adult patients with TR, and serially every 1 to 3 years, depending on severity. *(Level of Evidence: C)*
4. Pulse oximetry at rest and/or during exercise is indicated for the initial evaluation of adolescent and young adult patients with TR if an atrial communication is present, and serially every 1 to 3 years, depending on severity. *(Level of Evidence: C)*

CLASS IIa

1. If there is a symptomatic atrial arrhythmia, an electrophysiology study can be useful for the initial evaluation of adolescent and young adult patients with TR. *(Level of Evidence: C)*
2. Exercise testing is reasonable for the initial evaluation of adolescent and young adult patients with TR, and serially every 1 to 3 years. *(Level of Evidence: C)*

CLASS IIb

1. Holter monitoring may be considered for the initial evaluation of asymptomatic adolescent and young adult patients with TR, and serially every 1 to 3 years. *(Level of Evidence: C)*

6.5.3. Indications for Intervention in Tricuspid Regurgitation

CLASS I

1. Surgery for severe TR is recommended for adolescent and young adult patients with deteriorating exercise capacity (NYHA functional class III or IV). *(Level of Evidence: C)*
2. Surgery for severe TR is recommended for adolescent and young adult patients with progressive cyanosis and arterial saturation less than 80% at rest or with exercise. *(Level of Evidence: C)*
3. Interventional catheterization closure of the atrial communication is recommended for the adolescent or young adult with TR who is hypoxemic at rest and with exercise intolerance due to increasing hypoxemia with exercise, when the tricuspid valve appears difficult to repair surgically. *(Level of Evidence: C)*

CLASS IIa

1. Surgery for severe TR is reasonable in adolescent and young adult patients with NYHA functional class II symptoms if the valve appears to be repairable. *(Level of Evidence: C)*
2. Surgery for severe TR is reasonable in adolescent and young adult patients with atrial fibrillation. *(Level of Evidence: C)*

CLASS IIb

1. Surgery for severe TR may be considered in asymptomatic adolescent and young adult patients with increasing heart size and a cardiothoracic ratio of more than 65%. *(Level of Evidence: C)*
2. Surgery for severe TR may be considered in asymptomatic adolescent and young adult patients with stable heart size and an arterial saturation of less than 85% when the tricuspid valve appears repairable. *(Level of Evidence: C)*
3. In adolescent and young adult patients with TR who are mildly cyanotic at rest but who become very hypoxemic with exercise, closure of the atrial communication by interventional catheterization may be considered when the valve does not appear amenable to repair. *(Level of Evidence: C)*
4. If surgery for Ebstein's anomaly is planned in adolescents and young adult patients (tricuspid valve repair or replacement), a preoperative electrophysiological study may be considered to identify accessory pathways. If present, these may be considered for mapping and ablation either preoperatively or at the time of surgery. *(Level of Evidence: C)*

Surgical management of Ebstein's anomaly remains challenging (833). A Glenn anastomosis between the superior vena cava and right pulmonary artery is occasionally performed to reduce the volume load on the right ventricle. For adolescents and young adults, tricuspid valve repair has been attempted. Reconstruction of the valve is possible, especially when there is a mobile anterior leaflet free of tethering to the ventricular septum. Valvuloplasty may be performed with positioning of the displaced leaflet of the tricuspid valve to the normal level, sometimes with placation of the atrialized portion of the right ventricle to reduce its size. If TR is mild and hypoxemia at rest or exercise is problematic, closure of the atrial septal defect in the catheterization laboratory has been successful in eliminating the hypoxemia.

Occasionally, the tricuspid valve is not reparable, and valve replacement with a bioprosthesis or a mechanical valve may be necessary (834). When present, atrial communications should be closed unless significant postoperative TR or RV dysfunction is anticipated and the presence of an atrial septal defect may allow decompression of the right atrium. If an accessory pathway is present, this should be mapped and ablated either preoperatively in the electrophysiology laboratory or at the time of surgery.

6.6. Pulmonic Stenosis

6.6.1. Pathophysiology

Because the pulmonary valve is the least likely valve to be affected by acquired heart disease, virtually all cases of pulmonary valve stenosis are congenital in origin. Most patients with stenosis have a conical or dome-shaped pulmonary valve formed by fusion of the valve leaflets.

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Occasionally, the valve may be thickened and dysplastic, with the stenosis caused by inability of the valve leaflets to separate sufficiently during ventricular systole (835).

Symptoms are unusual in children or adolescents with pulmonary valve stenosis even when severe. Adults with long-standing severe obstruction may have dyspnea and fatigue secondary to an inability to increase cardiac output adequately with exercise. Exertional syncope or lightheadedness may occur in the presence of severe pulmonic stenosis with systemic or suprasystemic RV pressures, with decreased preload or dehydration, or with a low systemic vascular resistance state (such as pregnancy). However, sudden death is very unusual. Eventually, with long-standing untreated severe obstruction, TR and RV failure may occur.

At any age, if the foramen ovale is patent, RV compliance may be reduced sufficiently to elevate right atrial pressure, which allows right-to-left shunting and cyanosis. This increases the risk of paradoxical emboli.

6.6.2. Evaluation of Pulmonic Stenosis in Adolescents and Young Adults

CLASS I

1. An ECG is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients, and serially every 5 to 10 years for follow-up examinations. *(Level of Evidence: C)*
2. Transthoracic Doppler echocardiography is recommended for the initial evaluation of pulmonic stenosis in adolescent and young adult patients, and serially every 5 to 10 years for follow-up examinations. *(Level of Evidence: C)*
3. Cardiac catheterization is recommended in the adolescent or young adult with pulmonic stenosis for evaluation of the valvular gradient if the Doppler peak jet velocity is greater than 3 m per second (estimated peak gradient greater than 36 mm Hg) and balloon dilation can be performed if indicated. *(Level of Evidence: C)*

CLASS III

1. Diagnostic cardiac catheterization is not recommended for the initial diagnostic evaluation of pulmonic stenosis in adolescent and young adult patients. *(Level of Evidence: C)*

The clinical diagnosis of pulmonary valve stenosis is straightforward, and the severity can usually be determined accurately by 2D and Doppler echocardiography. Diagnostic catheterization is rarely required.

6.6.3. Indications for Balloon Valvotomy in Pulmonic Stenosis (UPDATED)

CLASS I

1. Balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and an RV–to–pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization. *(Level of Evidence: C)*
2. Balloon valvotomy is recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV–to–pulmonary artery peak-to-peak gradient greater than 40 mm Hg at catheterization. *(Level of Evidence: C)*

CLASS IIb

1. Balloon valvotomy may be reasonable in asymptomatic adolescent and young adult patients with pulmonic stenosis and an RV–to–pulmonary artery peak-to-peak gradient 30 to 39 mm Hg at catheterization. *(Level of Evidence: C)*

CLASS III

1. Balloon valvotomy is not recommended in asymptomatic adolescent and young adult patients with pulmonic stenosis and RV–to–pulmonary artery peak-to-peak gradient less than 30 mm Hg at catheterization. *(Level of Evidence: C)*

The clinical course of children and young adults with pulmonary valve stenosis has been well described. The Natural History of Congenital Heart Defects study (836) in the mid 1960s and early 1970s followed 564 patients with valvar pulmonary stenosis with cardiac catheterization at 4- and 8-year intervals. On admission to the study, an average of 15% of patients were less than 2 years old; 20% were 12 to 21 years old; and the remainder were 2 to 11 years old. At initial cardiac catheterization, they were divided into 4 groups based on severity: less than 25 mm Hg peak-to-peak gradient between the right ventricle and the pulmonary artery, trivial; 25 to 49 mm Hg, mild; 50 to 79 mm Hg, moderate; and greater than 80 mm Hg, severe.

Of the 261 patients (46% of the total) treated medically, most had trivial, mild, or moderate obstruction. None of these patients had cyanosis or congestive heart failure, and only 6% had symptoms. There were no deaths during the study. The pressure gradients were stable in the majority, with 14% of patients manifesting a significant increase and 14% a significant decrease. Most of the increases were in children less than 2 years old and/or those with initial gradients greater than 40 mm Hg. Those not in either category had only a 4% chance of an increase in the gradient greater than 20 mm Hg. There was little or no change in the overall status of the medically treated patients. During the period of observation, 304 patients, most with moderate or severe disease, were treated surgically. Only 1 death occurred among the 245 patients in this group who underwent surgery beyond infancy. At postoperative follow-up, the gradient had been reduced to insignificant levels in more than 90%, with no recurrence of pulmonary stenosis in those followed up to 14 years.

In 1993, the second Natural History of Congenital Heart Defects study (837) reported on the 16- to 29-year (mean 22 years) follow-up of the same group of patients. The probability of 25-year survival was 96%, not statistically different from the normal control group. Fewer than 20% of patients managed medically during the first Natural History Study subsequently required a valvotomy, and only 4% of the patients who had undergone surgery required a second operation. Most patients, whether managed medically or surgically, had mild obstruction by Doppler echocardiography. For patients who had an initial transpulmonary gradient less than 25 mm Hg in the first Natural History Study, 96% were free of cardiac operation over a 25-year period.

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Surgical relief of severe obstruction by valvotomy with a transventricular (838) or transpulmonary artery (839) approach predates the introduction of cardiopulmonary bypass. A nonsurgical approach with balloon valvotomy was described in 1982 (840) and by the late 1980s had become the procedure of choice in the United States for the typically domed, thickened valve, both for children (841) and adults (842,843). Surgery is still usually required for the dysplastic valve often seen in Noonan's syndrome. Although long-term follow-up of pulmonary balloon valvotomy is not yet available, the early and midterm results (up to 10 years) (844) suggest that the long-term results will be similar to surgical valvotomy, that is, little or no recurrence over a 22- to 30-year period. Some pulmonary regurgitation almost invariably occurs after valvuloplasty, but it is rarely clinically important in this group.

In those with severe or long-standing valvular obstruction, infundibular hypertrophy may cause secondary obstruction when the pulmonary valve is successfully dilated. This frequently regresses over time without treatment. Some have advocated transient pharmacological beta blockade, but there is insufficient information to determine whether this is effective or necessary.

From the Natural History Study data, it appears that congenital mild pulmonary stenosis is a benign disease that rarely progresses, that moderate or severe pulmonary stenosis can be improved with either surgery or balloon valvotomy at very low risk, and that patients who undergo surgery or balloon valvotomy have an excellent prognosis and a low rate of recurrence. Thus, the goal of the clinician is to ascertain the severity of the disease, treat those in whom it is moderate or severe, and infrequently follow up on those with mild disease (845).

6.7. Pulmonary Regurgitation

Pulmonary valve regurgitation is an uncommon congenital lesion seen occasionally with what has been described as idiopathic dilation of the pulmonary artery or with connective tissue disorders. In this condition, the annulus of the pulmonary valve dilates, which causes failure of the leaflets to coapt during diastole. Mild pulmonary regurgitation may be a normal finding on Doppler echocardiography.

Although pulmonary regurgitation is unusual as an isolated congenital defect, it is an almost unavoidable result of either surgical or balloon valvuloplasty of valvular pulmonic stenosis or surgical repair of tetralogy of Fallot. Among patients with pulmonic stenosis who underwent surgical valvotomy in the first Natural History Study (836), 87% had pulmonary regurgitation by Doppler echocardiography in the second Natural History Study (837), although it was audible in only 58%. The echocardiogram tended to overestimate severity compared with auscultation, with 20% considered moderate to severe by Doppler but only 6% by auscultation. In those with pulmonary regurgitation, the right ventricle tended to be larger, but RV systolic dysfunction was uncommon, being present in only 9%.

Pulmonary regurgitation also commonly occurs after successful repair of tetralogy of Fallot. Several studies have documented that the vast majority of children and young adults who underwent surgery in the late 1950s and 1960s continued to do well for up to 35 years after surgery (846). However, an increasing number of patients with long-standing pulmonary regurgitation have developed severe RV dilatation and diminished RV systolic performance, which can lead to an inadequate ability to augment cardiac output with exercise and, in some cases, congestive heart failure. This group has also been shown to have a significant incidence of ventricular arrhythmias known to be associated with late sudden death. Increased pulmonary artery pressure from LV dysfunction or residual peripheral pulmonary artery stenosis will increase the amount of regurgitation, and these conditions should be treated when present. Cardiac magnetic resonance has proven to be a useful tool for evaluating pulmonary regurgitant fraction, RV end-diastolic and end-systolic volumes, and RV ejection fraction. A wide variation has been observed, but many adolescents and young adults with repaired tetralogy of Fallot have regurgitant fractions exceeding 40% to 50%, with RV end-diastolic dimensions of more than 150 ml per m^2 (normal 75 ml per m^2) and RV ejection fractions of less than 0.40. Gatzoulis et al. have noted that QRS prolongation (greater than 180 m per second) relates to RV size and predicts malignant ventricular arrhythmias and sudden death after tetralogy of Fallot repair (847). Pulmonary valve replacement, usually with a homograft or xenograft, has been performed with low risk (833), has been shown to stabilize QRS duration, and, in conjunction with cryoablation, has decreased the incidence of pre-existing atrial and ventricular tachyarrhythmias (848). Pulmonary valve replacement has also been found to result in reduction in regurgitant fraction and RV end-diastolic volumes but little change in RV ejection fraction (849,850).

Most physicians would perform pulmonary valve replacement in patients with NYHA functional class II or III symptoms and severe pulmonary regurgitation, but for asymptomatic patients, the indications based on regurgitant fraction, RV end-diastolic or end-systolic volume, and RV ejection fraction remain unclear. Many would share the concern that it may be unwise to wait until RV function deteriorates, and that with pulmonary regurgitation, as with AR, valve replacement (see Section 3.2.3.8) should be considered before irreversible damage to ventricular performance occurs (851). That point has yet to be determined, however.

7. SURGICAL CONSIDERATIONS

Cardiac valve surgery began with off-pump trans-LV and/or trans-left atrial commissurotomy performed to treat rheumatic MS in the early 1950s. Since this limited beginning, valve surgery has flourished on the basis of advances in

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surgical experience and technology, particularly the development of cardiopulmonary bypass, effective prosthetic valves, and consistent intraoperative myocardial protection.

The availability of cardiopulmonary bypass allowed isolation of the heart from the circulation and the performance of true open heart operations. Early valve operations were by necessity conservative in nature and included open commissurotomy of the MV, simple repair of some types of MR and AR, and decalcification of aortic valves.

The development of cardiac valve prostheses in the early 1960s expanded the spectrum of pathologies in patients with valvular heart disease that could be treated surgically. Many different designs for prosthetic heart valves were studied experimentally and clinically during the 1970s, but by 1980, the basic designs of the prostheses used today had been established. Available heart valve prostheses can be grouped into 2 major categories: mechanical valves and bioprostheses. Mechanical valves have the advantage of structural stability but the disadvantage of requiring anticoagulation with warfarin. Bioprostheses have the advantage of not requiring anticoagulation with warfarin but the disadvantage of being subject to time-related structural valve failure. All heart valve replacement strategies are imperfect. An excellent review of long-term durability and complications of valve prostheses has been published by Grunkemeier et al. (852) based on 265 clinical studies involving more than 61 000 prostheses and a cumulative experience of 319 749 valve-years (Table 34).

After the development of cardiopulmonary bypass and valvular prostheses, the next important technological advance was development of cardioplegic myocardial protection, a strategy that allows intraoperative protection of ventricular function, even for patients with diffuse CAD, and at the same time provides a favorable surgical field for complex valve operations. As a result, abnormal preoperative myocardial function is no longer the major predictor of risk for patients undergoing valve surgery, and the overall in-hospital mortality and morbidity have decreased. In addition, effective myocardial protection has made possible the most recent technological trend in valve surgery, which is in the direction of complex valve reparative procedures and the avoidance of valve replacement.

7.1. American Association for Thoracic Surgery/ Society of Thoracic Surgeons Guidelines for Clinical Reporting of Heart Valve Complications

In 1988, standards for defining and reporting complications after heart valve operations were proposed by the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity, a joint committee of the American Association for Thoracic Surgery and the STS (853). These guidelines were revised in 1996 (854,855). The complications determined to be of critical importance in the 1996 guidelines are summarized as follows:

- Structural valvular deterioration refers to any change in function of an operated valve that results from an intrinsic abnormality that causes stenosis or regurgitation.
- Nonstructural dysfunction is a composite category that includes any abnormality that results in stenosis or regurgitation of the operated valve that is not intrinsic to the valve itself, exclusive of thrombosis and infection. This category includes inappropriate sizing, also called "valve prosthesis-patient mismatch" (856), and tissue ingrowth around the prosthesis that may cause a fixed stenosis or inhibit valve motion, causing stenosis and/or regurgitation.
- Valve thrombosis is any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or interferes with function of the valve.
- Embolism is any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed). This includes any new, temporary or permanent, focal or global neurological deficit and peripheral embolic event; emboli proven to consist of nonthrombotic material are excluded.
- Bleeding event (formerly anticoagulant hemorrhage) is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury or requires transfusion. The complication "bleeding event" applies to all patients, whether or not they are taking anticoagulants or antiplatelet drugs.
- Operated valvular endocarditis is any infection that involves an operated valve. Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, is included under this category and not in other categories of morbidity.

The consequences of the above events include reoperation; valve-related mortality; sudden unexpected, unexplained death; cardiac death; total deaths; and permanent valve-related impairment (854,855) in addition to cardiac-related symptoms such as dyspnea, fatigue, and angina. In addition, valve prosthesis may produce hemolysis due either to the valve itself or to associated perivalvular leak.

There is a wide range in the reported incidence of complications with the same prosthetic valve and between different valves (852). This is most likely due to variation among series rather than to valve type and model (857). It has been emphasized (858) that these variations include factors associated with patients (e.g., ventricular function, comorbidities), medical center (e.g., surgical variables, definitions of complications, thoroughness of follow-up), and data analysis (e.g., influences of patient-related factors) (857). In addition, published data represent only a small fraction of valves implanted (852,858).

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Table 34. Prosthetic Valve Clinical Studies

Type	Model	Position	Series	Valves	Valve-Years
Mechanical valves					
Ball	Starr-Edwards	Aortic	5	2339	19 069
		Mitral	8	2524	20 928
Disc	Björk-Shiley	Aortic	4	795	5954
		Mitral	6	1330	8895
	Monostrut	Aortic	4	4950	16 776
		Mitral	3	4265	14 747
	Medtronic Hall	Aortic	8	1964	11 918
		Mitral	4	638	3256
	Omniscience	Aortic	2	185	1239
		Mitral	1	103	716
	Omnicarbon	Aortic	2	232	1280
		Mitral	1	95	463
	Ultracor	Aortic	1	225	751
		Mitral	1	172	660
Bileaflet	St. Jude	Aortic	14	6813	33 379
		Mitral	15	5636	28 456
	Carbomedics	Aortic	5	2252	7928
		Mitral	4	1094	3917
	Edwards Tekna	Aortic	4	1039	4586
	Duromedics	Mitral	2	439	1903
	Sorin Bicarbon	Aortic	1	163	408
Total mechanical			95	37 253	187 230
Biological valves					
Porcine	Hancock I	Aortic	10	4118	30 260
		Mitral	6	2014	16 282
	Hancock II	Aortic	2	858	5010
		Mitral	3	551	3086
	Intact	Aortic	3	1265	2779
		Mitral	3	779	2066
	Carpentier-Edwards	Aortic	9	3069	15 962
		Mitral	7	1977	12 632
	Freestyle	Aortic	1	699	577
	Bicor	Aortic	1	856	2317
		Mitral	1	137	510
Pericardial	C-E Perimount	Aortic	10	4865	23 027
		Mitral	3	481	2179
	Mitroflow	Aortic	2	318	1800
		Mitral	1	96	576
Homograft	Homograft	Aortic	8	2119	13 457
Total biological			70	24 202	132 519
Total			265	61 455	319 749

Modified with permission from Grunkemeier GL, Li HH, Naftel DC, et al. Long-term performance of heart valve prostheses. Curr Probl Cardiol 2000;25:73–154 (852).

Many types of bias affect reported results (859), which might be overcome with randomized trials; however, randomized trials also have difficulties (860,861). The number of randomized studies of prosthetic heart valves is small, and the majority of those that have been reported are of insufficient size to add importantly to the knowledge already obtained from careful observational studies.

7.2. Aortic Valve Surgery

The types of operations available to treat aortic valve dysfunction include AVR with a mechanical or a bioprosthetic valve, AVR with an allograft (homograft) valve, pulmonic valve autotransplantation (Ross operation) (153,822–825,862), aortic valve repair, and left ventricle–to–descending aorta shunt. Each has specific advantages and disadvantages. Cardiopulmonary bypass is used in aortic valve operations, and these procedures are usually performed through a median sternotomy incision, although partial sternotomy (minimally invasive incisions) is gaining acceptance. See Sections 3.1.7 and 3.2.3.8 for indications for AVR or repair in patients with AS and AR.

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7.2.1. Risks and Strategies in Aortic Valve Surgery

The voluntary STS database (165) received reports regarding 9108 to 11 665 isolated AVRs per year during the years 1999 through 2004 (total of 62 834 operations). This voluntary registry is not inclusive of national practice, but it represents the best approximation currently available. Selected patient-related descriptors were mean age 66 years, female gender 42%, and previous cardiac surgery 16.5%. Approximately 76% of patients had AS, and the mean LV ejection fraction was 0.53. In-hospital mortality by year ranged from 2.9% to 3.6%, and the risk of permanent stroke was 1.5% to 1.8%. Experienced centers have reported mortality rates for primary isolated AVR of less than 1% to 2%, although the national average in the STS database is 3% to 4% (165) and is higher in low-volume centers (166). During the 1999 to 2002 time frame, the implantation of mechanical valves declined from 41% to 33% of total cases, with a corresponding increase in the implantation of bioprostheses from 50% to 65%, whereas the use of homografts was steady at approximately 2%.

The majority of patients undergoing AVR have other cardiac lesions, most commonly CAD, and more complex pathology has been associated with increased risk. Experienced centers have reported very little incremental risk associated with combined pathology, but the mortality rates for a combined AVR and CABG is 6% to 7% (165). Even technical expertise does not negate the influence of cardiac and noncardiac comorbidity associated with diffuse atherosclerosis or aneurysmal disease.

7.2.2. Mechanical Aortic Valve Prostheses

Designs of mechanical aortic valve prostheses currently available in the United States include ball-and-cage valves, single tilting disc prostheses, and bileaflet prostheses. Ball-and-cage valves have the disadvantage of noise and hemodynamic inefficiency and today are rarely used, although the mechanical stability of ball-and-cage prostheses has been excellent at follow-up intervals of more than 30 years. Single-tilting disc valves currently available in the United States are the Medtronic-Hall valve and the Omnicarbon valve. These valves have superior hemodynamic efficiency to ball-and-cage valves and have been structurally stable. The most severe disadvantage of the single-disc design is severe hemodynamic compromise if disc thrombosis or immobility occurs.

The most common mechanical valve design used in the aortic position is the bileaflet valve, with versions available in the United States being manufactured by St. Jude, CarboMedics, ATS Medical, and On-X. The bileaflet valves are relatively quiet, appear to be mechanically stable, and are relatively hemodynamically efficient. The operation for implantation of mechanical prostheses is standard, as is the surgery for reoperation when that is needed. The disadvantages of mechanical valves are the need to take warfarin for anticoagulation to prevent thromboembolism, the risk of bleeding complications, the risk of thromboembolism despite warfarin therapy, endocarditis, and hemodynamic inefficiency in smaller sizes. Also, the structural stability of mechanical valves does not eliminate the possibility of reoperation for other indications such as valve thrombosis, tissue ingrowth and valve dysfunction, periprosthetic leak, endocarditis, symptomatic patient-prosthesis mismatch, and multiple bleeding episodes secondary to warfarin therapy.

7.2.2.1. ANTITHROMBOTIC THERAPY FOR PATIENTS WITH AORTIC MECHANICAL HEART VALVES

After mechanical AVR, the goal of antithrombotic therapy is usually to achieve an INR of 2.5 to 3.5 for the first 3 months after surgery and 2.0 to 3.0 beyond that time (see Section 9.2). Low-dose aspirin (75 to 100 mg per day) is also indicated in addition to warfarin (808), as discussed in Section 9.2.1. At that level of anticoagulation, the risk of significant hemorrhage appears to be 1% to 2% per year. Although the goal of mechanical and materials engineering has been to produce a mechanical valve that does not require anticoagulation with warfarin, that goal has not yet been achieved. Trials diminishing or eliminating anticoagulation with warfarin or substituting platelet inhibitors for warfarin have so far noted a high rate of thromboembolism.

7.2.3. Stented and Nonstented Heterografts

7.2.3.1. AORTIC VALVE REPLACEMENT WITH STENTED HETEROGRAFTS

The most commonly used aortic valve prostheses in the United States today are stented heterografts that are constructed with bovine pericardial tissue or porcine aortic valve tissue arranged on a cloth and metal frame. These valves have the advantages of a low thromboembolism rate without warfarin, a simple and standard implantation technique, a standard reoperation risk, a low risk of catastrophic valve failure, and widespread availability in many valve sizes. The disadvantages of stented heterografts are structural valve deterioration, imperfect hemodynamic efficiency, a standard risk of prosthetic valve endocarditis, and a low (0.7% per year) but present risk of thromboembolism without warfarin anticoagulation. Stented pericardial heterografts have better hemodynamic performance than porcine heterografts, especially in smaller sizes (less than 21 mm) (863–866). In a randomized trial comparing stented porcine xenografts and stented pericardial valves (866), the reduced pressure gradients with the pericardial valve translated into greater reduction in LV mass at a mean 1.2-year follow-up period after AVR.

The first-generation stented heterografts (porcine heterografts) exhibited a freedom from structural valve deterioration of approximately 40% by 18 postoperative years. However, the rate of structural valve deterioration is age-related (168,867–880), being increased for younger patients, and in patients less than 40 years of age, approximately half of porcine valves fail by 10 years (Table 35). Bovine pericardial valves appear to have a lower rate of structural valve

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Table 35. Structural Valve Deterioration of Bioprosthetic Valves

Author, Year	Mean Follow-Up, y	Number of Valves		Time of SVD Estimate, y	Age, y	Freedom From SVD, %		Comments
		AVR	MVR			AVR	MVR	
Jamieson et al., 1988 (867)	5.6	572	509	10	30–59	81 ± 4	78 ± 5	Carpentier-Edwards standard porcine bioprosthesis
					Greater than 60	91 ± 3	71 ± 9	
Cohn et al., 1989 (868)	6.0	971	708	15	40 or less	68 ± 9	68 ± 10	Hancock porcine bioprosthesis (includes 146 combined AVR + MVR procedures)
					41–69	86 ± 2	84 ± 13	
					70 or greater	94 ± 3	84 ± 10	
Jones et al., 1990 1990 (869)	8.3	610	528	10	Less than 40	46 ± 7	47 ± 8	Hancock or Carpentier-Edwards porcine bioprosthesis (includes 88 combined AVR + MVR procedures)
					40–49	60	48 ± 8	
					50–59	79	61	
					60–69	92 ± 2	80 ± 6	
Burdon et al., 1992 (872)	7.3	857	793	15	16–39	33 ± 7	37 ± 6	Hancock I and Hancock modified orifice porcine bioprosthesis
					40–49	54 ± 10	38 ± 12	
					50–59	57 ± 6	38 ± 5	
					60–69	73 ± 6	61 ± 15	
					Greater than 70	93 ± 3	62 ± 6	
Burr et al., 1992 (873)	—	574	500	7	Less than 65	94 ± 1	88 ± 2	Carpentier-Edwards standard porcine bioprosthesis (similar results were obtained with Carpentier-Edwards supra-annular porcine bioprosthesis)
					65–69	98 ± 1	90 ± 4	
					70–79	100	95 ± 3	
					80 or greater	100	100	
				13–15	Less than 65	62 ± 8	37 ± 7	
					65–69	98 ± 3	63 ± 8	
					70–79	95 ± 5	74 ± 19	
					80 or greater	100	—	
Pelletier et al., 1992 (874)	7.0	451	547	10	Less than 45	70	55	Carpentier-Edwards standard (302 AVR, 324 MVR) improved annulus (97 AVR, 135 MVR), supra-annular (52 AVR, 88 MVR) porcine bioprostheses (includes 121 combined AVR + MVR and 5 combined MVR + TVR procedures)
					45–54	84	64	
					55–64	84	69	
					65 or greater	93	95	
Cosgrove et al., 1995 (875)	7.8	310	—	10	Less than 65	88.6	—	Carpentier-Edwards pericardial aortic bioprosthesis
					65 or greater	95.5	—	
Pelletier et al., 1995 (876)	4.5	416	—	10	Less than 60	86.3	—	Carpentier-Edwards pericardial aortic bioprosthesis
					60–69	95.3	—	
					70 or greater	100	—	
Cohn et al., 1998 (877)	6.1	843	—	10	50 or less	57	—	Hancock modified orifice porcine aortic valve
					51–69	77	—	
					70 or greater	96	—	
				15	50 or less	16	—	
					51–69	54	—	
					70 or greater	87	—	
Banbury et al., 2001 (168)	12	267	—	15	45	58	—	Carpentier-Edwards pericardial aortic bioprosthesis
					55	70	—	
					65	82	—	
					75	91	—	
Jamieson et al., 2001 (879)	6.2	836	332	12	51–60	92 ± 3		
					61–70	96 ± 2	90 ± 3	Medtronic Intact porcine bioprosthesis
					Greater than 70	98 ± 1	97 ± 3	

AVR indicates aortic valve replacement; MVR, mitral valve replacement; SVD, structural valve deterioration; and TVR, tricuspid valve replacement.

deterioration, with 15-year data indicating that 77% of valves in surviving patients of all ages are functioning without explantation, and among patients undergoing primary AVR at an age greater than 65 years, fewer than 10% underwent valve explantation by 15 postoperative years (168,876). The reported rate of structural valve deterioration for second-generation porcine valves appears so far to be equivalent to that of stented bovine valves.

7.2.3.2. AORTIC VALVE REPLACEMENT WITH STENTLESS HETEROGRAFTS

Stentless heterografts are valves constructed from porcine aortic valves that use a smaller amount of cloth for stabilization, sewing, and tissue ingrowth than a full cloth-metal stent. The major goal of stentless heterografts is to achieve enhanced hemodynamic efficiency relative to stented valves (881–886). The long-term importance of hemodynamic efficiency of prosthetic heart valves is currently a subject of

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investigation and disagreement. The argument favoring the use of stentless valves is that stented valves of any kind are at least partially stenotic (particularly in small sizes) and that even small postoperative gradients may lead to incomplete LV mass regression postoperatively (883,885–887), which will, in turn, lead to impaired long-term survival and symptom status. Some randomized and nonrandomized but comparative studies (885–887) have reported lower transvalvular gradients and more consistent regression of LV mass after AVR when stentless valves are used than with stented prostheses, whereas other studies show no differences (888,889). In addition, the long-term importance of LV mass regression is not clear.

One nonrandomized study reported improved postoperative survival with stentless than with stented porcine bioprostheses (890). However, in the several randomized trials comparing stented and stentless valves, there has been no difference in patient outcomes at 1 to 3 years after surgery (886–889). It is clear that the combination of large and active patients and small aortic valve prostheses can lead to high transprosthetic gradients (particularly with exercise) and symptoms related to patient-prosthesis mismatch (856). However, the importance of small transvalvular gradients is as yet unclear. Stentless heterografts have the disadvantage that their implantation is more complex than that for stented valves, and their long-term outcomes are unknown. There is a low incidence (7% to 10%) of early mild AR in some series (883,884,886), which may progress with time, but it is uncertain whether this differs from the experience with some stented bioprostheses (856,883,884). Observational studies with 8- to 10-year follow-up (891) appear to show a low risk of structural valve deterioration with stentless heterografts, and the hope is that improved hemodynamic design will lead to improved longevity. Time will tell. Stentless valves are implanted with techniques similar to those used for aortic valve homografts, but they have the advantage of increased availability compared with aortic valve homografts.

7.2.4. Aortic Valve Homografts

Aortic valve allografts (homografts) have been used for AVR since early in the cardiac surgical era (892), but the rapid failure rate of early homografts (30% structural valve deterioration by 10 years) and the complex implantation techniques required limited their use. The use of homografts has been revived by cryopreservation techniques that appear to diminish the rate of structural valve deterioration (169,171). Homografts may be implanted as a "free hand" valve in the subcoronary position; as a "mini-root" replacement, during which the valve is implanted within the native root cylinder; and as a full root replacement, during which the native aortic root is removed and entirely replaced with the homograft aortic root, the coronary arteries being reimplanted into the homograft. All these operations are more complex than the implantation of standard mechanical valves or stented heterografts. Total aortic root replacement is currently the most common homograft implantation strategy.

It had been hoped that aortic valve homografts would outlast heterografts, particularly in young patients, but to date, long-term data do not support this view. One possible advantage of homografts is in the avoidance of early endocarditis and in the treatment of aortic valve endocarditis (893–896), particularly complex aortic root endocarditis, although the literature does not demonstrate the superiority of any single prosthesis in these situations (852,897–900). The risk of thromboembolism is very low after homograft implantation, and hemodynamic efficiency is excellent even in small sizes. The biggest disadvantage of homografts is that reoperation after homograft AVR is more difficult than reoperation after placement of standard prostheses, because the entire homograft may become severely calcified. In a randomized trial comparing homografts and stentless bioprosthetic valves, there was no difference in hemodynamics or patient outcomes at 1 year after operation (901,902). As with stentless bioprostheses, AR may develop, and there is an increased likelihood of need for reoperation in patients under the age of 40 years (903).

7.2.5. Pulmonic Valve Autotransplantation

Pulmonic valve autotransplantation (Ross operation) is an operation developed in an attempt to provide a permanent biological aortic valve prosthesis using the pulmonic valve (153,822,823,825,862) In this operation, the pulmonic valve is excised and used to replace the aortic valve either as a subcoronary implantation or as a full aortic root replacement, while the pulmonic valve is then replaced with an alternative prosthesis, usually a pulmonic homograft. This operation has been performed in small numbers, and long-term follow-up studies have been inconsistent, which makes analysis of long-term advantages and disadvantages difficult. The known advantages of the procedure are that the autograft may grow in children, warfarin is not required, there is a low incidence of thromboembolism, the autograft is a hemodynamically efficient valve, and the incidence of endocarditis is low (904). The disadvantage of pulmonic autotransplantation is that the operation is much more complex than standard AVR and in most series has been associated with at least some increase in in-hospital mortality. There is also an incidence of early aortic valve failure based on technical considerations or dilatation of the aortic root, and the homograft used to replace the pulmonic valve is also subject to failure, sometimes early, within a few years of operation (862). Small, short-term randomized and nonrandomized comparisons of pulmonary autografts and aortic homografts have demonstrated no definite advantage of either in adults in terms of hemodynamics and patient outcome (905–907). Deterioration of the pulmonary homograft also offsets potential advantages of the autograft.

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Table 36. Probability of Death Due to Any Cause, Any Valve-Related Complications, and Individual Valve-Related Complications 15 Years After Randomization in the Veterans Affairs Cooperative Study on Valvular Heart Disease

	Aortic Valve			Mitral Valve		
Event	Mechanical (n = 198)	Porcine (n = 196)	*p*	Mechanical (n = 88)	Porcine (n = 93)	*p*
Death due to any cause	66 ± 3	79 ± 3	0.02	81 ± 4	79 ± 4	0.30
Any valve-related complications	65 ± 4	66 ± 5	0.26	73 ± 6	81 ± 5	0.56
Systemic embolism	18 ± 4	18 ± 4	0.66	18 ± 5	22 ± 5	0.96
Bleeding	51 ± 4	30 ± 4	<0.001	53 ± 7	31 ± 6	0.01
Endocarditis	7 ± 2	15 ± 5	0.45	11 ± 4	17 ± 5	0.37
Valve thrombosis	2 ± 1	1 ± 1	0.33	1 ± 1	1 ± 1	0.95
Perivalvular regurgitation	8 ± 2	2 ± 1	0.09	17 ± 5	7 ± 4	0.05
Reoperation	10 ± 3	29 ± 5	0.004	25 ± 6	50 ± 8	0.15
Structural valve failure	0 ± 0	23 ± 5	<0.001	5 ± 4	44 ± 8	<0.001

Values are actuarial percentages plus/minus standard error. Note: *p* values are for differences between mechanical and porcine valves. Data are from Hammermeister K, Sethi GK, Henderson WG, et al. 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;36:1152–8 (174). Reprinted with permission.

7.2.6. Aortic Valve Repair

Multiple strategies for aortic valve repair have been explored, some successfully. Aortic valve repair by decalcifying stenotic calcific aortic valves was used in the preprosthesis era but abandoned because of recalcification and restenosis. Revival of its use with modern myocardial protection and decalcification techniques still is associated with a high rate of restenosis. Repair of rheumatic aortic valves has, in general, not been successful over time. In contrast, repair of insufficient bicuspid aortic valves in the adult has been increasingly successful at limited numbers of centers (827,908,909). Among the advantages of this strategy are the lack of need for anticoagulation, a low thromboembolic risk, a low endocarditis risk, a hemodynamically efficient valve, and a straightforward reoperation, if needed. The disadvantages are lack of uniform applicability, lack of widespread experience with surgical techniques, and the need for reoperation. Long-term data are limited, but the risk of reoperation appears to be about 15% by 10 postoperative years. Although late calcification of these repaired valves has to be considered likely given enough time, calcification may be delayed in some patients with repaired bicuspid valves, who may avoid reoperation for decades.

Much progress has been made in the repair of aortic valves rendered insufficient by aortic root pathology (364,910–915). When an aortic root aneurysm exists, the operation to restore competence to the aortic valve involves resecting the aorta and resuspending the valve in association with a Dacron graft that is used to replace the aorta. Advantages of this strategy include avoidance of warfarin, a low thromboembolic risk, a very efficient valve, and what appears to be a low risk of prosthetic valve endocarditis. The disadvantages are, again, limited applicability in the setting of intrinsic leaflet pathology and the high level of surgical expertise and experience required.

7.2.7. Left Ventricle–to–Descending Aorta Shunt

In situations involving pathologies that make standard AVR operations particularly risky, such as multiple previous operations, severe aortic calcification, and previous radiation therapy, a left ventricle–to–descending thoracic aortic shunt using a Dacron graft containing a valve can be an effective alternative treatment (916). This procedure is performed through a left thoracotomy with or without cardiopulmonary bypass. A valved conduit is connected to the LV apex via a metal connector and then anastomosed to the descending intrathoracic aorta. Favorable short-term outcomes have been reported, but the long-term hemodynamics results and complication rate associated with this strategy are currently unknown.

7.2.8. Comparative Trials and Selection of Aortic Valve Prostheses

Two randomized trials have compared outcomes for patients receiving mechanical and bioprosthetic valves in the aortic position, the Edinburgh Heart Valve Trial (1975–1979) (917) and the Veterans Affairs Cooperative Study on Valvular Heart Disease (1979–1982) (174,918). Both compared the Bjork-Shiley tilting-disc valve with first-generation porcine heterografts. In the Veterans Affairs trial, 15-year survival rates were superior for patients with mechanical valves (34%) compared with those with bioprostheses (21%) in the aortic position ($p = 0.02$), but 20-year survival rates were no different in the Edinburgh trial. As expected, bleeding rates were significantly higher for patients with mechanical valves, and structural valve deterioration and reoperation rates were higher for patients with bioprostheses in both trials (174,917,918). The long-term results of the Veterans Affairs Cooperative Study (174) are shown in Table 36.

Despite the randomized design of these trials and the apparent slight advantage for patients receiving mechanical prostheses, the trend in the United States has been away

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from mechanical prostheses and towards biological valves for multiple reasons.

- Current bioprostheses appear to have lower rates of structural valve deterioration than those used during the randomized trials that involved first-generation bioprostheses. Reoperation rates for patients over 65 years of age are particularly low with modern stented bioprostheses (Table 35).
- The risks of reoperation have continued to decrease since these trials were completed, particularly the risk of a first reoperation.
- Patients undergoing AVR today represent an older population than those studied in the randomized trials.
- Young patients undergoing aortic valve surgery are often reluctant to accept warfarin therapy and the activity constraints associated with anticoagulants.
- There are some nonrandomized but relatively large comparative trials that have shown apparent survival benefit for patients receiving bioprostheses, particularly for those over the age of 65 years (919).

On the basis of these considerations, most patients over 65 years of age receive a bioprosthesis. There are no data involving large patient numbers that clearly show long-term advantages for one type of aortic valve operation over another or for any individual prosthesis over another.

At many major valve surgery centers, the age threshold for the use of bioprosthetic valves in the aortic position has decreased to well below 65 years in those patients who do not wish to take anticoagulation. The decision requires full discussion with the patient, with the understanding that there is a higher chance of the need for reoperation with a bioprosthesis.

In the previous 1998 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease, mechanical valves were recommended (Class IIa) in patients with end-stage renal failure, especially those undergoing chronic dialysis, because of the concern of accelerated calcification of bioprosthetic valves. Subsequent retropsective studies (919a) have demonstrated no significant difference in outcome of such patients treated with mechanical prostheses versus bioprostheses. The current writing committee has made no specific recommendations for valve selection in dialysis patients, but notes the difficulties in maintaining anticoagulation in these patients.

Selection among biological valve operations is based on logic and opinion rather than consistently defined differences and outcomes. Surgeon experience is important, because there are no long-term data justifying the use of operations that increase perioperative risk. The most common biological valve used is a stented heterograft because of its easy implantation, the ease of reoperation, the extensive data defining its late outcomes, and the lack of data supporting the use of more complex strategies. Although it had been hoped that homografts would have an improved failure rate relative to stented heterografts, at this point, data do not support that view. A stentless allograft or homografts are a good choice for patients with small aortic root sizes at risk for patient-prosthesis mismatch (856,863–865). Stentless heterografts have been effective in the short term, but the extent of their advantage is unclear in regard to valve efficiency, and long-term failure rates are not known (886,889,920). Current data noting a 20% failure rate by 10 postoperative years do not indicate improved long-term outcomes compared with stented bioprostheses. Pulmonic valve autotransplantation is used by some to allow growth of the autograft in children. Its use in adults has been limited by some increase in operative risk and data indicating a reoperation rate of approximately 20% by 10 postoperative years.

7.2.9. Major Criteria for Aortic Valve Selection

CLASS I

1. A mechanical prosthesis is recommended for AVR in patients with a mechanical valve in the mitral or tricuspid position. *(Level of Evidence: C)*
2. A bioprosthesis is recommended for AVR in patients of any age who will not take warfarin or who have major medical contraindications to warfarin therapy. *(Level of Evidence: C)*

CLASS IIa

1. Patient preference is a reasonable consideration in the selection of aortic valve operation and valve prosthesis. A mechanical prosthesis is reasonable for AVR in patients under 65 years of age who do not have a contraindication to anticoagulation. A bioprosthesis is reasonable for AVR in patients under 65 years of age who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future. *(Level of Evidence: C)*
2. A bioprosthesis is reasonable for AVR in patients aged 65 years or older without risk factors for thromboembolism. *(Level of Evidence: C)*
3. Aortic valve re-replacement with a homograft is reasonable for patients with active prosthetic valve endocarditis. *(Level of Evidence: C)*

CLASS IIb

1. A bioprosthesis might be considered for AVR in a woman of childbearing age (see Sections 5.7 and 5.8). *(Level of Evidence: C)*

7.3. Mitral Valve Surgery

MV surgery began with valve-conserving operations for rheumatic MS and expanded to treat a variety of pathologies once prosthetic valve replacement became available. Today, valve-conserving operations have become more common and are used to treat a variety of pathologies. Analysis of the outcomes after MV surgery is complex. Those outcomes are affected not only by the valve-coronary pathology treated but also by LV function, cardiac rhythm, and surgeon experience. Operations currently available to treat MV dysfunction include closed mitral commissurotomy, replacement with a mechanical prosthesis, replacement with a bioprosthesis, replacement with an MV homograft or Ross-type autograft, and a variety of reparative MV procedures.

The surgical approaches to MV surgery are varied. Closed or "off-pump" mitral commissurotomy can be performed either percutaneously with a balloon catheter or surgically through a left thoracotomy (see Sections 3.4.8 and 3.4.9).

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The standard approach for MV replacement or complex repair is use of a median sternotomy with cardiopulmonary bypass; however, many alternative incisions are now used, including partial sternotomy and small right thoracotomy access, strategies described as "minimally invasive." Video-assisted and robotic-assisted MV surgery are becoming more feasible, and standard outcomes have been described for small numbers of selected patients undergoing surgery at centers that specialize in these alternative surgical strategies.

When the MV is replaced, an attempt is made to preserve at least part of the subvalvular apparatus, that is, the chordae tendineae connecting the papillary muscles with the valve annulus. Experimental and clinical data show that long-term LV function may benefit by this strategy.

7.3.1. Mitral Valve Repair

MV surgery began with conservative operations for rheumatic MS; within the last 20 years, conservative operations to treat MR have been developed and popularized to treat degenerative and functional MV disease, as well as some patients with MV endocarditis. The outcomes of MV repair must be analyzed according to the pathologies treated rather than the operation alone.

7.3.1.1. MYXOMATOUS MITRAL VALVE

CLASS I

1. MV repair is recommended when anatomically possible for patients with severe degenerative MR who fulfill clinical indications, and patients should be referred to surgeons who are expert in repair. *(Level of Evidence: B)*
2. Patients who have undergone successful MV repair should continue to receive antibiotics as indicated for endocarditis prophylaxis. *(Level of Evidence: C)*
3. Patients who have undergone successful MV repair and have chronic or paroxysmal atrial fibrillation should continue to receive long-term anticoagulation with warfarin. *(Level of Evidence: B)*
4. Patients who have undergone successful MV repair should undergo 2D and Doppler echocardiography before discharge or at the first postoperative outpatient visit. *(Level of Evidence: C)*
5. Tricuspid valve repair is beneficial for severe TR in patients with MV disease that requires MV surgery. *(Level of Evidence: B)*

CLASS IIa

1. Oral anticoagulation is reasonable for the first 3 months after MV repair. *(Level of Evidence: C)*
2. Long-term treatment with low-dose aspirin (75 to 100 mg per day) is reasonable in patients who have undergone successful MV repair and remain in sinus rhythm. *(Level of Evidence: C)*
3. Tricuspid annuloplasty is reasonable for mild TR in patients undergoing MV repair when there is pulmonary hypertension or tricuspid annular dilatation. *(Level of Evidence: C)*

CLASS IIb

1. In patients with MR and a history of atrial fibrillation, a Maze procedure may be considered at the time of MV repair. *(Level of Evidence: B)*

Myxomatous MV disease produces MR based on rupture or elongation of chordae tendineae, valve leaflet instability, annulus dilatation, or multiple causes that result in excessive MV leaflet motion. In the majority of these conditions, experienced surgeons can repair the MV using strategies that involve removal of unsupported leaflet structures, transfer of chordae (467,468), or the use of artificial chordae to support unstable areas of the leaflet, the sliding of supported areas of the leaflet to cover the MV orifice, and stabilization of the size and shape of the MV annulus with an artificial ring (529,530,545,568–573). When possible, MV repair is the treatment of choice for degenerative valve disease, because patients in sinus rhythm do not need warfarin, the thromboembolism rate is low, valve efficiency and hemodynamics are good, there is little adverse effect on LV function, the risk of endocarditis is low, and the long-term survival rate is favorable compared with MV replacement (see Section 3.6.4). Concomitant tricuspid valve repair should be performed when there is severe TR or mild-to-moderate TR and tricuspid annular dilatation (see Section 3.7.4.3 and Section 3.8.3). In patients presenting for MV repair with chronic atrial fibrillation, a concomitant surgical procedure to eliminate atrial fibrillation may prevent future embolic events by restoring normal sinus rhythm (608–614). The decision to proceed with a surgical procedure to eliminate atrial fibrillation should be made based on the age and health of the patient, as well as the surgical expertise, because this procedure may add to the morbidity of the operation (see Section 3.6.4.2.4).

The likelihood of a successful MV repair is related to the extent of the MV dysfunction (with isolated posterior leaflet dysfunction being the most favorable condition); the presence and extent of calcification; the amount of pliable, noncalcified valve tissue; and surgeon experience. Recurrent MR after repair may occur with time, but in favorable situations, more than 90% of valves are still functioning well after 10 years (529,530).

7.3.1.2. RHEUMATIC HEART DISEASE

CLASS I

1. Percutaneous or surgical MV commissurotomy is indicated when anatomically possible for treatment of severe MS, when clinically indicated. *(Level of Evidence: C)*

Rheumatic MR is inconsistently reparable, and the long-term outcomes after repair are not as good as for valve repair for degenerative MV disease. Rheumatic pathology often leads to leaflet and chordal scarring, which restricts the leaflet motion, and leaflet scarring may be progressive after repair. Rheumatic MS that is not associated with severe chordal fusion or shortening or with calcification may be treated with either percutaneous or open mitral commissurotomy with a high degree of long-term success. Clinical indications for these procedures are discussed in Section 3.4.8.

7.3.1.3. ISCHEMIC MITRAL VALVE DISEASE

By definition, all patients with ischemic MR have significant CAD that usually has a significant effect on long-term survival. The pathology of ischemic MR has multiple

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subgroups, with the most common situation being functional MR, in which the valve leaflets are structurally normal, but LV chamber enlargement and papillary muscle displacement tether the MV via the chordal attachments and prevent leaflet coaptation (616–623). When functional MR is severe, it may be corrected by placement of an annuloplasty ring that decreases the annular circumference, shortens the intertrigonal distance, reduces the septal-lateral (anterior-posterior) annular diameter, and restores the geometry of the annulus, thereby allowing the MV leaflets to coapt (624–627,633–642). This strategy acutely decreases or eliminates MR, but because the fundamental abnormality is related to LV function, the late survival rate of these patients is relatively low compared with patients with other MV pathologies, and the recurrence rate of mitral dysfunction is higher. For patients with moderate functional MR, it is not yet clear whether MV repair improves outcomes.

Patients with ischemic MV disease who have anatomic MR based on infarction or rupture of the papillary muscles benefit from either mitral repair or MV replacement. Papillary muscle rupture often produces severe MR and hemodynamic decompensation, which is an indication for emergency surgery.

7.3.1.4. MITRAL VALVE ENDOCARDITIS

With increased surgical experience in mitral reparative techniques, MV endocarditis has become more consistently treatable with repair (760–762). There appears to be a low risk of recurrent infection, and in experienced hands, it is often possible to avoid the need for an MV prosthesis (see Section 4.6.1). Surgery, however, must not be delayed until extensive valve disruption has occurred.

7.3.2. Mitral Valve Prostheses (Mechanical or Bioprostheses)

Mechanical Prostheses: Ball-and-cage valves, single-tilting disc valves, and bileaflet prostheses are available MV prostheses. Ball-and-cage valves have been effective but can cause some degree of outflow tract obstruction by projecting into the LV outflow tract, a problem not present with bileaflet or disc valves. Most studies have shown that the thromboembolism risk is greater for patients with mechanical MV prostheses than for patients with aortic valves, even when adjusted for the presence of atrial fibrillation. Thus, anticoagulation for patients with mechanical MV prostheses is maintained at an INR of 2.5 to 3.5 indefinitely.

Bioprostheses: Both porcine heterografts and bovine pericardial heterografts are available in the United States for MV replacement. Porcine heterografts have been followed up for longer intervals, but limited data appear to show a slower rate of structural valve deterioration for second-generation porcine heterografts and bovine pericardial valves (921,922). The failure rate of mitral heterografts appears to be higher than that for aortic heterografts (Table 35). For example, in the VA Cooperative Study, 29% of aortic valve and 50% of mitral porcine heterografts needed reoperation by 15 postoperative years (Table 36) (174).

7.3.2.1. SELECTION OF A MITRAL VALVE PROSTHESIS

CLASS I

1. A bioprosthesis is indicated for MV replacement in a patient who will not take warfarin, is incapable of taking warfarin, or has a clear contraindication to warfarin therapy. *(Level of Evidence: C)*

CLASS IIa

1. A mechanical prosthesis is reasonable for MV replacement in patients under 65 years of age with long-standing atrial fibrillation. *(Level of Evidence: C)*
2. A bioprosthesis is reasonable for MV replacement in patients 65 years of age or older. *(Level of Evidence: C)*
3. A bioprosthesis is reasonable for MV replacement in patients under 65 years of age in sinus rhythm who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second MV replacement may be necessary in the future. *(Level of Evidence: C)*

The STS National Cardiac Surgery Database (165) indicates that the numbers of MV reparative procedures are increasing relative to MV replacement. For isolated MV operations during the years 2000 through 2004, valve repairs numbered 2335, 2755, 3779, 3978, and 3712, respectively, compared with 4215, 4141, 4517, 4145, and 3579 MV replacement operations, respectively. Mortality rates were 1.5% to 2.0% for repair versus 5.4% to 6.4% for MV replacement. Among patients receiving a MV replacement, more patients received mechanical valves than bioprostheses. Medicare data indicate that the mortality for isolated MV replacement in patients older than 65 years is 14.1%, which increases to 20.5% in low-volume centers (167). When MV pathology is combined with CAD, the risks of surgery increase. For the same 5 years noted above, an average of 3637 patients per year underwent MV repair combined with CABG (165), with mortality rates ranging from 7% to 8.7%, and 2814 patients per year underwent MV replacement plus CABG, with mortality rates in excess of 11%. The majority of patients in this group received bioprostheses. The selection of a valve is a multifactorial decision.

7.3.2.2. CHOICE OF MITRAL VALVE OPERATION

MV repair should be able to be achieved by experienced surgeons for the majority of patients with degenerative MV disease and ischemic valve disease, and patients should be referred to surgeons expert in repair. For patients with rheumatic MV disease and endocarditis, repair may be more difficult.

For patients undergoing MV replacement, preservation of the chordal apparatus preserves LV function and enhances postoperative survival compared with MV replacement in which the apparatus is disrupted (570,579–582), as discussed in Section 3.6.4.1. In the randomized trials, there was no difference in survival rate based on valve type; however, the failure rate of bioprostheses has been higher in

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the mitral than in the aortic position (Table 35), which adds impetus to the use of mechanical prostheses in younger patients.

The availability of surgical ablation procedures for atrial fibrillation offers the possibility of converting the patient to sinus rhythm and avoiding anticoagulation after MV repair or replacement with a bioprosthesis (608–614). If patients can be maintained in sinus rhythm, the advantage of a bioprosthesis is enhanced. For patients with a history of atrial fibrillation who are undergoing MV repair, a Maze-type procedure results in sinus rhythm in 75% to 90% of cases by 6 postoperative months, with long-term data indicating sustained results up to 8 years and reduced risk of stroke (611,614). The effect of ablation of atrial fibrillation for patients with multivalve disease or valve disease combined with CAD is not known.

7.4. Tricuspid Valve Surgery

CLASS I

1. Severe TR in the setting of surgery for multivalvular disease should be corrected. *(Level of Evidence: C)*

CLASS IIa

1. Tricuspid annuloplasty is reasonable for mild TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation. *(Level of Evidence: C)*

The most common cause of TR is dilatation of the tricuspid valve annulus caused by pulmonary hypertension. The tricuspid leaflets are usually normal, and tricuspid valve annuloplasty usually corrects or improves the situation. Severe TR should be treated with annuloplasty during operations for multivalvular disease (see Sections 3.7.4.3 and 3.8.3). Other causes of TR include rheumatic valvular disease, endocarditis, leaflet scarring due to inflammatory conditions, and adherence of tricuspid valve structures to transtricuspid pacing wires. When leaflet anatomy is severely abnormal, tricuspid valve replacement may be needed, but this situation is not common. There are no data clearly showing the advantage of one type of tricuspid prosthesis over another.

7.5. Valve Selection for Women of Childbearing Age

There is no ideal valve prosthesis for women of childbearing age who might wish to become pregnant (see detailed discussion in Section 5.8). Bioprostheses may be subject to premature heterograft or homograft failure. Because mechanical valves require anticoagulation, there is an increased risk of fetal abnormalities and mortality, and there may be an increased risk of maternal complications, including thromboembolism. Discussion with the patient concerning the risk of the prosthesis is important (see Section 5.8.4).

8. INTRAOPERATIVE ASSESSMENT

CLASS I

1. Intraoperative transesophageal echocardiography is recommended for valve repair surgery. *(Level of Evidence: B)*
2. Intraoperative transesophageal echocardiography is recommended for valve replacement surgery with a stentless xenograft, homograft, or autograft valve. *(Level of Evidence: B)*
3. Intraoperative transesophageal echocardiography is recommended for valve surgery for infective endocarditis. *(Level of Evidence: B)*

CLASS IIa

1. Intraoperative transesophageal echocardiography is reasonable for all patients undergoing cardiac valve surgery. *(Level of Evidence: C)*

Detailed and comprehensive evaluation of valve lesions during cardiac surgery has become possible and common since the development of transesophageal echocardiography. This includes confirmation of the preoperative diagnosis and associated pathology, provision of additional detail and depth about the severity and mechanism of valve dysfunction, detection of previously undiagnosed conditions, and evaluation of the surgical result in the operating room, which makes possible the immediate correction of detected problems. Studies have documented the impact of intraoperative transesophageal echocardiography on valve surgery, with changes in the operative plan based on transesophageal echocardiography findings reported in 11% to 14% of cases and detection of problems with surgical procedure and subsequent need to return to cardiopulmonary bypass reported in 2% to 6% (923–926). Other important aspects of transesophageal echocardiography during valve surgery include assessment of ventricular function and detection of intracardiac air and aortic dissection.

Currently, the application of transesophageal echocardiography during valve surgery varies a great deal from institution to institution. Availability of equipment and expertise are important factors in determining this application, and the committee recognizes that such resources may vary. Although controlled, randomized trials substantiating the benefit of intraoperative transesophageal echocardiography during valve surgery have not been performed, there are many nonrandomized studies, case series, and significant expert experience that support its utility in this setting.

Intraoperative transesophageal echocardiography is especially important during valve repair surgery. Examination before cardiopulmonary bypass provides insight into the mechanism of valve dysfunction and therefore facilitates surgical planning. More importantly, intraoperative transesophageal echocardiography allows immediate assessment of the repair after cardiopulmonary bypass. Intraoperative transesophageal echocardiography during valve replacement surgery with a stented prosthetic valve is also useful, although there will be a lower rate of problems detected after cardiopulmonary bypass. Valve replacement with a stentless xenograft, homograft, or autograft valve will have a higher likelihood of technical problems during surgery, and therefore, transesophageal echocardiography is virtually essential in this setting because it is currently the best way to assess valve function intraoperatively. Because of the potential for multiple valve involvement and associated lesions such as abscesses and fistulas, transesophageal echocardiog-

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raphy should also be performed during valve surgery for acute infective endocarditis. Patients undergoing valve surgery may have other indications for intraoperative transesophageal echocardiography, such as severely decreased LV function or hemodynamic instability. The committee recommends that institutions performing valve surgery establish consistent and credible intraoperative echocardiography programs with knowledgeable echocardiographers committed to and capable of providing accurate anatomic and functional information relevant to valve operations. Such services should be available during surgery to facilitate evaluation of unexpected difficulties. Although transesophageal echocardiography is generally a safe procedure when properly performed in appropriate patients, there are risks to its performance (927). Thus, preoperative screening for risk factors and the obtainment of informed consent should be a routine part of every intraoperative transesophageal study.

A physician trained in transesophageal echocardiography, be it a cardiologist, cardiac anesthesiologist, or cardiac surgeon, must perform the intraoperative transesophageal echocardiogram (928). Intraoperative transesophageal echocardiography studies may vary considerably in duration depending on complexity of the information being sought. For instance, evaluation of complex MV repair before cardiopulmonary bypass often requires a detailed, time-consuming study, whereas evaluation of severe calcific AS tends to be more limited and less time consuming. The physician must have sufficient time to obtain comprehensive images as needed to ensure an accurate diagnosis, facilitate perioperative decision making, and enhance patient outcome. Echocardiography technicians or sonographers should not manipulate an intraoperative transesophageal echocardiography probe, nor should they be put in a position to provide patient outcome-related interpretations or advice.

Several means of evaluating patients during valve surgery other than transesophageal echocardiography are available, but they are not a substitute for the direct anatomic information provided by transesophageal echocardiography. Measurements of intracardiac pressures and flows may be made with central venous and pulmonary artery catheters or by direct transmyocardial needle insertion after exposure of the heart. A surface echocardiographic transducer may be placed in a sterile sheath and passed onto the surgical field for application directly to the heart or the ascending aorta, a technique called epicardial and epiaortic echocardiography, as a useful alternative in patients in whom transesophageal probe insertion cannot be performed or is contraindicated (929). Information gained from all these techniques may be complementary and may be combined to obtain a more comprehensive characterization of the lesion.

In general, whenever possible, the decision to treat a valve lesion surgically should be made before the patient is in the operating room. Specifically, in cases of MR, intraoperative assessment of the degree of MR can be misleading owing to the unloading effects of general anesthesia. In a patient having surgery for another reason (e.g., CABG or another valve), intraoperative transesophageal echocardiography occasionally might provide the basis for this decision, but it should not replace preoperative assessment of the valve lesion with transthoracic echocardiography or catheterization. Intraoperative transesophageal echocardiography can confirm the preoperative diagnosis, provide additional details that may guide the surgical procedure, and help to guide management of hemodynamics. It remains the best means of immediately assessing the technical results of the surgical procedure in the operating room.

8.1. Specific Valve Lesions

8.1.1. Aortic Stenosis

The surgical treatment for AS is almost always replacement with a prosthetic valve. Intraoperative transesophageal echocardiography (926) can be used to measure the size of the aortic annulus to facilitate selection of the proper size prosthesis and also, in patients with bicuspid valves, to provide information regarding aortic root dilatation and need for repair (see Section 3.3). After implantation of the prosthesis, transesophageal echocardiography can detect technical problems such as paravalvular regurgitation or abnormal leaflet motion. Stentless prostheses and homografts are more prone to distortion, with resulting regurgitation, and should be assessed in the operating room by transesophageal echocardiography. Excessive cardiac vent return or arterial pulsatility during cardiopulmonary bypass may be indications of significant AR after AVR. Transesophageal echocardiography can be used to confirm the diagnosis. Transesophageal imaging can also determine the adequacy of coronary reimplantation by both direct imaging of the coronaries and assessment of LV function.

8.1.2. Aortic Regurgitation

Although the severity and significance of AR is partially dependent on afterload and may be difficult to quantify with transesophageal echocardiography during surgery, transesophageal echocardiography usually provides high-resolution images of the aortic valve and is quite helpful in determining the mechanism and cause of regurgitation. The amount of cardiac vent return and arterial pulsatility during cardiopulmonary bypass may provide some indication of severity as well. The surgical treatment for AR is usually replacement with a prosthetic valve, but valve repair is sometimes attempted. Measurements of the size of the aortic root may direct the surgeon toward root replacement rather than simple replacement of the regurgitant valve. Intraoperative transesophageal echocardiography should be used to evaluate the results of an aortic valve repair immediately after cardiopulmonary bypass. Considerations of the transesophageal echocardiography evaluation of a prosthetic aortic valve after cardiopulmonary bypass are similar to those for AS.

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8.1.3. Mitral Stenosis

Most adult patients presenting for surgery for MS have rheumatic heart disease, although extremely severe mitral annular calcification on occasion may cause significant stenosis. Intraoperative transesophageal echocardiography can provide anatomic information, especially about the subvalvar structures, that is difficult to directly visualize through the left atriotomy and is critical in deciding whether to replace or repair a rheumatic valve. The presence of thrombus in the left atrium may be detected with transesophageal echocardiography as well. Intraoperative transesophageal echocardiography should be used to evaluate the results of a mitral commissurotomy immediately after cardiopulmonary bypass, primarily to detect significant MR. Residual stenosis may be difficult to quantify by echocardiography. For example, the pressure half-time method to measure MV area is probably not accurate immediately after a commissurotomy and should not be relied on solely to assess adequacy of the commissurotomy (403). Although the Doppler-derived transmitral pressure gradient is easily obtained and may help in this situation, this may underestimate MS severity in the presence of a low cardiac output. The transmitral gradient can be measured by direct transduction of LV and left atrial pressures if there is concern about residual stenosis. If a prosthetic MV is implanted, transesophageal echocardiography can detect technical problems such as paravalvular regurgitation or abnormal leaflet motion. Small, insignificant central and paravalvular leaks are commonly seen immediately after cardiopulmonary bypass and should not be a cause for concern (930).

8.1.4. Mitral Regurgitation

Patients undergoing surgery for MR usually have either myxomatous degeneration (MVP) or ischemic heart disease. Other less common causes of MR that requires surgery are infective endocarditis and rheumatic heart disease. Because the change in hemodynamic loading conditions caused by general anesthesia during surgery may lead to underestimation of the severity of MR by intraoperative transesophageal echocardiography (632,633,931,932), the decision to operate is best made before surgery based on the symptoms and preoperative testing. If intraoperative evaluation is required as a precursor to MV repair or replacement, the operator must attempt to reproduce both preoperative afterload and preload conditions. Intraoperative transesophageal echocardiography may provide additional information about the mechanism of regurgitation and may be helpful to direct the decision whether to repair or replace the valve (923,924,933). Thus, intraoperative transesophageal imaging should be used whenever a repair is contemplated. Intraoperative transesophageal echocardiography should also be used to evaluate the results of an MV repair immediately after cardiopulmonary bypass to assess for residual MR, systolic anterior motion of the valve leaflets, and restriction of mitral opening with stenosis. Representative loading conditions may need to be created with volume or vasopressors to fully assess the adequacy of the MV repair immediately after the patient is weaned from cardiopulmonary bypass. If a prosthetic MV is implanted, transesophageal echocardiography can detect technical problems such as paravalvular regurgitation or abnormal leaflet motion. Small, insignificant central or paravalvular leaks are commonly observed immediately after cardiopulmonary bypass, and should not be a cause for concern (930). It is possible to injure the left circumflex coronary artery or tether a cusp of the aortic valve with a suture placed in the mitral annulus. Therefore, assessment of LV function and examination of the aortic valve and adjacent structures should always be performed with transesophageal echocardiography after MV surgery.

8.1.5. Tricuspid Regurgitation

TR that requires surgery is most often secondary to annular dilation with right-sided heart enlargement, which is usually corrected with tricuspid valve repair. Secondary TR can change with the hemodynamic loading conditions. Therefore, the decision to address TR surgically is best made before induction of general anesthesia and surgery whenever possible (see Sections 3.7.4 and 3.8). Intraoperative transesophageal echocardiography can provide detailed information about the mechanism of TR that is useful in deciding whether to repair or replace a valve and should be used when a repair is contemplated. Intraoperative transesophageal echocardiography should be used to evaluate the results of a tricuspid valve repair immediately after cardiopulmonary bypass to assess for residual regurgitation and restriction of the tricuspid valve opening with stenosis. If a prosthetic tricuspid valve is implanted, transesophageal echocardiography can detect technical problems such as paravalvular regurgitation or abnormal leaflet motion.

8.1.6. Tricuspid Stenosis

Tricuspid stenosis that requires surgery is most commonly due to rheumatic heart disease and is treated by replacement of the valve with a prosthesis. As with other prosthetic valve replacements, transesophageal echocardiography can detect technical problems such as paravalvular leaks or immobile leaflets after cardiopulmonary bypass and allow correction of the problem during the same operation.

8.1.7. Pulmonic Valve Lesions

In adults, the pulmonic valve is much less commonly operated on than the aortic, mitral, and tricuspid valves. It is often difficult to image with transesophageal echocardiography, and decisions to operate on the pulmonic valve should be made based on preoperative studies such as transthoracic echocardiography or cardiac magnetic resonance whenever possible. Pulmonic valve lesions are treated surgically by prosthetic valve replacement in adults, and transesophageal echocardiography may be able to detect technical problems such as paravalvular leaks or immobile

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leaflets in the operating room after cardiopulmonary bypass. When the issue of pulmonic stenosis is raised during heart surgery, direct measurement of RV and pulmonary artery pressures with catheters or needles can be very helpful.

8.2. Specific Clinical Scenarios

8.2.1. Previously Undetected Aortic Stenosis During CABG

CAD and AS are commonly present in the same patient. On occasion, intraoperative transesophageal echocardiography detects previously undiagnosed AS in a patient undergoing CABG surgery. Indications for AVR in this situation are the same as described in Section 10.4. If the AS is moderate or severe, AVR is indicated. Controversy persists as to whether AVR should be performed during CABG surgery when mild AS is present. There may be difficulty in accurately assessing the severity of AS with intraoperative transesophageal echocardiography by Doppler techniques in some patients. Confirmation of the severity of the gradient may be obtained after the heart is exposed by direct transduction of the LV and aortic pressures. Epicardial echocardiography may also provide additional, helpful information.

8.2.2. Previously Undetected Mitral Regurgitation During CABG

On occasion, intraoperative transesophageal echocardiography may detect previously undiagnosed, significant MR in a patient undergoing CABG surgery (see Sections 3.6.5, 7.3.1.3, and 10.5). An examination of the valve with transesophageal echocardiography should be performed to determine the mechanism of the MR. If there is a structural abnormality such as prolapse or flail, the valve should be repaired or replaced. Ischemic MR due to LV remodeling and apical tenting of the leaflets can be very dynamic and may respond to acute hemodynamic management in the operating room by increasing or decreasing in severity according to changes in afterload and LV size. Patients with severe ischemic MR should undergo MV repair or MV replacement (see Sections 3.6.5 and 7.3.1.3). Controversy exists as to whether patients having CABG surgery with moderate or mild MR should undergo MV repair as well. However, the hemodynamic effects of drugs received during surgery often lessen the severity of the MR, and mild intraoperative MR may increase postoperatively. Hence, it is reasonable to perform MV repair when there is moderate and, in many cases, mild MR detected on intraoperative transesophageal echocardiography.

9. MANAGEMENT OF PATIENTS WITH PROSTHETIC HEART VALVES

The results of valve surgery with regard to survival, functional class, valve function, and complications are dependent on patient related factors, cardiac function, type of surgery, type of prosthesis, and medical comorbidities (857).

9.1. Antibiotic Prophylaxis

9.1.1. Infective Endocarditis

All patients with prosthetic valves need appropriate antibiotics for prophylaxis against infective endocarditis (see Section 2.3.1).

9.1.2. Recurrence of Rheumatic Carditis

Patients with rheumatic heart disease continue to need antibiotics as prophylaxis against recurrence of rheumatic carditis (see Section 2.3.2).

9.2. Antithrombotic Therapy (Table 37)

CLASS I

1. After AVR with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors,* warfarin is indicated to achieve an INR of 2.0 to 3.0. If the patient has risk factors, warfarin is indicated to achieve an INR of 2.5 to 3.5. *(Level of Evidence: B)*
2. After AVR with Starr-Edwards valves or mechanical disc valves (other than Medtronic Hall prostheses), in patients with no risk factors,* warfarin is indicated to achieve an INR of 2.5 to 3.5. *(Level of Evidence: B)*
3. After MV replacement with any mechanical valve, warfarin is indicated to achieve an INR of 2.5 to 3.5. *(Level of Evidence: C)*
4. After AVR or MV replacement with a bioprosthesis and no risk factors,* aspirin is indicated at 75 to 100 mg per day. *(Level of Evidence: C)*
5. After AVR with a bioprosthesis and risk factors,* warfarin is indicated to achieve an INR of 2.0 to 3.0. *(Level of Evidence: C)*
6. After MV replacement with a bioprosthesis and risk factors,* warfarin is indicated to achieve an INR of 2.0 to 3.0. *(Level of Evidence: C)*
7. For those patients who are unable to take warfarin after MV replacement or AVR, aspirin is indicated in a dose of 75 to 325 mg per day. *(Level of Evidence: B)*
8. The addition of aspirin 75 to 100 mg once daily to therapeutic warfarin is recommended for all patients with mechanical heart valves and those patients with biological valves who have risk factors.* *(Level of Evidence: B)*

CLASS IIa

1. During the first 3 months after AVR with a mechanical prosthesis, it is reasonable to give warfarin to achieve an INR of 2.5 to 3.5. *(Level of Evidence: C)*
2. During the first 3 months after AVR or MV replacement with a bioprosthesis, in patients with no risk factors,* it is reasonable to give warfarin to achieve an INR of 2.0 to 3.0. *(Level of Evidence: C)*

CLASS IIb

1. In high-risk patients with prosthetic heart valves in whom aspirin cannot be used, it may be reasonable to give clopidogrel (75 mg per day) or warfarin to achieve an INR of 3.5 to 4.5. *(Level of Evidence: C)*

All patients with mechanical valves require warfarin therapy, as indicated in Table 37 (934). Aspirin is recommended for all patients with prosthetic heart valves: aspirin alone in patients with bioprostheses and no risk factors, and aspirin combined with warfarin in patients with mechanical

*Risk factors include atrial fibrillation, previous thromboembolism, LV dysfunction, and hypercoagulable condition.

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Table 37. Recommendations for Antithrombotic Therapy in Patients With Prosthetic Heart Valves

	Aspirin (75–100 mg)	Warfarin (INR 2.0–3.0)	Warfarin (INR 2.5–3.5)	No Warfarin
Mechanical prosthetic valves				
AVR–low risk				
Less than 3 months	Class I	Class I	Class IIa	
Greater than 3 months	Class I	Class I		
AVR–high risk	Class I		Class I	
MVR	Class I		Class I	
Biological prosthetic valves				
AVR–low risk				
Less than 3 months	Class I	Class IIa		Class IIb
Greater than 3 months	Class I			Class IIa
AVR–high risk	Class I	Class I		
MVR–low risk				
Less than 3 months	Class I	Class IIa		
Greater than 3 months	Class I			Class IIa
MVR–high risk	Class I	Class I		

Depending on patients' clinical status, antithrombotic therapy must be individualized (see special situations in text). In patients receiving warfarin, aspirin is recommended in virtually all situations. Risk factors: atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable condition. International normalized ratio (INR) should be maintained between 2.5 and 3.5 for aortic disc valves and Starr-Edwards valves. Modified with permission from McAnulty JH, Rahimtoola SH. Antithrombotic therapy in valvular heart disease. In: Schlant R, Alexander RW, editors. Hurst's The Heart. New York, NY: McGraw-Hill, 1998:1867–74 (934).

AVR indicates aortic valve replacement; and MVR, mitral valve replacement.

heart valves and high-risk patients with bioprostheses. In high-risk patients who cannot take aspirin, the addition of clopidogrel to warfarin therapy should be considered. Even with the use of warfarin, risk of thromboemboli is 1% to 2% per year (171,172,174,214,852,935), but the risk is considerably higher without treatment with warfarin (936). The risk of a clinical thromboembolism is on average 0.7% per year in patients with biological valves in sinus rhythm; this figure is derived from several studies in which the majority of patients were not undergoing therapy with warfarin (171,172,174,214,937). Almost all studies have shown that the risk of embolism is greater with a valve in the mitral position (mechanical or biological) than with one in the aortic position (172,178,852,936,938). With either type of prosthesis or valve location, the risk of emboli is probably higher in the first few days and months after valve insertion (937), before the valve is fully endothelialized (804).

It is frequently difficult to maintain a patient at a fixed or relatively fixed level of anticoagulation owing to changes in absorption of medication, the effects of various foods and medications, and changes in liver function. Therefore, in clinical practice, the patient's anticoagulation level is maintained within a certain therapeutic range. This can be optimized through a program of patient education and close surveillance by an experienced healthcare professional.

9.2.1. Mechanical Valves

All patients with mechanical valves require anticoagulation. For mechanical prostheses in the aortic position, the INR with warfarin therapy should be maintained between 2.0 and 3.0 for bileaflet valves and Medtronic Hall valves and between 2.5 and 3.5 for other disc valves and Starr-Edwards valves; for prostheses in the mitral position, the INR should be maintained between 2.5 and 3.5 for all mechanical valves (172,174,852,938–947). There is a difference of opinion regarding the Starr-Edwards valve in the aortic position, with the minority opinion recommending that INR be maintained between 2.0 and 3.0. The recommendation for higher INR values in the mitral position is based on the greater risk of thromboembolic complications with mechanical valves in the mitral position (171,852,936,938,942,943,946,947) and the greater risk of bleeding at higher INRs (946). In patients with aortic mechanical prosthesis who are at higher risk of thromboembolic complications, INR should be maintained at 2.5 to 3.5, and the addition of aspirin should be considered (see below). These include patients with atrial fibrillation, previous thromboembolism, and a hypercoagulable state. Many would also include patients with severe LV dysfunction in this higher-risk group (948). Some prostheses are thought to be more thrombogenic than others (particularly the tilting-disc valves), and a case could be made for increasing the INR to between 3 and 4.5; however, this level of anticoagulation is associated with a considerably increased risk of bleeding (938,949).

The addition of low-dose aspirin (75 to 100 mg per day) to warfarin therapy (INR 2.0 to 3.5) not only further decreases the risk of thromboembolism (808,946,950–953) but also decreases mortality due to other cardiovascular diseases. A slight increase in the risk of bleeding with this combination should be kept in mind (950,954). The risk of gastrointestinal irritation and hemorrhage with aspirin is dose dependent over the range of 100 to 1000 mg per day, and the antiplatelet effects are independent of dose over this range (955,956). There are no data in patients with pros-

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thetic heart valves receiving warfarin and aspirin in doses of 100 to 325 mg per day. Doses of 500 to 1000 mg per day clearly increase the risk of bleeding (957–959). The addition of aspirin (75 to 100 mg per day) to warfarin should be strongly considered unless there is a contraindication to the use of aspirin (i.e., bleeding or aspirin intolerance). This combination is particularly appropriate in patients who have had an embolus while undergoing warfarin therapy, those with known vascular disease, and those who are known to be particularly hypercoagulable. As an example, such combination therapy is recommended by a committee concerning the use of antithrombotic therapy in women during pregnancy (807). The method of anticoagulation in pregnant patients is controversial and is discussed in Section 5.8.

Thromboembolic risk is increased early after insertion of the prosthetic heart valve. The use of UFH early after prosthetic valve replacement, before warfarin achieves therapeutic levels, is controversial. Many centers start UFH as soon as the risk of increased surgical bleeding is reduced (usually within 24 to 48 h), with maintenance of aPTT between 55 and 70 s. After an overlap of UFH and warfarin for 3 to 5 days, UFH is discontinued when an INR of 2.0 to 3.0 is achieved. In some patients, achievement of therapeutic INR must be delayed several days after surgery because of mitigating complications.

9.2.2. Biological Valves

Because of an increased risk of thromboemboli during the first 3 months after implantation of a biological prosthetic valve, anticoagulation with warfarin is often used, especially when the valve is in the mitral position (937), although most centers use only aspirin for biological valves in the aortic position. The risk is particularly high in the first few days after surgery, and many centers start UFH as soon as the risk of increased surgical bleeding is reduced (usually within 24 to 48 h), with maintenance of aPPT between 55 and 70 seconds. After an overlap of UFH and warfarin for 3 to 5 days, UFH may be discontinued when an INR of 2.0 to 3.0 is achieved. After 3 months, the tissue valve can be treated like native valve disease, and warfarin can be discontinued in more than two thirds of patients with biological valves (174,937,960). In the remaining patients with associated risk factors for thromboembolism, such as atrial fibrillation, previous thromboembolism, or hypercoagulable condition, lifelong warfarin therapy is indicated to achieve an INR of 2.0 to 3.0. Many would also recommend continuing anticoagulation in patients with severe LV dysfunction (ejection fraction less than 0.30) (948).

9.2.3. Embolic Events During Adequate Antithrombotic Therapy

In the patient who has a definite embolic episode while undergoing adequate antithrombotic therapy, the dosage of antithrombotic therapy should be increased, when clinically safe, as follows:

- Warfarin, INR 2.0 to 3.0: warfarin dose increased to achieve INR of 2.5 to 3.5
- Warfarin, INR 2.5 to 3.5: warfarin dose may need to be increased to achieve INR of 3.5 to 4.5
- Not taking aspirin: aspirin 75 to 100 mg per day should be initiated
- Warfarin plus aspirin 75 to 100 mg per day: aspirin dose may also need to be increased to 325 mg per day if the higher dose of warfarin is not achieving the desired clinical result
- Aspirin alone: aspirin dose may need to be increased to 325 mg per day, clopidogrel 75 mg per day per day added, and/or warfarin added.

9.2.4. Excessive Anticoagulation

In most patients with INR above the therapeutic range, excessive anticoagulation can be managed by withholding warfarin and monitoring the level of anticoagulation with serial INR determinations (804). Excessive anticoagulation (INR greater than 5) greatly increases the risk of hemorrhage. However, rapid decreases in INR that lead to INR falling below the therapeutic level increase the risk of thromboembolism. Patients with prosthetic heart valves with an INR of 5 to 10 who are not bleeding can be treated by withholding warfarin and administering 1 to 2.5 mg of oral vitamin K1 (phytonadione) (804,961). The INR should be determined after 24 h and subsequently as needed. Warfarin therapy is restarted and adjusted dose appropriately to ensure that the INR is in the therapeutic range. In emergency situations, the use of fresh frozen plasma is preferable to high-dose vitamin K1 (962), especially parenteral vitamin K1, because use of the latter increases the risk of overcorrection to a hypercoagulable state. Low-dose intravenous vitamin K (1 mg) appears safe in this situation (963).

9.2.5. Bridging Therapy in Patients With Mechanical Valves Who Require Interruption of Warfarin Therapy for Noncardiac Surgery, Invasive Procedures, or Dental Care

CLASS I

1. In patients at low risk of thrombosis, defined as those with a bileaflet mechanical AVR with no risk factors,* it is recommended that warfarin be stopped 48 to 72 h before the procedure (so the INR falls to less than 1.5) and restarted within 24 h after the procedure. Heparin is usually unnecessary. *(Level of Evidence: B)*
2. In patients at high risk of thrombosis, defined as those with any mechanical MV replacement or a mechanical AVR with any risk factor, therapeutic doses of intravenous UFH should be started when the INR falls below 2.0 (typically 48 h before surgery), stopped 4 to 6 h before the procedure, restarted as early after surgery as bleeding stability allows, and continued until the INR is again therapeutic with warfarin therapy. *(Level of Evidence: B)*

*Risk factors: atrial fibrillation, previous thromboembolism, LV dysfunction, hypercoagulable conditions, older-generation thrombogenic valves, mechanical tricuspid valves, or more than 1 mechanical valve.

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CLASS IIa

1. It is reasonable to give fresh frozen plasma to patients with mechanical valves who require interruption of warfarin therapy for emergency noncardiac surgery, invasive procedures, or dental care. Fresh frozen plasma is preferable to high-dose vitamin K1. *(Level of Evidence: B)*

CLASS IIb

1. In patients at high risk of thrombosis, therapeutic doses of subcutaneous UFH (15 000 U every 12 h) or LMWH (100 U per kg every 12 h) may be considered during the period of a subtherapeutic INR. *(Level of Evidence: B)*

CLASS III

1. In patients with mechanical valves who require interruption of warfarin therapy for noncardiac surgery, invasive procedures, or dental care, high-dose vitamin K1 should not be given routinely, because this may create a hypercoagulable condition. *(Level of Evidence: B)*

The risk of increased bleeding during a procedure performed with a patient receiving antithrombotic therapy has to be weighed against the increased risk of a thromboembolism caused by stopping the therapy. The risk of stopping warfarin can be estimated and is relatively slight if the drug is withheld for only a few days. As an example, in a worst-case scenario (e.g., a patient with a mechanical prosthesis with previous thromboemboli), the risk of a thromboembolism when the patient is not taking warfarin is 10% to 20% per year. Thus, if therapy were stopped for 3 days, the risk of an embolus would be 0.08% to 0.16%. There are theoretical concerns that stopping the drug and then reinstituting it might result in hypercoagulability or that there might be a thrombotic "rebound." An increase in markers for activation of thrombosis with abrupt discontinuation of warfarin therapy has been observed (964), but it is not clear whether the clinical risk of thromboembolism increases (965). In addition, when warfarin therapy is reinstituted, there are theoretical concerns about a hypercoagulable state caused by suppression of protein C and protein S before the drug affects the thrombotic factors. Although these risks are only hypothetical, individuals at very high risk should be treated with heparin until INR returns to the desired range.

Management of antithrombotic therapy must be individualized, but some generalizations apply (934). Antithrombotic therapy should not be stopped for procedures in which bleeding is unlikely or would be inconsequential if it occurred, for example, surgery on the skin, dental cleaning, or simple treatment for dental caries. Eye surgery, particularly for cataracts or glaucoma, is usually associated with very little bleeding and thus is frequently performed without alterations to antithrombotic treatment. When bleeding is likely or its potential consequences are severe, antithrombotic treatment should be altered. If a patient is taking aspirin, it should be discontinued 1 week before the procedure and restarted as soon as it is considered safe by the surgeon or dentist. Clopidogrel should be stopped at least 5 days before the procedure.

Spyropoulos et al. performed a retrospective analysis of costs and clinical outcomes associated with LMWH for perioperative bridging in patients receiving long-term oral anticoagulant therapy (966). The mean total healthcare costs in the perioperative period were significantly lower (by $13 114) in patients receiving long-term oral anticoagulant therapy with LMWH than in those receiving it with UFH for an elective surgical procedure. The cost savings associated with LMWH use were accomplished through the avoidance or minimization of inpatient stays and no increase in the overall rate of clinical adverse events in the postoperative period (966).

For patients with a bileaflet mechanical aortic valve and no risk factors, warfarin should be stopped before the procedure so that the INR is less than 1.5 (which is often 48 to 72 h after warfarin is discontinued) (934,967) and restarted within 24 h after a procedure. Admission to the hospital or a delay in discharge to give heparin is usually unnecessary (965,968–970). Patients at high risk of thrombosis include all patients with mechanical mitral or tricuspid valve replacements and patients with an AVR and any risk factors. Such risk factors include atrial fibrillation, previous thromboembolism, hypercoagulable condition, older-generation mechanical valves, LV dysfunction (ejection fraction less than 0.30), or more than 1 mechanical valve (971–973). When UFH is used, it should be started when INR falls below 2.0 (i.e., 48 h before surgery) and stopped 4 to 6 h before the procedure. UFH should be restarted as early after surgery as bleeding stability allows, and the aPTT should be maintained at 55 to 70 s until warfarin is therapeutic. LMWH is attractive because it is more easily used outside the hospital. One study of bridging therapy for interruption of warfarin included 215 patients with mechanical valves. In the total group of 650 patients, the risk of thromboembolism (including possible events) was 0.62%, with 95% confidence intervals of 0.17% to 1.57%. Major bleeding occurred in 0.95% (0.34% to 2.00%) (974). However, concerns about the use of LMWH for mechanical valves persists, and package inserts continue to list a warning for this use of these medications (815).

High-dose vitamin K1 should not be given routinely, because this may create a hypercoagulable condition. For emergency situations, fresh frozen plasma is preferable to high-dose vitamin K1 (see Section 9.2.4).

9.2.6. Antithrombotic Therapy in Patients Who Need Cardiac Catheterization/Angiography

In an emergency or semiurgent situation, cardiac catheterization can be performed in a patient taking warfarin, but preferably, the drug should be stopped, on average, 72 h before the procedure so that INR is less than 1.5 (see above). The drug should be restarted as soon as the procedure is completed. This is true for patients with biological valves who are receiving antithrombotic therapy and for those with mechanical valves. If

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a patient has more than 1 risk factor that predisposes to thromboembolism, heparin should be started when INR falls below 2.0 and should be continued when warfarin is restarted. After an overlap of 3 to 5 days, heparin may be discontinued when the desired INR is achieved. If the catheterization procedure is to include a transseptal puncture (especially in a patient who has not had previous opening of the pericardium), patients should be removed from all antithrombotic therapy, and INR should be less than 1.2; the same is true if an LV puncture is to be performed (975). In patients who are to undergo transseptal or LV puncture and are receiving heparin therapy, heparin should be discontinued 4 to 6 h before the procedure(s) and can be restarted without a bolus more than 4 h after the sheath in the peripheral vessel has been removed.

9.2.7. Thrombosis of Prosthetic Heart Valves

CLASS I

1. Transthoracic and Doppler echocardiography is indicated in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity. *(Level of Evidence: B)*
2. Transesophageal echocardiography and/or fluoroscopy is indicated in patients with suspected valve thrombosis to assess valve motion and clot burden. *(Level of Evidence: B)*

CLASS IIa

1. Emergency operation is reasonable for patients with a thrombosed left-sided prosthetic valve and NYHA functional class III–IV symptoms. *(Level of Evidence: C)*
2. Emergency operation is reasonable for patients with a thrombosed left-sided prosthetic valve and a large clot burden. *(Level of Evidence: C)*
3. Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves with NYHA functional class III–IV symptoms or a large clot burden. *(Level of Evidence: C)*

CLASS IIb

1. Fibrinolytic therapy may be considered as a first-line therapy for patients with a thrombosed left-sided prosthetic valve, NYHA functional class I–II symptoms, and a small clot burden. *(Level of Evidence: B)*
2. Fibrinolytic therapy may be considered as a first-line therapy for patients with a thrombosed left-sided prosthetic valve, NYHA functional class III–IV symptoms, and a small clot burden if surgery is high risk or not available. *(Level of Evidence: B)*
3. Fibrinolytic therapy may be considered for patients with an obstructed, thrombosed left-sided prosthetic valve who have NYHA functional class II–IV symptoms and a large clot burden if emergency surgery is high risk or not available. *(Level of Evidence: C)*
4. Intravenous UFH as an alternative to fibrinolytic therapy may be considered for patients with a thrombosed valve who are in NYHA functional class I–II and have a small clot burden. *(Level of Evidence: C)*

Obstruction of prosthetic heart valves may be caused by thrombus formation, pannus ingrowth, or a combination of both. The cause may be difficult to determine and requires knowledge of the clinical presentation and findings on echocardiography, including transesophageal echocardiography (976–981). If the prosthesis is obstructed by pannus, fibrinolytic therapy will be ineffective, and the valve needs to be replaced. Fibrinolytic therapy for a left-sided prosthetic valve obstructed by thrombus is associated with significant risks (cerebral emboli in 12% to 15% of cases) and is often ineffective. Fibrinolytic therapy in such patients is reserved for those in whom surgical intervention carries a high risk and those with contraindications to surgery (976–980,982–986).

In patients with a "small clot" who are in NYHA functional class I or II, treatment with short-term intravenous UFH therapy or continuous infusion of fibrinolytic therapy may be considered (976–980,982–986). The size threshold for this recommendation is difficult to define because of the lack of large cohort studies and differing thresholds from small studies (ranging from 5 to 10 mm, as determined by transesophageal echocardiography), below which intravenous UFH or fibrinolytic therapy is safe and effective (976–978,984). The risk associated with clot size is a continuous function, with 1 study showing an odds ratio of 2.41 per 1-cm^2 increment (978). Data support the use of urokinase, streptokinase, or recombinant tissue plasminogen activator as the fibrinolytic agents in this situation. Factors that identify patients at risk for adverse outcomes of fibrinolytic therapy include active internal bleeding, history of hemorrhagic stroke, recent cranial trauma of neoplasm, diabetic hemorrhagic retinopathy, large thrombi, mobile thrombi, hypertension (greater than 200 over 120 mm Hg), hypotension or shock, and NYHA functional class III–IV symptoms. If fibrinolytic therapy is successful, it should be followed by intravenous UFH until warfarin achieves an INR of 3.0 to 4.0 for aortic prosthetic valves and 3.5 to 4.5 for mitral prosthetic valves. If partially successful, fibrinolytic therapy may be followed by a combination of subcutaneous UFH twice daily (to achieve an aPTT of 55 to 80 s) plus warfarin (INR 2.5 to 3.5) for a 3-month period (985).

Patients with small thrombi who receive intravenous UFH as first-line therapy and who do not respond successfully may receive a trial of continuous-infusion fibrinolytic therapy. If fibrinolytic therapy is unsuccessful or there is an increased risk associated with fibrinolytic therapy, reoperation should be considered. An alternative in patients who remain hemodynamically stable is to convert intravenous UFH to combined therapy with subcutaneous UFH (twice daily to an aPTT of 55 to 80 s) and warfarin (INR 2.5 to 3.5) for 1 to 3 months on an outpatient basis to allow for endogenous fibrinolysis (985). If intravenous UFH, fibrinolytic therapy, combined UFH/fibrinolytic therapy, or combined UFH/warfarin is successful, warfarin doses should be increased so that INR is between 3.0 and 4.0 (approximately 3.5) for prosthetic aortic valves and between 3.5 and 4.5 (approximately 4.0) for prosthetic MVs. These patients should also receive low-dose aspirin.

Thrombosis of mechanical tricuspid valve prostheses may be treated with fibrinolytic therapy, although experience with this is limited (987,988).

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9.3. Follow-Up Visits

CLASS I

1. For patients with prosthetic heart valves, a history, physical examination, and appropriate tests should be performed at the first postoperative outpatient evaluation, 2 to 4 weeks after hospital discharge. This should include a transthoracic Doppler echocardiogram if a baseline echocardiogram was not obtained before hospital discharge. *(Level of Evidence: C)*
2. For patients with prosthetic heart valves, routine follow-up visits should be conducted annually, with earlier re-evaluations (with echocardiography) if there is a change in clinical status. *(Level of Evidence: C)*

CLASS IIb

1. Patients with bioprosthetic valves may be considered for annual echocardiograms after the first 5 years in the absence of a change in clinical status. *(Level of Evidence: C)*

CLASS III

1. Routine annual echocardiograms are not indicated in the absence of a change in clinical status in patients with mechanical heart valves or during the first 5 years after valve replacement with a bioprosthetic valve. *(Level of Evidence: C)*

9.3.1. First Outpatient Postoperative Visit

The first outpatient evaluation after valve surgery usually occurs 3 to 4 weeks after hospital discharge. By this time, the patient's physical capabilities and expected improvement in functional capacity can be assessed.

The workup on this visit should include an interval or complete history and physical examination, ECG, chest X-ray, 2D and Doppler echocardiography, complete blood count, blood urea nitrogen/creatinine, electrolytes, lactate dehydrogenase, and INR, if indicated. The main focus of the examination is on signs that relate to function of the prosthesis or that might suggest the presence of infection or a myocardial infarction, conduction, or valvular disorder. Severe perivalvular MR may be inaudible on physical examination, a fact to remember when one considers the possible causes of functional deterioration in a patient. In patients who undergo surgery in the setting of acute valvular infection, the first postoperative visit may occur at the end of a postoperative course of antibiotics. Surveillance blood cultures may be indicated at this visit if 1 or more weeks have passed since cessation of antibiotics to confirm bacteriologic cure.

Echocardiography is the most useful noninvasive test. It provides information about prosthesis stenosis/regurgitation, valve area, assessment of other valve disease(s), pulmonary hypertension, atrial size, LV and RV hypertrophy, LV and RV size and function, and pericardial effusion/thickening. It is an essential component of the first postoperative visit because it allows an assessment of the effects and results of surgery, as well as serving as a baseline for comparison should complications or deterioration occur later.

Every prosthetic heart valve has an intrinsic degree of obstruction (857,989–992); one reason for obtaining a baseline Doppler echocardiogram early after valve replacement is so that this intrinsic gradient can be measured and compared with subsequent measurements if necessary. The gradient varies among different types of prosthetic valves. Doppler echocardiography also detects the prosthetic valve regurgitation that is normal for various types of mechanical valve.

Multiple other noninvasive tests (e.g., cardiac magnetic resonance) have emerged for the assessment of valvular and ventricular function, but these should be performed only in selected patients for specific indications. Fluoroscopy can reveal abnormal rocking of a dehiscing prosthesis, limitation of the occluder if the latter is opaque, and strut fracture of the convexoconcave Björk-Shiley valve. Radionuclide angiography or cardiac magnetic resonance is useful to determine whether functional deterioration is the result of reduced ventricular function and is performed if the same data cannot be obtained by echocardiography. Cardiac magnetic resonance is safe for all commercially available prosthetic heart valves.

9.3.2. Follow-Up Visits in Patients Without Complications

Patients who have undergone valve replacement are not cured but still have serious heart disease. They have exchanged native valve disease for prosthetic valve disease and must be followed with the same care as patients with native valve disease (993). The clinical course of patients with prosthetic heart valves is influenced by several factors (857), including LV dysfunction, progression of other valve disease, pulmonary hypertension, other cardiac diseases, complications of prosthetic heart valves, and clinical heart failure. The interval between routine follow-up visits depends on the patient's needs. Anticoagulant regulation does not require visits to the physician's office but should be closely supervised by an experienced healthcare professional.

The asymptomatic uncomplicated patient needs to be seen only at 1-year intervals, at which time a complete history and thorough physical examination should be performed. ECG and chest X-ray examinations are not routinely indicated but are valuable in individual patients. Additional tests that are often performed include hemoglobin, hematocrit, and lactate dehydrogenase. No further echocardiographic testing is required after the initial postoperative evaluation in patients with mechanical valves who are stable and who have no symptoms or clinical evidence of LV dysfunction, prosthetic valve dysfunction, or dysfunction of other heart valves, in keeping with the ACC/AHA/ASE 2003 Guidelines for the Clinical Application of Echocardiography (2). Once regurgitation is detected, close follow-up with 2D and Doppler echocardiography every 3 to 6 months is indicated. Echocardiography is indicated in any patient with a prosthetic heart valve whenever there is evidence of a new murmur or change in clinical status, when there are questions about prosthetic valve integrity and function, and when there are concerns about ventricular function.

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9.3.3. Follow-Up Visits in Patients With Complications

CLASS I

1. Patients with LV systolic dysfunction after valve surgery should receive standard medical therapy for systolic heart failure. This therapy should be continued even if there is improvement of LV dysfunction. *(Level of Evidence: B)*

LV dysfunction and clinical heart failure after valve replacement may be the result of

- preoperative LV dysfunction that persists or improves only partially
- perioperative myocardial damage
- other valve disease that has progressed
- complications of prosthetic heart valves
- associated heart disease such as CAD and systemic hypertension.

Any patient with a prosthetic heart valve who does not improve after surgery or who later shows deterioration of functional capacity should undergo appropriate testing, including 2D and Doppler echocardiography and, if necessary, transesophageal echocardiography and cardiac catheterization with angiography to determine the cause. Patients with postoperative LV systolic dysfunction, even if asymptomatic, should receive standard medical therapy for systolic heart failure, and this therapy should be continued indefinitely even if there is improvement in systolic function and/or symptoms. All patients should also receive primary and secondary prevention measures to reduce the risk of future cardiovascular events.

9.4. Reoperation to Replace a Prosthetic Valve

Reoperation to replace a prosthetic heart valve is a serious clinical event. It is usually required for moderate to severe prosthetic dysfunction (structural and nonstructural), dehiscence, and prosthetic endocarditis. Reoperation may also be needed for recurrent thromboembolism, severe intravascular hemolysis, severe recurrent bleeding from anticoagulant therapy, and thrombosed prosthetic valves In a patient with a small aortic annulus, valve prosthesis-patient mismatch may occur after AVR (856,989–992,994,995), especially if a stented bioprosthesis is used. If a patient with AS does not improve clinically after AVR, prosthetic valve function should be evaluated. In selected situations, repeat AVR to replace a malfunctioning prosthesis may be necessary.

The patient who is in stable condition without prosthetic valve endocarditis under many circumstances undergoes reoperation with only slightly greater risk than that accompanying the initial surgery. For the patient with catastrophic prosthetic valvular dysfunction, surgery is clearly indicated and urgent. The patient without endocarditis or severe prosthetic valve dysfunction requires careful hemodynamic evaluation, and the decision about reoperation should then be based on hemodynamic abnormalities, symptoms, ventricular function, and current knowledge of the natural history of the particular prosthesis.

10. EVALUATION AND TREATMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH VALVULAR HEART DISEASE

Many patients with valvular heart disease have concomitant CAD, but there are only limited data regarding the optimal strategies for diagnosis and treatment of CAD in such patients. Thus, management decisions are usually developed by blending information from the randomized studies of treatment of CAD and the smaller published series of patients undergoing surgical treatment of valvular heart disease.

10.1. Probability of Coronary Artery Disease in Patients With Valvular Heart Disease

The probability of developing CAD in the general population (996) and the prevalence of CAD in patients who come to medical attention (997) can be estimated on the basis of age, sex, and clinical risk factors. The prevalence of CAD in patients with valvular heart disease is determined by these same variables (998). Risk factors for coronary atherosclerosis in patients with valvular disease should be approached with the prevention and risk reduction strategies that have been recommended for the general population (999).

Ischemic symptoms are important markers of CAD in the general population. Thus, the prevalence of CAD (average) has been estimated at 90% in middle-aged men with typical angina AS, 50% in those with atypical angina, 16% in those with nonanginal chest pain, and 4% in asymptomatic subjects (997). On the basis of data from the Framingham Study, the rate of CAD increases with age, and in asymptomatic individuals who are low risk, it ranges from 1% to 6%. In those aged less than 45 years, the risk is 1% to 2% (1000). In contrast, ischemic symptoms in patients with valvular heart disease may have multiple causes, such as LV chamber enlargement, increased wall stress or wall thickening with subendocardial ischemia (1001), and RV hypertrophy (1002). Angina is thus a less specific indicator of CAD in patients with valvular heart disease than in the general population.

Among patients with severe AS, angina is a common symptom in young patients with normal coronary arteries and congenital or rheumatic AS. On the other hand, CAD is a common finding in older symptomatic men with AS. Among patients with AS, the prevalence of CAD is 40% to 50% in those with typical angina, an average 25% in those with atypical chest pain, and an average 20% in those without chest pain (1003–1010). Even in patients less than 40 years old with no chest pain and no coronary risk factors, the prevalence of CAD is 0% to 5% (998,1005,1011). In elderly patients (greater than 70 years old), angina is a strong determinant of CAD (sensitivity 78%, specificity 82%) (1012). Calcification of the aortic valve is also associated with a high presence of CAD (90%) (1013). In general, because angina is a poor marker of CAD in patients with

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AS, coronary angiography is recommended in symptomatic patients before AVR in men older than 35 years; premenopausal women older than 35 years with coronary risk factors, as well as asymptomatic men older than 45 years; women older than 55 years; and those with 2 or more coronary risk factors.

CAD is less prevalent in patients with AR than in those with AS (1003–1010,1014–1020), which is related in part to the younger age of patients with AR. The prevalence of CAD in patients with MS (an average of 20%) is lower than in patients with aortic valve disease (1015,1017,1018, 1021,1022), an observation explained principally on the basis of differences in age and gender. Nonetheless, because of the impact of untreated CAD on perioperative and long-term postoperative survival, preoperative identification of CAD is of great importance in patients with AR or MS and those with AS. Thus, in symptomatic patients and/or those with LV dysfunction, preoperative coronary angiography is recommended in men aged greater than 35 years, premenopausal women aged greater than 35 years with coronary risk factors, and postmenopausal women.

The relation between MR and CAD is unique in that CAD is frequently the cause of this valve lesion. The management of these patients is discussed in Section 3.6.5. Neither angina nor heart failure symptoms are reliable markers of CAD in these patients. In patients undergoing catheterization to evaluate the cause and severity of MR, CAD is present in an average of 33% (1023,1024). In patients undergoing catheterization for acute ischemic syndromes, an average of 20% have associated MR (1025). Those with chronic CAD and MR usually have lower LV ejection fractions and more extensive CAD than those without MR (1023,1026). However, CAD is infrequent in patients with degenerative MV disease undergoing surgery. In a large series, only 1.3% of such patients had CAD, and they only had single-vessel disease. Thus, routine coronary angiography is not indicated in patients undergoing MV surgery for MR due to MV degeneration in the absence of symptoms and without risk factors when they are less than 45 years of age (1027).

10.2. Diagnosis of Coronary Artery Disease

CLASS I

1. Coronary angiography is indicated before valve surgery (including infective endocarditis) or mitral balloon commissurotomy in patients with chest pain, other objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including age). Patients undergoing mitral balloon valvotomy need not undergo coronary angiography solely on the basis of coronary risk factors. *(Level of Evidence: C)*
2. Coronary angiography is indicated in patients with apparently mild to moderate valvular heart disease but with progressive angina (Canadian Heart Association functional CLASS II or greater), objective evidence of ischemia, decreased LV systolic function, or overt congestive heart failure. *(Level of Evidence: C)*
3. Coronary angiography should be performed before valve surgery in men aged 35 years or older, premenopausal women aged 35 years or older who have coronary risk factors, and postmenopausal women. *(Level of Evidence: C)*

CLASS IIa

1. Surgery without coronary angiography is reasonable for patients having emergency valve surgery for acute valve regurgitation, aortic root disease, or infective endocarditis. *(Level of Evidence: C)*

CLASS IIb

1. Coronary angiography may be considered for patients undergoing catheterization to confirm the severity of valve lesions before valve surgery without pre-existing evidence of CAD, multiple coronary risk factors, or advanced age. *(Level of Evidence: C)*

CLASS III

1. Coronary angiography is not indicated in young patients undergoing nonemergency valve surgery when no further hemodynamic assessment by catheterization is deemed necessary and there are no coronary risk factors, no history of CAD, and no evidence of ischemia. *(Level of Evidence: C)*
2. Patients should not undergo coronary angiography before valve surgery if they are severely hemodynamically unstable. *(Level of Evidence: C)*

The resting ECG in patients with valvular heart disease frequently shows ST-segment changes due to LV hypertrophy, LV dilatation, or bundle-branch block, which reduces the accuracy of the ECG at rest and during exercise for the diagnosis of concomitant CAD.

Similarly, resting or exercise-induced regional wall-motion abnormalities are nonspecific markers for CAD in patients with underlying valvular heart disease who have LV hypertrophy and/or chamber dilatation (1028–1030), as are myocardial perfusion abnormalities induced by exercise or pharmacological stress (1029,1031–1034). Limited data are available on the use of myocardial perfusion imaging with thallium-201 or technetium-99m perfusion agents in patients with severe valvular disease. Although some studies of perfusion imaging in AS have demonstrated a sensitivity of 87% and a specificity of 77%, the presence of CAD is missed in 13% of patients with CAD (1035). Given the importance of determining the presence of CAD, coronary angiography remains the most appropriate method for the definitive diagnosis of CAD (1004). Noninvasive imaging is useful when CAD is suspected in patients with mild valve stenosis or regurgitation and normal LV cavity size and wall thickness.

In patients undergoing emergency valve surgery for acute AR, aortic dissection, or endocarditis with hemodynamic instability, cardiac catheterization, aortography, and coronary angiography are rarely required, are associated with increased risk, and might delay urgent surgery unnecessarily (221,224–227). Angiography should be considered only when the valve diagnosis cannot be determined by noninvasive imaging and when patients have known CAD, especially those with previous CABG (see Section 3.2.2.3).

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10.3. Treatment of Coronary Artery Disease at the Time of Aortic Valve Replacement

CLASS I

1. Patients undergoing AVR with significant stenoses (greater than or equal to 70% reduction in luminal diameter) in major coronary arteries should be treated with bypass grafting. *(Level of Evidence: C)*

CLASS IIa

1. In patients undergoing AVR and coronary bypass grafting, use of the left internal thoracic artery is reasonable for bypass of stenoses of the left anterior descending coronary artery greater than or equal to 50% to 70%. *(Level of Evidence: C)*
2. For patients undergoing AVR with moderate stenosis (50% to 70% reduction in luminal diameter), it is reasonable to perform coronary bypass grafting in major coronary arteries. *(Level of Evidence: C)*

As noted previously, more than 33% of patients with AS who are undergoing AVR have concomitant CAD. More than 50% of patients older than 70 years have CAD. Several studies have reported the outcomes of patients undergoing combined CABG and AVR. Although combined myocardial revascularization and AVR increases cross-clamp time (1036) and has the potential to increase perioperative myocardial infarction and early postoperative mortality compared with patients without CAD undergoing isolated AVR (1037–1040), in several series, combined CABG has had little or no adverse effect on operative mortality (1041–1047). Moreover, combined CABG and AVR reduces the rates of perioperative myocardial infarction, operative mortality, and late mortality and morbidity compared with patients with significant CAD who do not undergo revascularization at the time of AVR (1045,1046,1048,1049). In addition to severity of CAD, the multivariate factors for late postoperative mortality include severity of AS, severity of LV dysfunction, age greater than 70 years (especially in women), and presence of NYHA functional class IV symptoms (1046,1050,1051). Incomplete revascularization is associated with greater postoperative systolic dysfunction (1052,1053) and reduced survival rates (1054) after surgery compared with patients who receive complete revascularization. For more than a decade, improved myocardial preservation techniques have been associated with reduced overall operative mortality (1055), and it has become standard practice to bypass all significant coronary artery stenoses when possible in patients undergoing AVR. The committee recommends this approach.

10.4. Aortic Valve Replacement in Patients Undergoing Coronary Artery Bypass Surgery

CLASS I

1. AVR is indicated in patients undergoing CABG who have severe AS who meet the criteria for valve replacement (see Section 3.1.7). *(Level of Evidence: C)*

CLASS IIa

1. AVR is reasonable in patients undergoing CABG who have moderate AS (mean gradient 30 to 50 mm Hg or Doppler velocity 3 to 4 m per second). *(Level of Evidence: B)*

CLASS IIb

1. AVR may be considered in patients undergoing CABG who have mild AS (mean gradient less than 30 mm Hg or Doppler velocity less than 3 m per second) when there is evidence, such as moderate-severe valve calcification, that progression may be rapid. *(Level of Evidence: C)*

Patients undergoing CABG who have severe AS should undergo AVR at the time of revascularization. Decision making is less clear in patients who have CAD that requires CABG when these patients have mild to moderate AS. Controversy persists regarding the indications for "prophylactic" AVR at the time of CABG in such patients. This decision should be made only after the severity of AS is determined by Doppler echocardiography and cardiac catheterization.

Confirmation by cardiac catheterization is especially important in patients with reduced stroke volumes, mixed valve lesions, or intermediate mean aortic valve gradients (between 30 and 50 mm Hg) by Doppler echocardiography, because many such patients may actually have severe AS (as discussed in Section 3.1.6). The more complex and controversial issue is the decision to replace the aortic valve for only mild AS at the time of CABG, because the degree of AS may become more severe within a few years, necessitating a second, more difficult AVR operation in a patient with patent bypass grafts.

It is difficult to predict whether a given patient with CAD and mild AS is likely to develop significant AS in the years after CABG. As noted previously (see Section 3.1.3), the natural history of mild AS is variable, with some patients manifesting a relatively rapid progression of AS with a decrease in valve area of up to 0.3 cm^2 per year and an increase in pressure gradient of up to 15 to 19 mm Hg per year; however, the majority may show little or no change (61,86–95,107,1056). The average rate of reduction in valve area is 0.12 cm^2 per year (61), but the rate of change in an individual patient is difficult to predict.

Retrospective studies of patients who have come to AVR after previous CABG have been reported in which the mean time to reoperation was 5 to 8 years (1057–1062). The aortic valve gradient at the primary operation was small, less than 20 mm Hg, but the mean gradient increased significantly to greater than 50 mm Hg at the time of the second operation. These reports represent selected patients in whom AS progressed to the point that AVR was warranted. The number of patients in these surgical series who had similar gradients at the time of the primary operation but who did not have significant progression of AS is unknown.

Although definitive data are not yet available, patients with intermediate aortic valve gradients (mean gradient 30 to 50 mm Hg at catheterization or transvalvular velocity of 3 to 4 m per second by Doppler echocardiography) who are undergoing CABG may warrant AVR at the time of revascularization (181–185), whereas patients with gradients below 10 mm Hg do not need valve replacement. The

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degree of mobility and calcification are also important factors predicting more rapid progression of aortic disease and should be taken into consideration, particularly in those with gradients between 10 and 25 mm Hg (98,181,185–187,1063–1066). Because of the lack of data, controversy exists regarding AVR at the time of CABG, and the strength of these recommendations is reduced.

10.5. Management of Concomitant Mitral Valve Disease and Coronary Artery Disease

Most patients with both MV disease and CAD have ischemic MR, as discussed in Sections 3.6.5 and 7.3.1.3. In patients with 1 to 2+ MR, ischemic symptoms usually dictate the need for revascularization. Patients with more severe ischemic MR usually have significant LV dysfunction, and the decision to perform revascularization and MV repair is based on symptoms, severity of CAD, LV dysfunction, and inducible myocardial ischemia.

In patients with MV disease due to diseases other than ischemia, significantly obstructed coronary arteries identified at preoperative cardiac catheterization are generally revascularized at the time of MV surgery. There are no data to indicate the wisdom of this general policy, but because revascularization usually adds little morbidity or mortality to the operation, the additional revascularization surgery is usually recommended.)

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Key Words: ACC/AHA practice guideline ■ valvular heart disease ■ heart valves ■ cardiac murmur ■ valve lesion ■ thoracic surgery.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2006 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE

Committee Member	Research Grant	Speakers' Bureau	Stock Ownership/ Patents	Board of Directors	Consultant/Advisory Board
Robert O. Bonow, MD	None	None	None	None	Had a prior relationship with Wyeth Pharmaceuticals regarding anorectic drugs
Blasé A. Carabello, MD	None	None	None	None	None
Kanu Chatterjee, MD	None	• Astra-Zeneca • Bristol-Myers Squibb • MSD • Scios	None	None	• CV Therapeutics • Yamanouchi
Antonio C. de Leon, Jr., MD	None	None	None	None	None
David P. Faxon, MD	None	• Aventis-Sanofi • Bristol-Myers Squibb	• Medical Technologies International	None	• Boston Scientific • Johnson & Johnson
Michael D. Freed, MD	None	None	None	None	None
William H. Gaasch, MD	None	None	None	None	None
Bruce W. Lytle, MD	None	None	• Johnson & Johnson	None	• Shares purchased on open market. No options.
Rick A. Nishimura, MD	None	None	None	None	None
Patrick O'Gara, MD	None	None	None	None	None
Robert O'Rourke, MD	• Merck • Pfizer	None	None	None	None
Catherine M. Otto, MD	• St. Jude Medical	None	• Patent pending on use of ACE inhibitors	None	None
Pravin M. Shah, MD	None	None	None	None	• FenPhen litigation
Jack Shanewise, MD	None	None	None	None	None

This table represents the relationships of committee members with industry that were reported orally at the initial writing committee meeting and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. It does not necessarily reflect relationships with industry at the time of publication.

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APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2006 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE

Peer Reviewer*†	Representation	Research Grant	Speakers' Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Mazen Abu-Fadel	• Content Reviewer—ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None
Dr. Lishan Akolg	• Organizational Reviewer—Society of Thoracic Surgeons	None	None	None	• Guidant • J & J Cardiovations • Medical CV • Medtronic • Myocor • St. Jude Medical
Dr. Joseph Alpert	• Content Reviewer—Individual	None	Exeter, Inc	None	• EK Guard • Novartis • Sanofi-Aventis
Dr. Jeffrey Anderson	• Content Reviewer—Individual	None	• Bristol-Myers Squibb/Sanofi • diaDexus • Merck	None	Merck
Dr. Larry Baddour	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee	None	None	None	None
Dr. Simon Body	• Organizational Reviewer—Society of Cardiovascular Anesthesiologists	• Bayer Diagnostics	None	None	None
Dr. Ann Bolger	• Official Reviewer (cardiology)—AHA Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee	None	None	None	None
Dr. Charles Bridges	• Organizational Reviewer—Society of Thoracic Surgeons	None	None	None	None
Dr. Jay Brophy	• Official Reviewer—Board of Governors	None	None	None	None
Dr. Matthew Budoff	• Content Reviewer—AHA Cardiovascular Imaging and Intervention Committee	None	• General Electric	None	None
Dr. Melvin Chietlin	• Content Reviewer—Individual Review	None	None	None	None
Dr. John Child	• Content Reviewer—ACC/AHA Management of Adults With Congenital Heart Disease	None	None	None	None
Dr. Michael Crawford	• Content Reviewer—Individual	None	None	None	None
Dr. Ted Feldman	• Organizational Reviewer—Society for Cardiovascular Angiography and Interventions	• Abbott • Atritech • Bristol-Myers Squibb • Cardiac Dimensions • Cordis • Evalve	None	None	• Bristol-Myers Squibb • Cardiac Dimensions • Cordis • Guidant • Myocor
Dr. Linda Gillam	• Official Reviewer—Board of Trustees Review	None	None	None	None

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Peer Reviewer*†	Representation	Research Grant	Speakers' Bureau/ Honoraria	Stock Ownership	Consultant/ Advisory Board
Dr. Ami Iskandrian	• Content Reviewer—ACCF Cardiovascular Imaging Committee • Content Reviewer—AHA Cardiovascular Imaging and Intervention Committee • Content Reviewer—AHA Cardiac Imaging Committee	• Astellas Pharma • Bristol-Myers Squibb • CV Therapeutics • GE Healthcare • Molecular Insight	None	None	• Acusphere *(Blinded Reader)* • CV Therapeutics • International Atomic Energy (IAEA)
Dr. Donald Larsen	• Content Reviewer—AHA Cerebrovascular Imaging and Intervention Committee	None	• Microvention	• Gardant	• Microtherapeutics
Dr. Peter Lockhart	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee	None	None	None	None
Dr. Joseph Mathew	• Organizational Reviewer—Society of Cardiovascular Anesthesiologists	None	None	None	None
Dr. Debabrata Mukherjee	• Content Reviewer—ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None
Dr. Robert Robbins	• Official Reviewer (surgery)—AHA	None	None	None	None
Dr. Carlos Ruiz	• Content Reviewer—ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None
Dr. Richard Shemin	• Content Reviewer—ACCF Cardiovascular Surgery Committee • Organizational Reviewer—Society of Thoracic Surgeons	None	None	None	• 3F Therapeutics • Edwards Life Sciences • St. Jude Medical
Dr. Stanton Shernan	• Organizational Reviewer—Society of Cardiovascular Anesthesiologists	None	None	None	None
Dr. Thoralf Sundt	• Content Reviewer—ACCF Cardiac Catheterization and Intervention Committee	• CarboMedics	None	None	None
Dr. Kathryn Taubert	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee	None	None	None	None
Dr. Zoltan Turi	• Organizational Reviewer—Society for Cardiovascular Angiography and Interventions	None	None	None	None
Dr. Roberta Williams	• Content Reviewer—ACC/AHA Management of Adults With Congenital Heart Disease	None	None	None	None
Dr. William Zoghbi	• Content Reviewer—Individual	None	None	None	None

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication. *Participation in the peer review process does not imply endorsement of the document. †Names are listed in alphabetical order within category of review.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; and AHA, American Heart Association.

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APPENDIX 3. ABBREVIATION LIST

ACC = American College of Cardiology
ACCF = American College of Cardiology Foundation
ACE = angiotensin converting enzyme
AHA = American Heart Association
aPTT = activated partial thromboplastin time
AR = aortic regurgitation
AS = aortic stenosis
AVR = aortic valve replacement
CAD = coronary artery disease
CABG = coronary artery bypass surgery
ECG = electrocardiogram
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
INR = international normalized ratio
LMWH = low-molecular-weight heparin
LV = left ventricular
MR = mitral regurgitation
MS = mitral stenosis
MV = mitral valve
MVP = mitral valve prolapse
NYHA = New York Heart Association
RV = right ventricular
STS = Society of Thoracic Surgeons
TR = tricuspid regurgitation
2D = two-dimensional
UFH = unfractionated heparin

APPENDIX 4. AUTHOR RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2008 GUIDELINE UPDATE ON VALVULAR HEART DISEASE: FOCUSED UPDATE ON INFECTIVE ENDOCARDITIS WRITING COMMITTEE

Committee Member	Consultant	Speakers' Bureau/ Honoraria	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Rick A. Nishimura	None	None	None	None	None	None
Dr. Blase A. Carabello	None	None	None	None	None	None
Dr. David P. Faxon	• Boston Scientific • Bristol-Myers Squibb • GlaxoSmithKline • Johnson & Johnson	None	None	None	None	None
Dr. Michael D. Freed	None	None	None	None	None	None
Dr. Bruce W. Lytle	None	None	None	None	None	None
Dr. Patrick T. O'Gara	None	None	None	None	None	None
Dr. Robert A. O'Rourke	None	None	None	None	None	None
Dr. Pravin M. Shah	• Edwards LifeSciences	None	None	None	None	None

This table represents the relationships of committee members with industry that were reported orally at the initial writing committee meeting and updated in conjunction with all meetings and conference calls of the writing committee during the document development process. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

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APPENDIX 5. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY—ACC/AHA 2008 GUIDELINE UPDATE ON VALVULAR HEART DISEASE: FOCUSED UPDATE ON INFECTIVE ENDOCARDITIS

Peer Reviewer*	Representation	Consultant	Speakers' Bureau/ Honoraria	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Ann F. Bolger	• Official AHA Reviewer	None	None	None	None	None	None
Dr. Paul L. Douglass	• Official Reviewer—ACCF Board of Trustees	• Aventis • Merck • Novartis	• Bayer Healthcare • Bristol-Myers Squibb • Pfizer	None	None	None	None
Dr. Timothy J. Gardner	• Official AHA Reviewer	None	None	None	None	None	None
Dr. Chittur A. Sivaram	• Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Dr. David Aguilar	• Content Reviewer—AHA Heart Failure & Transplant Committee	None	None	None	None	None	None
Dr. Larry M. Baddour	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, & Kawasaki Disease Committee	• American College of Physicians • Enturia • UpToDate	None	None	None	None	None
Dr. Louis I. Bezold	• Content Reviewer—ACC Congenital Heart Disease & Pediatric Committee	None	None	None	None	None	None
Dr. Robert O. Bonow	• Content Reviewer—2006 Writing Committee Chair	None	None	None	None	None	None
Dr. A. Michael Borkon	• Content Reviewer—ACC Cardiovascular Surgery Committee	None	None	None	None	None	None
Dr. Jeffrey A. Feinstein	• Content Reviewer—ACC Congenital Heart Disease & Pediatric Committee	None	None	None	None	None	None
Dr. Gary S. Francis	• Content Reviewer—AHA Heart Failure & Transplant Committee	• Boehringer Ingelheim • Johnson & Johnson • NitroMed • Novartis • Otsuka	None	None	• National Institutes of Health† • Pfizer†	None	None
Dr. Wayne L. Miller	• Content Reviewer—AHA Heart Failure & Transplant Committee	None	None	None	None	None	None
Dr. Judith E. Mitchell	• Content Reviewer—AHA Heart Failure & Transplant Committee	• Astellas • GlaxoSmithKline • NitroMed	None	None	None	None	None
Dr. John B. O'Connell	• Content Reviewer—AHA Heart Failure & Transplant Committee	None	None	None	None	None	None
Dr. Geoffrey L. Rosenthal	• Content Reviewer—ACC Congenital Heart Disease & Pediatric Committee	None	None	None	None	None	None

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Peer Reviewer*	Representation	Consultant	Speakers' Bureau/ Honoraria	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Dr. Anne Rowley	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, & Kawasaki Disease Committee	None	None	None	None	None	None
Dr. Hartzell V. Schaff	• Content Reviewer—ACC Cardiovascular Surgery Committee	None	None	None	• AtriCure • Bolton Medical • Jarvik Heart • Medtronic • Sorin Group/ Carbomedics • St. Jude • Thoratec • W.L. Gore and Associates	• Sorin Group† • St. Jude†	None
Dr. Kathryn A. Taubert	• Content Reviewer—AHA Rheumatic Fever, Endocarditis, & Kawasaki Disease Committee	None	None	None	None	None	None

This table represents the relationships with industry that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10 000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Names are listed in alphabetical order within each category of review. †Significant (greater than $10 000) relationship.

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